OUTCOMES FOR POSTERIOR SEGMENT-INVOLVING UVEITIS: FROM HETEROGENEITY TO A CORE OUTCOME SET

By

MOHAMMAD OMAR SALEH TALLOUZI

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Institute of Applied Health Research
College of Medical and Dental Sciences
University of Birmingham
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Abstract

Background:

Uveitis describes a group of diseases characterised by intraocular inflammation. Uveitis is the fifth commonest cause of visual loss in the developed world and accounts for about 10–15% of total blindness. Intermediate, posterior and panuveitis are the most critical forms of uveitis named as Posterior Segment-Involving Uveitis (PSIU). They often share common clinical features and higher risk of complications (e.g. uveitic macular oedema (UMO)), requiring additional treatment either systemic or local injection-based therapy. UMO describes the accumulation of fluids at the central part of the retina, known as the macula. It is the leading cause of sight-loss in PSIU affecting around one-third of patients. To date, there has been a lack of consensus guidelines over the treatment of UMO. Furthermore, trials include a range of heterogeneous outcomes which may lack relevance to key stakeholders (patients and carers) and means that it is challenging to compare results from trials and undertake evidence synthesis.

The doctoral research forming my thesis aimed to: (i) assess the effectiveness of the available pharmacological therapies used in the treatment of UMO; (ii) develop an international consensus on a standardised set of outcomes using a multi methods approach to create a core outcome set (COS) for non-infectious PSIU

Methods:

The first part of the thesis employed a systematic review to assess the effectiveness of the available pharmacological therapies used in the treatment of UMO across comparative studies (randomised/non-randomised trials and observational studies). The review included all systemic, local or topical pharmacological agents identified among those studies.

The second part of the thesis describes a two phase process of developing a standardised set of outcomes for use in effectiveness trials for non-infectious PSIU. Phase 1: to identify a comprehensive list of outcomes based on (a) systematic review of clinical trials in PSIU and (b) findings from key respondent focus groups and interviews (patients, carers, healthcare professionals and health policy-makers/commissioners). A triangulation design (systematic review, focus group discussions, and interviews) was used to obtain complementary data related to the topic and form a comprehensive list of outcomes. Phase 2: to prioritise outcomes through a consensus process with the key stakeholder groups (patients, carers, healthcare professionals and health policy-makers/commissioners) based on (a) an online web-based survey (Delphi exercise) and (b) a face-to-face consensus meeting.

Results:

The systematic review found corticosteroids to be the most frequently studied therapies, with various routes of administration being used. Corticosteroids are effective in UMO; however, significant adverse events were reported in those studies, with the distribution between local and systemic adverse events being reflective of their route of administration. Additionally, a number of immunomodulatory agents have been used in treating UMO, however, it was difficult to draw significant conclusions regarding these treatments. The systematic review also identified a list of outcomes across those included studies.

Qualitative research with the key stakeholders (patients with PSIU and their carers; and healthcare professionals (ophthalmologists, nurse practitioners and policy-makers/commissioners)) were used to explore the stakeholder perspectives on outcomes that mattered in PSIU management for inclusion in the COS. Healthcare professionals' views were similar to those of patients and carers. Analysis of the qualitative data and systematic review identified 57 outcomes grouped into 11 outcome domains that were considered as important

to the key stakeholders for consideration in the COS. The qualitative research presented a broader picture of the impact of PSIU and related treatment on patients' lives that was not addressed in the studies identified through the systematic review.

The long-list of candidate outcomes (n=57) was reduced through a two round online Delphi survey with key stakeholders, resulting in 9 outcomes directly qualifying for inclusion in the COS and 15 outcomes being carried forward to consensus meeting at which 7/15 were agreed for inclusion. The final COS comprised 16 outcomes organised into 4 outcome domains comprising visual function, Health-Related Quality of Life (HRQoL), treatment side effects and disease control.

Conclusion

My thesis focused on the most sight-threatening forms of intraocular inflammation, PSIU, and its major complication, UMO. The first part of the thesis provided a comprehensive overview of the pharmacological agents used to treat UMO. The thesis highlights the need for further head-to-head studies for many of the major immunomodulatory drugs, and the need to conduct studies that are either exclusive to UMO or are designed to include stratification according to presence or absence of UMO and report the UMO-subgroup data.

The second Part of the thesis presented a robust methodology recommended by the COMET initiative to develop the first standardised set of outcomes (COS) for use in effectiveness trials of non-infectious PSIU. This COS comprises 16 outcomes grouped into 4 outcome domains that represents the priorities of all key stakeholders and is suitable for evaluation in clinical trials to inform clinical decision-making and health policy. Adoption of this COS would improve the value of future uveitis clinical trials, and minimise research waste. Some of the outcomes identified do not yet have internationally agreed methods for measurement and should be the subject of future research.

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I dedicate this work to my dearest wife (Rawia) for her constant support. I dedicate this work to my parents who always believe in me. Last, but not least, I dedicate this work to my kids Yaman, Lara and Talia. Talia, in particular, taught me how to be determined in achieving my targets.

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Contribution statement

Chapters in this thesis represent my own work. My supervisors provided supervisory support and inputted to the design of the research, data analysis, and interpretation of the findings. The team also provided guidance on the thesis structure and critical review and feedback on the thesis chapters. Professors Calvert and Denniston oversaw the design of the project.

I conducted and analysed the systematic review and completed all stages of the systematic review including identifying, selecting, extracting and appraising data. Dr Moore supervised the systematic review, helped with search strategy and data analysis. He also reviewed the first draft of the systematic review protocol (The effectiveness of pharmacological agents for the treatment of Uveitic Macular Oedema (UMO): a systematic review protocol). Professor Denniston reviewed and edited the first draft of the systematic review manuscript (The effectiveness of pharmacological agents for the treatment of Uveitic Macular Oedema (UMO)): a systematic review). David Moore, Professor Calvert, Professor Denniston and Professor Murray guided the development and the structuring of the systematic review.

I ran the focus group discussions and interviews. I organised, conducted and analysed the Delphi exercise. Dr. Mathers helped facilitate the focus group discussion, gave instruction and guidance on the analysis of the qualitative data and reviewed the first draft of the manuscript (Outcomes important to adult patients with Non-infectious Posterior Segment-Involving Uveitis: A qualitative study). All supervisors were involved in identifying the list of outcomes and outcome domains and established definitions of outcomes and outcome domains. I, Professor Murray and Professor Denniston led the participant recruitment process. Professor Murray and Professor Denniston provided clinical advice. I organised, conducted and chaired the consensus meeting. I have also analysed the data that came out of the meeting.

Thesis Publications

- Chapter 3 of this thesis is the published **systematic review protocol:**

  Tallouzi, M.O., Moore, D.J., Calvert, M., Murray, P.I., Bucknall, N. and Denniston, A.K., 2016. The effectiveness of pharmacological agents for the treatment of uveitic macular oedema (UMO): a systematic review protocol. *Systematic reviews*, *5*(1), p.29.

  Available online: https://doi.org/10.1186/s13643-016-0203-y

- Chapter 4 of this thesis is the published **systematic review:**

  Tallouzi, M.O., Moore, D.J., Barry, R.J., Calvert, M., Mathers, J., Murray, P.I. and Denniston, A.K., 2019. The Effectiveness of Pharmacological Agents for the Treatment of Uveitic Macular Oedema (UMO): A Systematic Review. *Ocular immunology and inflammation*, 27(4), pp.658.

  Available online: https://doi.org/10.1080/09273948.2019.1569243

- Chapter 5 of this thesis is the published **study protocol:**

  Tallouzi, M.O., Mathers, J.M., Moore, D.J., Murray, P.I., Bucknall, N., Blazeby, J.M., Calvert, M. and Denniston, A.K., 2017. COSUMO: study protocol for the development of a core outcome set for efficacy and effectiveness trials in posterior segment-involving uveitis. *Trials*, *18*(1), p.576.

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- Chapter 6 of this thesis is the published **qualitative research study:**

  Tallouzi, M.O., Moore, D.J., Bucknall, N., Murray, P.I., Calvert, M. Denniston, A.K., and Mathers, J.M 2020. Outcomes important to patients with Non-infectious Posterior Segment-Involving Uveitis: A qualitative study. *BMJ Open Ophthalmology*, 1–12

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- Chapter 8 of this thesis is the published **COS study**

  Tallouzi MO, Mathers JM, Moore DJ, Bucknall N, Calvert MJ, Murray PI, Denniston AK; COSUMO Working Group. Development of a Core Outcome Set for Clinical Trials in Non-infectious Uveitis of the Posterior Segment. Ophthalmology:S0161-6420(21)00070-1.

  Available online: https://doi.org/10.1016/j.ophtha.2021.01.022

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List of abbreviations

Anti-TNF	Anti-Tumour Necrosis Factor
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
BCVA	Best Corrected Visual Acuity
BMEC	Birmingham and Midland Eye Centre
BUS	Birdshot Uveitis Society
CINAHL	Cumulative Index to Nursing and Allied Health Literature.
COMET	Core Outcome Measurement in Effectiveness Trials
COS	Core Outcome Set
CPROR	Centre for Patient Reported Outcome Research
FFA	Fundus Fluorescein Angiogram
HRQoL	Health-Related Quality of Life
IRAS	Integrated Research Application System.
MEDLINE	Medical Literature analysis and Retrieval System Online
NICE	National Institute for Health and Care Excellence
OCT	Optical Coherence Topography
PInGU	Patient Involvement Group in Uveitis
PRO	Patients Reported Outcome
PROM	Patients Reported Outcome Measure
UIG	Uveitis Information Group
UMO	Uveitic Macular Oedema
RCT	Randomized Controlled Trial

Thesis outline

This thesis represents a five-year project on the development of a Core Outcome Set (COS) for non-infectious Posterior Segment-Involving Uveitis (PSIU). The first chapter introduces the anatomy of the eye and the visual pathway. It also describes the complexity of evaluating uveitis, the current inconsistency in outcome selection in clinical trials of PSIU and provides a rationale for the development of a standardised agreed set of outcomes and its future potential value. This chapter also describes the aims of the thesis. The subsequent chapters represent the process of developing the Core Outcome Set in non-infectious PSIU and discuss the pharmacological therapy in the treatment of UMO.

Chapter 2 provides a general overview of the methods used to develop a COS and justifies the approach taken.

Chapter 3 and 4 report the protocol and the results of the systematic review of the effectiveness of pharmacological agents for the treatment of Uveitic Macular Oedema (UMO). Presented data were also used to identify outcomes in included effectiveness trials to inform a comprehensive list of outcomes and aid the development of the Core Outcome Set.

Chapter 5 represents the study protocol describing multi methods used to define a long-list of outcomes comprising a systematic review and qualitative study followed by a consensus process of Delphi exercise and face-to-face consensus meeting.

Chapter 6 and 7 represent the qualitative research methods used to understand patients, carers and healthcare professionals' perspectives on what sort of outcomes they thought to be important for adult patients with non-infectious PSIU. Presented data are used to contribute to the long-list of outcomes to feed into the Delphi exercise and help the development of the core outcome set.

Chapter 8 addresses the central aim of the thesis and presents a robust methodology recommended by the Core Outcome Set Measures in Effectiveness Trials (COMET) initiative in the development of a Core Outcome Set for clinical trials in non-infectious PSIU. The findings of this chapter describe in detail the stages used to arrive at a standardised set of outcomes for use in PSIU trials. Stage 1: A comprehensive list of outcomes was identified through both a systematic review of effectiveness trials of PSIU and qualitative research with stakeholders. Stage 2: A two round Delphi exercise was used to ascertain what outcomes participants think are important for adult PSIU to be included in the core set. Pre-defined consensus criteria were used to establish which outcomes were included in the COS. This was followed by a consensus meeting with key stakeholders to agree the final list of outcomes in the core outcome set.

Chapter 9 discusses the findings of this work in relation to the aims of the research and how this thesis adds to the current literature. Further discussion considers the methodological strengths and weaknesses of the thesis, the implications of the findings, and recommendations for future research.

Chapter 1: Background

1.1 Introduction

Chapter one introduces the anatomy of the eye and the visual pathway, defines uveitis and explores its classifications and descriptors and considers the manifestations and grading tools to assess its activity. The chapter discusses uveitis complications focusing on the most sight-threatening of uveitic macular oedema (UMO) and the available treatment in the field. Finally, this chapter discusses the importance of reported and measured outcomes in clinical trials and evaluates the current inconsistency of reported outcomes across uveitis trials. It also provides a rationale for the development of a standardised agreed set of outcomes to be used in clinical trials and its future potential value and presents the aim of the thesis.

1.2 Anatomy and physiology of the eye

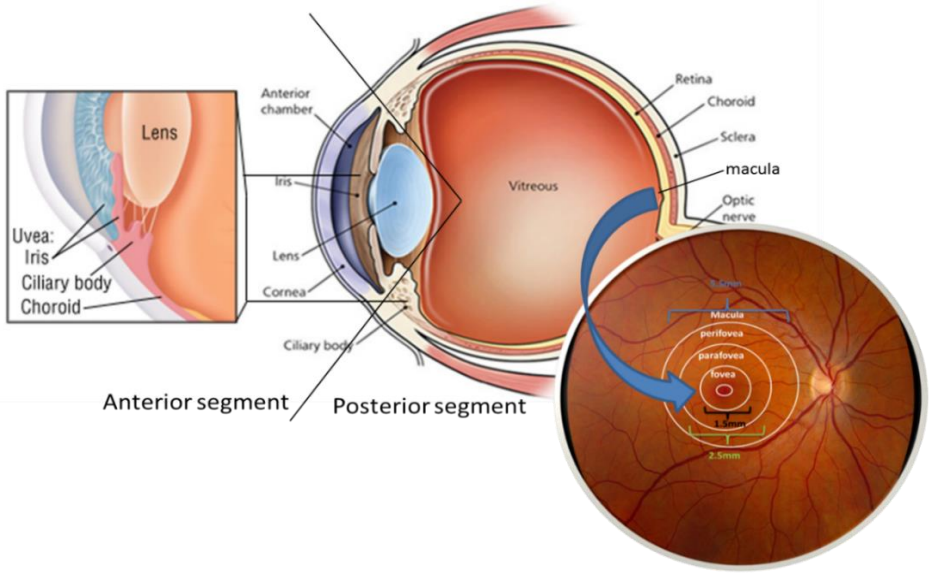
The eye is a highly specialised organ; its main function is to focus the light onto specialised sensory cells located on the retina at the back of the eye. The eye consists of two main parts: the anterior and posterior segment. The anterior segment makes up one-third of the eye and includes structures in front of the vitreous humour comprised of the conjunctiva, cornea, iris, ciliary body, lens, anterior chamber (space between the cornea and iris), and the posterior chamber (space between the iris and the lens). The posterior segment of the eye accounts for two-thirds of the eye and includes the vitreous, retina, choroid and optic disc (1, 2). Figure 1 shows the anatomical structure of the eye that will be discussed as follows:

- **Conjunctiva:** this is the thin loose connective tissue that covers the inner part of the eyelid (palpebral conjunctiva) and the sclera (bulbar conjunctiva) (3).

- **Sclera:** this is the thick outer coat of the eye. It is normally white and opaque. The sclera is

comprised of three layers: episclera (loose fibre and elastic connective tissue underneath the conjunctiva); sclera proper (dense tissue that gives a white colour), and lamina fusca (elastic fibres forming the inner part of the sclera with small arteries and veins). The sclera is a useful coat to protect the eye contents, maintain a constant eye shape providing a major source of nourishment to the outer layers of the eye (3).

Figure 1: Anatomical structure of the eye



This image was adapted from Aurosiksha teaching course of Anatomy and Physiology of Uvea (2012), accessed 30/04/2020 (https://www.aurosiksha.org/ex-course-preview/MXNzTDNTYlFpcXNGcnpwQVdWUVFMZz09) (4)

- **Iris:** this is the coloured part of the eye that regulates the amount of light entering the eye.

- **Pupil:** this is a hole in the centre of the iris that adjusts the amount of the light passing through to the lens of the eye. The amount of light transmitted through the pupil is regulated by the sympathetic and parasympathetic innervation of the iris that causes widening and narrowing of the sphincter (dilation and constriction) of the pupil reaction (5).

- **Cornea:** this is the transparent avascular window of the eye and accounts for two-thirds of the eye's refraction (bending light waves to focus them onto the retina). It forms the

anterior part of the outer coat of the eye and extends posteriorly to the sclera (2).

- **Lens:** this is a transparent biconvex structure situated behind the pupil. It is the most important refractive structure of the eye after the cornea (5).

- **Ciliary body:** this is the intermediate layer of the uveal tract that lies between the iris and the choroid. The anterior part of the ciliary body (pars plicata) forms ciliary processes that are responsible for producing aqueous humour. Regulation of aqueous humour outflow is the key principle of maintaining a normal intraocular pressure. Drainage of aqueous humour is achieved either via trabecular meshwork into the canal of Schlemm through the anterior chamber angle which then drains via aqueous veins into the general circulation (90%), or via uveoscleral outflow (10%). Aqueous humour also provides metabolic support for the lens, cornea and vitreous and helps to maintain ocular transparency (6).

- **Vitreous**: this is the large cavity behind the lens that extends to the retina. It is filled with transparent vitreous humour gel and acts as a shock absorber, protecting ocular structures and maintaining passive "transport and removal" of metabolites. Vitreous contains hyaluronic acid and collagen fibrils that connect the gel to the retinal membrane (5).

- **Retina:** this is the inner lining of the eye. It is located in the posterior segment between the vitreous anteriorly and the choroid posteriorly. The retina is composed of multiple layers including the innermost layer of the inner limiting membrane which forms the basal membrane of the retinal Müller glial cells, the nerve fibre layer and the ganglion cell layer which include the nuclei of the ganglion cells forming the optic nerve. The inner plexiform contains synapses between ganglion cells, bipolar, amacrine, and horizontal cells, while the inner nuclear layer is composed of bipolar cells, amacrine cells, horizontal and retinal Müller glial cells (7). Multiple specialised neurons are found in the retinal layers including

photoreceptors, bipolar cells and ganglion cells. These transmit visual information. Photoreceptors are highly specialised cells in the inner part of the retina characterised by photo pigments and their ability to convert light energy into neural signals to be recognised by the brain. This process is known as phototransduction (8).

- **Macula:** this represents a circle centred on the centre of the fovea (a depression at the centre of the macula) with a radius equal to the distance from the centre of the fovea to the nasal edge of the optic disc. The macula is a highly specialised part of the retina responsible for central vision and colour vision that is impaired when the macula is diseased. The macula has a high concentration of photoreceptor cells with various sub-divisions including foveola, foveal avascular zone, fovea, parafovea, and perifovea (9). Further details are shown in Figure 1.

- **Choroid:** this is the middle vascular and pigmented layer which lies between the retina and sclera. It is the most posterior part of the uveal tract. The choroid provides the main blood supply to the outer retinal layers and retinal pigmented epithelium (10). Impairment of the oxygen supply and blood flow from the choroid to the retina is a major source of pathophysiology for a number of retinal diseases (e.g. macular degeneration, choroidal vasculopathy) (11).

  The pigment in this layer helps to absorb any excess light and prevents light scatter thereby improving the quality of the image produced by the retina. Four layers were identified in the anatomical structure of the choroid including Haller's layer (the outermost layer), Sattler's layer, choriocapillaris and Bruch's membrane (the innermost layer) (12).

- **Optic disc:** this is the circular and visible part of the optic nerve named as the optic nerve head. It is composed of axons derived from the ganglion cell layer of the retina (8). The

optic disc is located 3 to 4 mm to the nasal side of the macula and appears pink to orange in colour. The normal optic disc diameter varies in size from 1.2 to 2.5mm. The central depression of the optic disc is known as the optic cup. It may vary in size through the average normal ratio is 0.3-0.5mm. A change in the appearance of the optic disc such as pallor and/or increase in the size of the cup disc ratio may indicate optic nerve disease (13).

- **Optic nerve:** this is the second cranial nerve, and transmits all information from the eye to the brain**.** It is formed by the convergence of the ganglion axonal and glial cells (8).

1.3 Visual pathway

The light enters the cornea and passes through a series of clear optical media (aqueous humour, through the pupil, lens, vitreous humour) to fall on the retina (the inner lining at the back of the eye). The cornea and the lens act as the main refractive mediums for focusing light on the retina; 70% of the refractive power is regulated by the cornea, and 30% is facilitated by the lens. The refractive power of the lens is altered by contraction or relaxation of the suspensory ligaments that attach the lens to the ciliary muscles. It is worth noting that the cornea cannot modify its refractive power (14, 15).

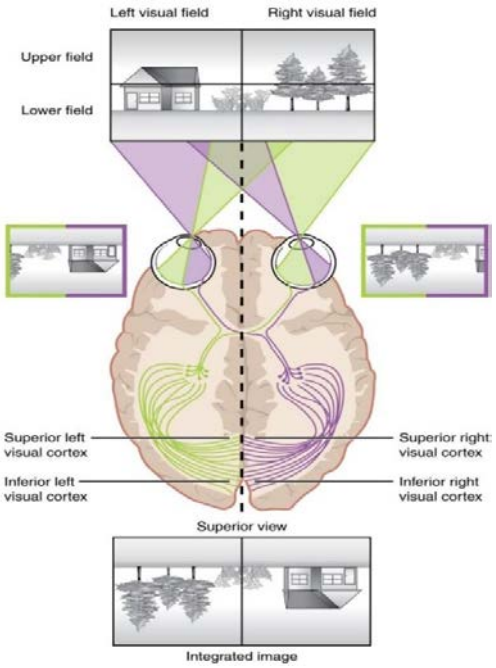
By the time light reaches the retinal neurons, its energy is converted into electrochemical neuronal signals by the photoreceptors (phototransduction) which then pass through the bipolar cells and into the ganglion cells. The ganglion cells axons exit the retina at the optic nerve passing through the optic foramen into the brain(16). A formed image on the retina is inverted vertically and transposed left to right as shown in Figure 2, so that the inferior retina is projected into the superior visual field. Thus there is an inverted relationship between the visual system and the visual field.

Information from the ganglion cell axons is transmitted via the optic nerve. The optic nerve

from each eye gathers at the optic chiasm. At this point the nasal nerve fibres from each eye decussate in the optic chiasm (axons from the right nasal side go to the left, and axons from the left nasal side go to the right) forming the optic tract. It is important to note that axons forming the temporal side of each eye do not cross over at the chiasm (14) (Refer to Figure 2).

The lateral geniculate nucleus (LGN) is located in the midbrain and responsible for one-third of visual pathway axons. The LGN acts as a station holding the information from each eye separate before transferring them to the visual cortex via optic radiations. The occipital lobe of the cerebral cortex contains the visual cortex that has the ability to process received visual information to form the final image (14-16). Each eye has the ability to produce a single image, however specialised cells in the occipital cortex allow us to process the visual input from both eyes simultaneously and perceive our three dimensional (3D) picture combining two single images into a single visual perception known as binocular fusion (17). Figure 2 illustrates the visual pathway.

Figure 2: Visual pathway



This image was taken from Anatomy & Physiology, (http://cnx.org/content/col11496/1.6/), Accessed 05/06/2020 (18)

1.4 Uveitis

Uveitis is, by definition, an inflammation of the uveal tract (the middle layer of tissue in the wall of the eye) comprising the iris, the ciliary body and the choroid (Figure 1).The term uveitis has however been extended to encompass inflammation in adjacent structures to the uvea such, as the retina and the vitreous (19). Uveitis is one of the leading causes of preventable blindness in the United States (20, 21), and accounts for approximately 10-15% of the causes of total blindness in Western countries and up to 25% of total blindness in the developing world (21). Although uveitis is a well-known cause of blindness, there is only scant knowledge concerning the prevalence and incidence of uveitis among those with severe sight impairment. The complications like cataract and glaucoma, macular abnormalities are included in many epidemiological studies about blindness, how many of these attributable to uveitis is not specified (22).

The annual incidence of uveitis is estimated at 14-50 per 100,000 with a prevalence of around 38–200 per 100,000 general populations (23-26). In contrast to some of the commoner sight-threatening eye conditions which tend to affect the older population, uveitis may affect any age group and is relatively common in those of working age group. It is equally distributed between the genders. In a UK retrospective study of 315 patients, reduction of visual acuity in at least one eye was estimated in approximate 70% of patients with uveitis who were attending the eye clinics, with half reporting bilateral visual impairment (20).

1.4.1 Uveitis classification system and descriptors

There are two main uveitis classifications – anatomical by Standardisation of Uveitis Nomenclature (SUN) (27), and by cause as described by the International Uveitis Study Group (IUSG) (28). Additionally, the SUN reported descriptors related to the duration and onset of uveitis (27). Further details are discussed below.

1.4.1.1 Anatomical classification

The Standardisation of Uveitis Nomenclature (SUN) notes described the primary site of visible inflammation for each type (27). Four anatomical classifications were identified (anterior, intermediate, posterior and panuveitis) describing the main affected part of the uveal tract (27, 29).

- ***Anterior uveitis*** describes the inflammation of the anterior part of the uveal tract (anterior chamber). The SUN definition describes the anterior as a subset of uveitis where the anterior chamber is the major visible site of inflammation. This includes iritis, iridocyclitis and anterior cyclitis (27).
- ***Intermediate uveitis*** describes the inflammation of the middle part of the uveal tract (ciliary body and vitreous). The SUN definition describes intermediate uveitis as a subset of uveitis where the vitreous is the major visible site of inflammation. It includes pars planitis (27).

- ***Posterior uveitis*** describes the inflammation of the posterior part of the uveal tract (choroid, with adjacent structures). The SUN definition describes posterior uveitis as the subset of uveitis where the choroid is the major site of inflammation. It includes focal, multifocal, or diffuse choroiditis, chorioretinitis, retinochoroiditis, retinitis and neuroretinitis (27).

- ***Panuveitis*** encompasses all forms of uveitis involving multiple sites of the eye (anterior, intermediate and posterior) (27).

1.4.1.2 IUSG Clinical classification

The International Uveitis Study Group (IUSG) approved a classification form related to the causation of uveitis (28).

- **Infectious uveitis:** those forms of uveitis are caused by an infectious agent. This includes:
    - Bacteria such as Mycobacterium tuberculosis (tuberculosis) and Treponema pallidum (syphilis)
    - Parasites such as Toxoplasma gondii in toxoplasmosis
    - Viral such as herpes simplex , varicella-zoster cytomegalovirus (30).
- **Non-infectious uveitis:** those forms of uveitis are not associated with an infectious agent. They may be:
    - Associated with a systemic disease such as ankylosing spondylitis, sarcoidosis, multiple sclerosis, Behcet's disease, inflammatory bowel disease, psoriasis and others (31).
    - Not associated with a systemic disease. Some may have a distinct pattern that has been labelled as a syndrome (e.g. Birdshot Chorioretinopathy, Vogt-Koyanagi-Harada) (19). Where no underlying cause is found, cases are commonly labelled "idiopathic" (19). Non-infectious uveitis is the most common pathology observed (32).
- **Masquerade syndromes:** those forms include neoplastic and non-neoplastic diseases that mimic uveitis and are not inflammatory uveitis.
    - Neoplastic causes may include, lymphoma, leukaemia, uveal malignant melanoma, retinoblastoma, and metastases (33).
    - Non-neoplastic conditions may include trauma, retinal detachment, pigment dispersion syndrome (PDS) (34), drug reactions, post-vaccination uveitis, anterior segment ischaemia (e.g. due to carotid artery disease, irradiation, extraocular muscle disinsertion) (30, 35).

1.4.1.3 Uveitis Descriptors

Additionally, the SUN defined descriptors for classifying forms of uveitis related to duration and onset. Uveitis duration may be: limited (defined as ≤3 months) or persistent (defined as >3 months). The course of uveitis is described as acute (an episode characterised by sudden onset and limited duration as lasting less than 3 months); chronic (persistent duration with relapse in <3 months period of stopping treatment), and recurrent which refers to a flare-up of the disease after complete resolution of the previous episode (being inactive without treatment) in a period of ≥3 months (36, 37).

1.4.2 Clinical manifestations of uveitis

Clinical manifestation of uveitis can vary depending on the anatomical classification, duration and severity of the disease (27, 38).

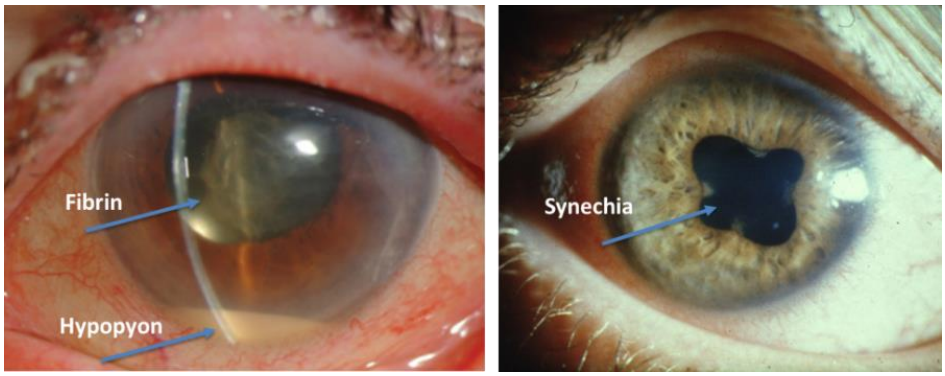
1.4.2.1 Anterior uveitis

Anterior uveitis is the most common form of uveitis, and accounts for 46-52 % of uveitis presenting to the hospital eye service (39, 40). This form of uveitis is often associated with HLA B27. The most common systemic disease association is ankylosing spondylitis, but other associations include Reiter's syndrome, inflammatory bowel disease, juvenile idiopathic arthritis, psoriatic arthritis, and sarcoidosis. It also arises from viral infection of herpes simplex virus , varicella zoster virus and cytomegalovirus (41).

The common symptoms of anterior uveitis are eye pain, redness of the eye, photophobia (sensitivity to light) and blurred vision. Circumcorneal injection is a classic sign of anterior uveitis (i.e. dusky red appearance from dilatation of the ciliary vessels at the junction of the sclera-conjunctival area) (See Figure 3A) with or without keratic precipitates(38, 42). Cellular infiltration (presence of white cells) and/or leak of protein (flare) into the anterior chamber

may be seen in active disease and can be scored using the grading tool described by the SUN group (27). In severe uveitis findings may include a massive leukocytic response leading to sedimentation of white cells in the anterior chamber (a hypopyon) adhesions between the iris and the anterior lens surface (posterior synechiae) and the presence of fibrin in the anterior chamber (Figure 3) (38, 42).

Figure 3: Hypopyon, posterior synechiae and fibrin



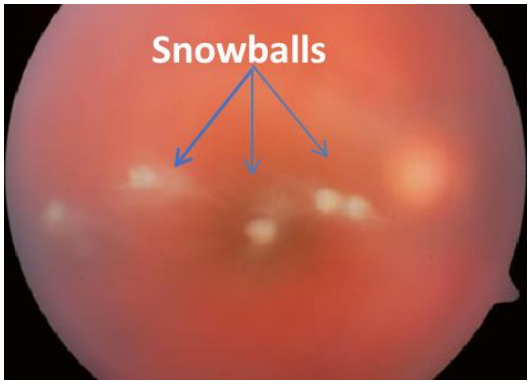
1.4.2.2 Intermediate uveitis

Intermediate uveitis represents around 1-11% of all uveitis presenting to hospital eye service (39, 40). This form of uveitis is associated with sarcoidosis, multiple sclerosis, however, in some cases, systemic infections (e.g. Lyme disease, syphilis, tuberculosis) have been reported (43).

The symptoms of intermediate uveitis are seeing floaters from vitreous debris and blurred vision. In severe cases, patients can present with loss of vision due to either aggregation of floaters in the vitreous or macular oedema. Anterior uveitis may also be present in some of those cases (38, 42).

Vitreous inflammation is seen clinically as vitreous haze and vitreous snowballs (yellow-white inflammatory aggregates (44). Furthermore, snow banking (exudates on the inferior part of the pars plana) is a clinical finding associated in some forms of intermediate uveitis (Figure 4) (45).

Figure 4: Vitreous snowballs

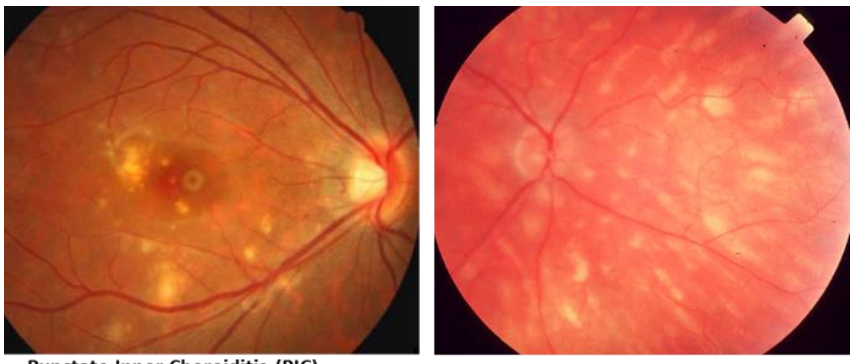


1.4.2.3 Posterior uveitis

Posterior uveitis represents around 11% of all uveitis presenting to the hospital eye service (39, 40). This form of uveitis is associated with Behcet's disease, Vogt-Koyanagi-Harada disease and birdshot chorioretinopathy. Infection-related causes include toxoplasmosis, tuberculosis, syphilis, herpes simplex virus, varicella zoster virus, cytomegalovirus (40, 43).

The symptoms of posterior uveitis are blurred vision, floaters, flashing lights, loss of peripheral vision; it is usually painless (39). Vitreous inflammation including vitreous haze, and vitreous opacities are seen in posterior uveitis with foci of inflammation to the choroid and/or retina Additionally the optic disc may be involved in the inflammation (44). Figure 5 demonstrates the retinal and choroidal inflammations in posterior uveitis.

Figure 5: Inflammation of the choroid



Punctate Inner Choroiditis (PIC)

Birdshot choroiditis.

1.4.2.4 Panuveitis

Panuveitis represents around 21-32% of all uveitis presenting to hospital eye care (39, 40). The symptoms of panuveitis are a combination of those seen in anterior, intermediate and posterior uveitis (43).

1.5 Complications of uveitis

Uveitis may cause a number of complications, particularly in chronic cases. The most common complications of uveitis are macular oedema, cataract and glaucoma (20). Other related complications that lead to permanent ocular damage including macular scarring or atrophy, epiretinal membrane (ERM), lamellar macular hole and optic disc atrophy (20, 22, 45).

1.5.1 Cataract

Cataract describes any opacity in a normal transparent lens of the eye. Cataract formation is also a common cause of sight-loss in uveitis, usually associated with sustained inflammation or prolonged exposure to corticosteroids or both (46). Treatment of a cataract is through surgical removal of the cloudy lens followed by a lens implant. Cataract was reported in 15-50% of patients with uveitis (45). The incidence of cataract in uveitis increases as the duration and severity of the disease increase (47)

1.5.2 Glaucoma

Glaucoma describes a progressive optic neuropathy, normally related to raised intraocular pressure. It was reported as the third most common complication in uveitis and a leading cause of visual disturbance and blindness (48). Glaucoma is usually treated with medication (topical or/and systemic) or surgery (49). The incidence of raised intraocular pressure (>21 mmHg) in acute uveitis is approximately 29-41%, while the incidence of glaucoma is 8% that increases with the duration of uveitis to 11% (48).

1.5.3 Choroidal neovascularization (CNV)

Choroidal neovascularization (CNV) describes the process of capillaries from the choriocapillaris growing though Bruch's membrane and proliferating in the sub-RPE (type 1 neovascularization) and/ or subretinal space (type 2 neovascularization) to form a choroidal neovascular membrane (CNVM). There may be associated haemorrhage, exudation, serous retinal detachment, pigment epithelial detachment, or scar formation (50).

Choroidal neovascularization resulting in a CNVM is an uncommon but serious complication PSIU associated with visual impairment (51). Among the 4041 eyes (2307 patients) with PSIU (e.g. punctate inner choroidopathy, multifocal choroiditis, serpiginous choroiditis, and Vogt-Koyanagi-Harada syndrome) only 81 (2%) reported having CNV (51). The pathogenesis of inflammatory CNV is similar to the wet age-related macular degeneration (AMD) and includes hypoxia and release of vascular endothelial growth factors, stromal cell derived factor 1-alpha, and other inflammatory mediators (52). The importance of VEGF in the pathogenesis of CNV is related to the effectiveness of anti-VEGF agents in the treatment of CNV not only in uveitis, but also in the context of AMD, myopia and other conditions (53, 54).

1.5.4 Uveitic macular oedema

Macular oedema (MO) describes an abnormal fluid collection in the macular region. This can arise in numerous retinal conditions including diabetic retinopathy, branch or central retinal vein occlusion, post-operative inflammation (e.g. following cataract surgery) and central serous chorioretinopathy (7). It is also the leading reversible cause of sight-loss in uveitis affecting around one-third of patients (23, 55, 56). Macular oedema is a sight-threatening condition in uveitis patients and it is known in this context as Uveitic Macular Oedema (UMO) (23, 55).

UMO accounts for 41% of visual impairment and 29% of blindness (25, 57). Additionally, loss of contrast sensitivity, colour vision and distortion of vision (metamorphopsia) by which straight lines appear wavy, and a central scotoma (a partial loss of central vision or blind spot) were reported in UMO (58). Further details on clinical presentation were also reported earlier in this chapter based on uveitis anatomical classification.

1.5.4.1 Pathogenesis of Uveitic macular oedema

The mechanism of uveitic macular oedema (UMO) is a complex inflammatory process which is poorly understood. UMO is not a disease in its own right but occurs as a result of inflammatory processes leading to accumulation of fluid at the macular area (42). The healthy retina is achieved through passive and active systems that maintain retinal haemostasis, and keep the retina relatively dehydrated. Imbalance in the process of retinal fluid entry and exit leads to fluid accumulation (59). This macular oedema is associated with retinal thickness increasing above the average normal macular thickness (approximately 210µm), which impairs retinal transparency and interferes with photon transmission leading to reduced visual acuity (7).

The most common explanation for UMO concerns a breakdown in the blood-retinal barrier (BRB) at the macular area. Fluid enters the neurosensory retina from numerous sources including vitreous, retinal blood vessels and choroid via the retinal pigmented epithelium. This process is controlled by the inner and outer blood retinal barriers (60). The outer BRB refers to the barrier formed at the RPE cell layer and functions, in part, to regulate the movement of solutes and nutrients from the choroid to the sub- retinal space. In contrast, the inner BRB is located in the inner retinal microvasculature and comprises the microvascular endothelium which line these vessels. The tight junctions located between these cells mediate highly selective diffusion of molecules from the blood to the retina and the barrier is essential in

maintaining retinal homeostasis. It is therefore a breakdown in BRB that would be either in the inner retinal vessels or the retinal pigment epithelium that results in macular oedema (61, 62)".

1.5.4.2 Types of uveitis associated with macular oedema and risk factors

The most sight-threatening forms of uveitis are those forms affecting the vitreous and the posterior structures of the eye (e.g. intermediate, posterior and panuveitis). These are sometimes known collectively as posterior segment-involving uveitis (PSIU), a convenient grouping for clinical trials and treatment appraisals (28, 36). Although UMO may occur occasionally in anterior uveitis, it is much more common in PSIU (63). Risk factors for CMO are smoking (64), duration of uveitis (65), comorbidities such as cardiovascular disease, hypertension, diabetes, or hyperlipidaemia (66), and age (patients older than 50 years) (67).

1.6 Assessment of uveitis and associated macular oedema

1.6.1 Visual acuity

Visual acuity (VA) is the standard test in the clinical practice of ophthalmology which evaluates the ability of people's eyes to see the details of objects clearly at a given distance. Visual acuity is a measure of the spatial resolution of objects at a given distance using the visual process that is based on the clarity of the refractive parts of the eye (cornea and lens), clarity of ocular media (aqueous and vitreous) and healthy retina, optic nerve and visual pathways. VA is one of the main outcomes in clinical trials for patients with uveitis including those with UMO (68). Macular oedema has a significant effect on visual acuity and it is a key factor of central impairment of the visual field (69).

VA may be reduced in uveitis due to a number of causes notably UMO, cataract and glaucoma (49). Likelihood of visual loss in patients with UMO includes the presence of recurrent and prolonged episodes of inflammation that results in accumulative damage to the eye structure

including macular scar and/or damage to the optic nerve (optic atrophy) (49). Additionally, delaying the surgical interventions of the cataract or glaucoma surgery would lead to a significant visual and functional loss (20, 49).

1.6.1.1 Charts used to measure visual acuity

Two different charts are commonly used to measure visual acuity. Both are based on high contrast optotypes (letters) and are designed for measuring distance vision. These are the Snellen chart and the LogMAR chart (Log of the Minimum Angle of Resolution) (68, 70). The Snellen chart is designed with the number of letters in each row increasing as the row goes down. Visual acuity is recorded as a fraction with the numerator equal to the distance from the chart and the denominator refers to the size of the smallest line they can read on the chart (63).

The LogMAR has been designed with an equal number of letters in each row (5 letters) with spaces between letters and rows that are equal to the letter size. The chart is based on the logarithmic progression to the size of letters in each row. The LogMAR chart was designed to be more logical with a more consistent progression than the Snellen chart. The LogMAR chart is the preferred test for visual acuity and has become the standard chart for clinical research and trials, however the Snellen chart is still widely used in clinical practice due to being quick to use and familiar (68, 70)

Reporting visual acuities in clinical trials from Snellen charts are usually in metres in the UK and feet in the USA and are represented as a fraction of chart distance and letter size (63). Reporting visual acuities in clinical trials are usually either as 'number of letters read' or converted into a LogMAR fraction (63, 71).

1.6.2 Contrast sensitivity

Contrast sensitivity is an important part of the visual function that measures the person's ability to distinguish things from their own background (72, 73). Standard visual acuity measurements are based on high contrast charts and will not recognise the visual impact of reduced contrast sensitivity until it is extremely advanced, impacting patients' visual performance (74). Contrast sensitivity is correlated with better image identification and functional ability including driving, walking, working and communicating (75). Reduction of contrast sensitivity is also correlated with risk of falls and an increase in the socioeconomic cost on a personal and healthcare level (76).

Interestingly, it has been reported that contrast sensitivity is affected more than distance visual acuity in patients with UMO (77), however in general data on contrast sensitivity is limited in UMO compared to other types of macular oedema such as diabetic macular oedema (78). Contrast sensitivity measurement is not routinely undertaken in eye clinics and has not been used as an outcome measure for clinical trials in PSIU (21).

1.6.3 Uveitis activity

Slit-lamp examination is a standard examination technique in the clinical practice of ophthalmology used to assess the anterior segment of the eye and record the degree of uveitis activity. Measuring disease activity is important in evaluating treatment response and informing the management decision to either continue or escalate current treatment or consider using alternative treatment options. Therefore, accurate tools to assess the disease activity and the consequences of this activity (disease damage) are needed to support treatment decisions (20).

The activity of the disease is based on the clinical findings of the severity of inflammation

within the anterior chamber and vitreous cavity. The SUN workshop published grading tools that aids the assessment of uveitis severity and provides an indication of disease activity based on the amount of inflammation present in the anterior chamber (cells and flare; (Table 1)) (27, 79).

Table 1: Grading of AC cells and flare

AC Cells			AC Flare	
Grade	**Number of Cells**		**Grade**	**Description of Flare**
0	None		**0**	None
0.5	1–5		**1+**	Faint
1+	6–15		**2+**	Moderate (iris and lens details clear)
2+	16–25		**3+**	Marked (iris and lens details hazy)
3+	26–50		**4+**	Intense (fibrin or plastic aqueous)
4+	>50			

This table was adapted from Standardisation of Uveitis Nomenclature (SUN) Working Group, 2005. Standardisation of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. American Journal of Ophthalmology, 140(3), pp.509-516 (27).

Assessment of the vitreous activity provides an important indicator of inflammation in the posterior segment of the eye, for example, vitreous haze (presence of proteinaceous exudate in the vitreous) and vitreous cells (number of inflammatory white cells in the vitreous). Clinical grading of vitreous haze was first described by Nussenblatt in 2005 (79) and accepted by the Standardisation of Uveitis Nomenclature Working Group (SUN), and has been supported by the Food and Drug Administration (FDA) for use in uveitis clinical trials (21).

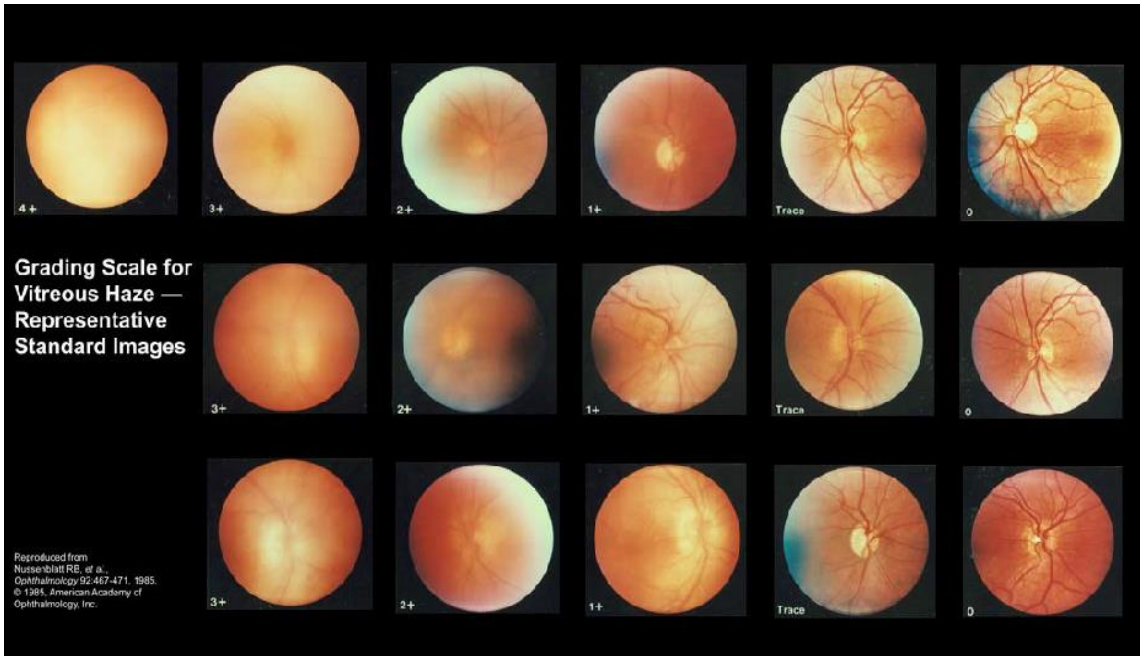
The tool is based on using an indirect biomicroscope to view the optic nerve head, retinal vessels, and optic nerve fibre layer and the posterior retina and comparing the clarity of view to the closest match on a standard chart of colour fundus photographs (Figure 6; Table 2)

Table 2: Grading of vitreous haze

Score	Description	Clinical findings
0	Nil	None (clear vitreous)
0.5+	Trace	Slight blurring of optic disc margins; normal striations of the NFL not visible
1+	Mild	Blurring of optic nerve and retinal vessels
2+	Moderate	Blurring of optic nerve and retinal vessels
3+	Marked	Optic nerve visible, borders blurred marked
4+	Severe	Optic nerve head not visible

Grading tool was adapted from Nussenblatt et al 1985 Nussenblatt, R.B., Palestine, A.G., Chan, C.C. and Roberge, F., 1985. Standardisation of virtual inflammatory activity in intermediate and posterior uveitis. Ophthalmology, 92(4), pp.467-471.(79)

Figure 6: Grading of vitreous haze



Assessment of vitreous haze is very subjective, and reliability is affected by the clinician's experience. Low levels of vitreous haze may be difficult to detect (80, 81). Vitreous haze responds more acutely to inflammation and its resolution, while vitreous cells may persist for a long time after inflammation control. Although the location of vitreous haze is not included in the grading tool of uveitis, it is important to note that central vitreous haze is a risk factor for vision loss and developing macular oedema compared to peripheral vitreous haze that might not need treatment (36).

All these measures of disease activity described here are subjective. The variation of measurements between observers means that a single-step change in inflammation activity is commonly not regarded as significant and most clinical trials require a two-step change in inflammation activity on the SUN scale (or a return to zero) to be considered a significant endpoint. A summary of the disease activity was described by the SUN group (27) (Table 3).

Table 3: Activity of uveitis terminology

Term	Definition
Inactive	Grade 0 cells
Worsening activity	Two-step increase in level of inflammation (e.g. AC cells and vitreous haze) or increase from grade 3+ to 4+
Improved activity	Two-step decrease in level of inflammation (e.g. AC cells, vitreous haze) or decrease to grade 0
Remission Inactive	Inactive disease for ≥3 months after discontinuing all treatments for eye disease

This table was taken form Standardisation of Uveitis Nomenclature (SUN) Working Group, 2005. Standardisation of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. American Journal of Ophthalmology, 140(3), pp.509-516 – AC: Anterior Chamber

1.7 Imaging techniques in uveitis and associated macular oedema

1.7.1 Stereoscopic fundus camera

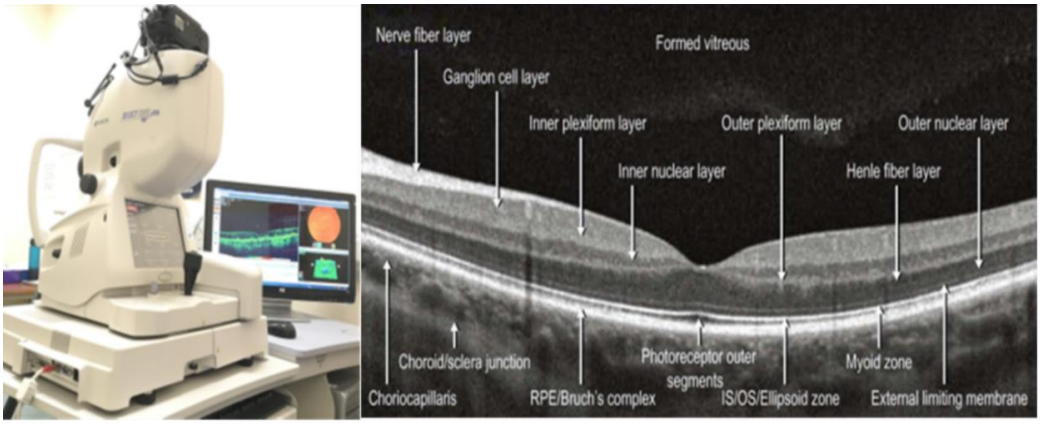
Clinical findings may also be photographed by stereoscopic fundus cameras and visualised using a stereoscopic viewer to enable a permanent record and allow independent assessment, such as in a trial reading centre (82).

1.7.2 Optical coherence tomography

Optical coherence tomography (OCT) is a non-invasive imaging technique used in the assessment of retinal disease, glaucoma and corneal disorders (83, 84). The invention of OCT in ophthalmology has become an important imaging technique particularly in the diagnosis and management of retinal and macular disorders (83, 84). OCT uses a low coherent light source to generate interference patterns from an incident and retina-reflected light to generate cross-sectional images of the retina, visualisation of all the retinal layers and resolution down to a few microns (85-88).

OCT is able to assess the retinal anatomy and provide a detailed structure to the retinal layers as shown in Figure 7, as well as produce a retinal thickness map to quantify and analyse the retinal layers function (89).

Figure 7: Normal retinal anatomy



Duker, Jay S., Nadia K. Waheed, and Darin Goldman. Handbook of Retinal OCT: Optical Coherence Tomography E-Book. Elsevier Health Sciences, 2013 (89)

1.7.3 Fundus Fluorescein Angiography (FFA)

Fundus Fluorescein Angiography (FFA) is an invasive procedure that allows a two-dimensional image using a fluorescent water-soluble intravenous dye (fluorescein) that is injected into a peripheral vein. An angiogram is obtained using a retinal camera or a scanning laser ophthalmoscope (SLO) to excite the fluorescein using blue light (wavelength 490nm) (86, 90). FFA provides information on the flow characteristics and the degree of patency of the retinal blood vessels, choroid, optic nerve and understanding the function and integrity of other retinal structures (e.g. RPE) (91). FFA has the ability to provide information about the retinal vasculature and detect any changes (e.g. vasculitis) that could be seen as staining or leakage from the retinal blood vessels (arteries, veins or capillaries). It is also a useful tool to monitor the treatment response in many uveitis conditions (e.g. Behcet's disease, Birdshot chorioretinopathy, acute retinal necrosis and others). UMO is seen as an area of hyperfluorescence on the FFA images arising from fluorescein leakage from the dysfunctional blood retina barrier (BRB) (92).

1.8 Treatment of uveitis and UMO

Treatment of uveitis and its associated macular oedema is a major priority in tackling sight-loss. A successful uveitis strategy requires the clinician to consider many of the following variables (93):

1. The aetiology of uveitis (infectious vs non-infectious)-directing treatment towards primarily anti-microbial/antifungal agents vs primarily immunosuppressive strategies.
2. The anatomical type of uveitis – topical treatment may be sufficient for anterior inflammation whereas PSIU will require local or systemic therapy.
3. The presence of associated systemic disease determines the type of treatment

required, route of administration needed; and whether to involve other specialities in the management plan (e.g. rheumatology for Behcet's disease).

4. The severity of the disease which might suggest adjustment or additional therapy
5. The potential complications from the uveitis (e.g. UMO; glaucoma), or any associated systemic disease or the treatment (adverse events).

The main focus of my thesis is non-infectious PSIU and uveitis associated macular oedema, and this section will mainly cover the treatment options for these forms of uveitis.

1.8.1 Corticosteroids

In current clinical practice, the mainstay of treatment for uveitis and associated macular oedema is corticosteroids, delivered by various routes including: topical e.g. prednisolone 0.5%, betamethasone 0.1%, dexamethasone 0.1%, prednisolone 1%, that are effective in managing anterior uveitis but this is not the most potent route of administration in UMO; systemic (oral) e.g. prednisolone, (intravenous) e.g. methylprednisolone which has been proven to be effective in PSIU when associated with systemic underlying disease (94, 95); local which includes periocular injection (sub-Tenon and orbital floor injection) and intraocular (intravitreal injection or implant) (96, 97).

Further, administration of medication via intravitreal route aims to release the drug in the vitreous cavity and target the macula in the posterior segment of the eye. The introduction of the intravitreal implants allow a gradual release of corticosteroids into the vitreous cavity over a prolonged period of time and acts as a long-lasting drug for up to six months (e.g. dexamethasone) or two to three years (e.g. fluocinolone) (95). Repeated dexamethasone implants have been shown to improve inflammation, reduce the retinal thickness and restore the retinal function (98).

Corticosteroids are effective in the management of UMO because they provide an anti-inflammatory effect; however, adverse events regardless of the route of administration are well-recognised. Cataract progression and raised intraocular pressure are common adverse events in topical and local routes of administration. Furthermore, intravitreal injection carries the risk of injection-related complications including endophthalmitis and retinal detachment (99). Administration via the systemic route is reported to carry the risk of hypertension, hyperglycemia/diabetes, osteoporosis, peptic ulcer, adrenal insufficiency, and increased risk of infections (100).

1.8.2 Non-corticosteroid immunomodulatory

Immunomodulatory agents are the second line in the treatment of uveitis and form an alternative to corticosteroids in those who have responded poorly or had no clinical drug effect (inefficacy), or adversely reacted to corticosteroids (e.g. systemic side effects, raised intraocular pressure) or poor tolerance. Limited data are available to support the use of immunomodulatory agents in UMO (101-103). Most of the immunomodulatory agents are only used systemically (oral, intravenous, or subcutaneous), whilst intravitreal use has been reported for both methotrexate and anti-TNF agents (104-107). Non-corticosteroid immunomodulatory therapies include four different subclasses.

I. **First, T cell inhibitors (**e.g. cyclosporine, tacrolimus)

Cyclosporine was used for its immunosuppressive properties and was found to be useful in experimental autoimmune uveitis. A retrospective cohort study reported the use of cyclosporine in uveitis patients and the benefits of controlling the inflammation, improving or stabilising vision (108).

II. **Second, antimetabolites** (e.g. methotrexate, mycophenolate mofetil, azathioprine)

Methotrexate is a well-established antimetabolite and traditionally one of the commonest immunosuppressive agents in ocular inflammation. Methotrexate expands the remission period of uveitis and reduces macular oedema. Methotrexate can seriously harm or end a pregnancy and may cause liver cirrhosis (109, 110).

Mycophenolate mofetil is increasingly used in ocular inflammatory disease as a corticosteroid-sparing agent with evidence of effectiveness in reducing inflammation and improvement of vision in non-infectious uveitis (111, 112). The most common side effects are gastrointestinal disturbances, infection and insomnia (113, 114) and less common liver function abnormalities (113).

Azathioprine is another agent that is widely used as a corticosteroid-sparing agent that controls inflammation in patients with intermediate, posterior uveitis and panuveitis, however, there is limited evidence supporting the improvement of patients' visual outcomes (115). The most common side effects are nausea, vomiting, and hepatic disease (116).

- **Third, alkylating agents** (e.g. cyclophosphamide)

Cyclophosphamide has been shown to be effective in many systemic autoimmune diseases associated with uveitis (e.g. granulomatosis with polyangiitis) (117, 118), Behcet's disease (119) and Vogt- Koyanagi-Harada syndrome (120), but has a significant adverse event profile. A retrospective cohort study reported the benefits of cyclophosphamide in the majority of uveitis patients and its tendency to achieving remission over a period of 6 months (121).

- **Fourth, biological agents** (e.g. interferons, anti-tumour necrosis factor (anti-TNF agents))

Biological agents are biologically synthesised agents that can be used to target specific pathways such as blocking cell signalling molecules ('cytokines') in the inflammatory process (122, 123).

- **Anti-Tumour necrosis factor (TNF)**

Anti-Tumour necrosis factors (TNF) are either monoclonal antibodies (e.g. adalimumab and infliximab) or soluble TNF receptor fusion protein (e.g. Etanercept) used to suppress the response of tumour necrosis factor (TNF) during the inflammatory response (124).

Recently adalimumab was approved by the National Institute for Clinical and Health Excellence (NICE) for the treatment of non-infectious PSIU (intermediate, posterior, and panuveitis) in adult patients, and children aged two years old and over.

The most common adverse events of the anti-TNF are flu-like syndrome, nausea, vomiting, fatigue, diarrhoea, leukopenia, elevated liver enzyme and allergic reactions (19, 125). Adalimumab increases the risk of upper respiratory tract infection 46%, sinusitis 34% and malignancy 15% (e.g. leukaemia and melanoma) (124). Whilst skin rash, headache and fatigue are the most reported adverse events (126). Table 4 summaries immunomodulatory agents used in uveitis.

- **Interferon-α**

Interferon-α has been used to treat a number of forms of uveitis, notably in Behcet's disease (127). The most common adverse events were infection at the site of injection, redness, flu-like symptoms, tiredness, depression and transient increase in the liver enzyme (127, 128).

Other Agents

Other agents used including carbonic anhydrase (e.g. acetazolamide) (129) and Anti-VEGF agents (e.g. bevacizumab, ranibizumab) (56, 130) and non-steroidal anti-inflammatory drugs (NSAIDs) (131).

Table 4: Common immunosuppressant used in uveitis

Class	Drug	Description	Route of administration	Disease Entities or cause
T cell inhibitors	Cyclosporine	T cell inhibitors	Oral, Intravenous	Non-infectious uveitis
	Tacrolimus	T cell inhibitors	Oral, Intravenous	Non-infectious uveitis
Antimetabolites	Azathioprine	Compete with the normal metabolic process and	Oral, Intravenous	Non-infectious uveitis, Birdshot, VKH
	Methotrexate	block protein synthesis	Subcutaneous, intravitreal	Non-infectious uveitis, Birdshot, VKH
	Mycophenolate mofetil	and inhibiting the activated T cell	Oral, Intravenous	Non-infectious uveitis, Birdshot, VKH
Alkylating agents	Cyclophosphamide	T cell inhibitors	Oral, Intravenous	Non-infectious uveitis
Biological agents (Anti TNF)	Adalimumab	Anti–TNF-α	Subcutaneous,	Idiopathic uveitis, sarcoidosis, BSRC, TINU, VKH disease, pars planitis; other: HLA-B27, JIA)
	Infliximab	Anti–TNF-α	Intravenous	(including BD, BCR, sarcoidosis, idiopathic vasculitis, VKH disease
	Etanercept	Anti–TNF	Subcutaneous	Non-infectious uveitis
	Golimumab	Anti–TNF	Subcutaneous	Non-infectious uveitis, Sarcoidosis
Other biological agents	Secukinumab	Anti–IL17	Subcutaneous and intravenous	Paediatric Non-infectious uveitis, JIA, BD, sarcoidosis, VKH disease (including BD, BCR, sarcoidosis, idiopathic vasculitis, VKH disease)
	Tocilizumab	Anti-IL6	Subcutaneous Intravenous	rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, cytokine release syndrome
	Sarilumab	Anti-IL6	Subcutaneous	Non-infectious uveitis
	Interferons	Increase regulatory T cell	Subcutaneous	VKH, idiopathic panuveitis, BD

Details in the table were taken from: Dick, et al, 2018. Guidance on non-corticosteroid systemic immunomodulatory therapy in non-infectious uveitis: Fundamentals of Care for Uveitis (FOCUS) Initiative. Ophthalmology, 125(5), pp.757-773. (101)

BD Behcet's disease, VKH Vogt–Koyanagi–Harada disease, (132) Juvenile Idiopathic Arthritis, TINU Tubulointerstitial Nephritis and Uveitis Syndrome, BCR Birdshot chorioretinopathy disease, IL interleukin

1.9 Outcomes in clinical trials

1.9.1 Clinical trials

Clinical trials are designed to provide important evidence on the efficacy/effectiveness and safety of interventions, medical devices and/or treatments (133). Clinical trials seek to assess whether the given treatment has achieved the intended results for patients with PSIU by measuring the difference between the groups who are involved in the trial or assessing the difference within the group before and after the administration of the treatment (134). Safety in clinical trials involves assessing any adverse events associated with the intervention (135). Assessing the long-term adverse event profile may be a difficult task to complete prior to the study licencing (136). Thus, clinical trials are important to inform future patients' care and help develop clinical guidelines and healthcare policies (137).

Randomised clinical trials (RCT) are considered to be the gold standard for assessing healthcare interventions. Patients are randomly allocated to either receive the drug under investigation or an alternative, commonly the standard of care (best approved treatment to date) or inactive substance that looks like the drug (placebo). RCTs can also compare two therapies on top of standard care (133).

Well-conducted RCTs yield unbiased estimates of effect in-terms of efficacy (the performance of an intervention or treatment under ideal condition) or effectiveness (performance of the intervention or treatment in a real-world) to the selected sample in the trial compared to other study designs (138). However, the estimate may only apply to the sample in the selected trial and extending the results to another group or individuals needs justification (139). Well-designed trials aim to reduce the risk of selection bias (selecting the participant and the control), and reduce the potential for confounding factors (133).

1.9.2 Definitions of outcomes in clinical trials

Outcomes in clinical trials are measurements or observations that aim to assess the efficacy/effectiveness and safety of an intervention or treatment (140, 141). This would include all variables that are monitored through the clinical trial to evaluate the impact of the treatment or intervention of any given health-related condition of a given population, including PSIU (142). Outcomes to be reported should be pre-specified in the trial protocol and well-designed trials would ideally have outcomes that are deemed important in the context of the clinical disease, patient's care and patient's perspective. The findings of the trials for these outcomes are used to inform treatment decisions (140).

1.9.3 Types of outcomes reported in clinical trials

1.9.3.1 Primary outcomes

The primary outcome is the variable that is considered to be the most important endpoint in the study and able to answer the research question (143). Some trials have one primary outcome while others have multiple primary outcomes; however, due to issues of multiple statistical testing, the use of multiple primary outcomes is not recommended (144). For example, two studies by Sangwan et al. and Callanan et al. measured one primary outcome (e.g. change in uveitis recurrence rate) to evaluate the effectiveness of fluocinolone acetonide Intravitreal Implant for the treatment of non-infectious posterior uveitis (94, 145). On the other hand, Lasave et al. used a group of primary outcomes (e.g. best corrected visual acuity, change of central macular thickness and disease complication) to compare intravitreal bevacizumab injection against intravitreal triamcinolone acetonide injection for the treatment of non-infectious UMO (21).

1.9.3.2 Composite outcomes

Composite outcomes are a collection of two or more variable outcomes that are used to assess the primary or the secondary outcome (146). For example, Hassan et al. used composite endpoints scoring of visual acuity; intraocular inflammation as assessed by vitreous haze, central retinal thickness, posterior segment inflammatory outcome assessed by fluorescein angiography and tapering of steroid dose to assess the primary efficacy outcome of tocilizumab in patients with non-infectious Uveitis (147). It is important for researchers to clearly define, report and discuss each individual component of the composite outcome to enhance the interpretation and analysis in relation to the primary outcome (148, 149).

1.9.3.3 Secondary outcomes

Secondary outcomes are additional variables that are collected, and which may provide additional information on the treatment effect and contextualise the finding of the primary outcome. For example, secondary outcomes often include unwanted or undesired effects of the treatment (148) or specific measures of disease activity (e.g. graded uveitis activity) (150). Classifying outcomes as secondary outcomes does not mean they are not important (141). For example, in the Kempen et al. study of systemic anti-inflammatory therapy against fluocinolone acetonide implant, a single primary outcome was used (best corrected visual acuity) to assess effectiveness, but additional secondary outcomes provided important information on patient-reported quality of life (QoL), uveitis activity (anterior chamber and vitreous activity), and local and systemic complications of uveitis or therapy (150).

1.9.3.4 Surrogate outcomes

Surrogate outcomes are measurements that are effectively a substitute for direct measures of how patient feels, function, or survive, where such direct measures are difficult to measure or

the primary endpoint is undesired (e.g. death) or a number of events is very small and it is unpractical to conduct a trial to gather statistically clinical endpoints (151). The FDA accepts clinical disease activity scores such as vitreous haze as a surrogate outcome in uveitis (80). The use of surrogate endpoints may not, however, reflect a clinically meaningful outcome of how a patient feels or functions, and may not be perceived as meaningful to patients (152).

1.9.3.5 Patient reported outcomes

Patient reported outcomes (PROs) are a report of patients' health status from the patients themselves without being modified by clinicians. PROs are sets of items that are able to explore the health state using the patients' perspective and assess Health-Related Quality of Life (HRQoL) (153). Patient reported outcome measures (PROMs) are widely accepted as important outcome measures to provide evidence on the efficacy and effectiveness of the intervention, disease burden and cost-effectiveness from a patient's perspective (154). Thus, PROs are useful to enhance decisions about healthcare choices (where to seek treatment), monitor treatment side effects and help patients to make an informed decision about treatment (155).

The use of PROs is growing fast in both clinical trials and practice, showing their values across various ophthalmic conditions including cataract, glaucoma and age-related macular degeneration (153). Using PROs in clinical trials are important to provide information to researchers, policy-makers and health authorities to inform licencing of drugs and clinical guidelines (156).

Uveitis is a life-long disease and the aim of the treatment would be to improve HRQoL. PROMs are useful measures to assess the psychosocial status in-terms of coping with such chronic disease and the level of support and care received by the patient. Uveitis may have a significant impact on a (HRQoL) (157), impacting many aspects of people's lives including employment,

activities of daily living and sport and recreation (158).

Although HRQoL is a subjective measure depending on the individual's perception of the impact of disease and/or treatment on the health status, as a measure it conveys information reported by the patient that is not filtered by clinicians. PROMs are able to answer whether the treatment has improved their symptoms, health and well-being; assess patients satisfaction with treatment and care received (159). PROMs are a useful measure to improve clinical care and have been well recognised by the FDA and European Medical Association (EMA) (160, 161).

1.9.3.5.1 HRQoL generic measures

Numerous instruments are used to measure HRQoL. The impact of uveitis and UMO on HRQoL can be assessed using generic patient-reported outcome measures such as the EuroQol five dimension scale (EQ-5D) and Short Form Six Dimension health index (SF-6D) (162). The EQ-5D, five-level version (EQ-5D-5L) measures five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (163, 164). The patient's health state is calculated by combining the level from each dimension representing a total of 3125 (EQ-5D-5L) compared to 243 (EQ-5D-3L) possible states (165).

SF-6D covers physical functioning, role limitations, social functioning, pain, vitality, and mental health (166). The SF-36 health survey measures 8 dimensions including general health, physical functioning, role limitation caused by physical disability, bodily pain, social functioning, role limitation caused by emotional disability (emotional role), and mental health (167). Both the EQ-5D-5L and the SF-6D (derived from the SF-36) can be used to generate health utility scores, cardinal values that reflect an individual's preferences for different health outcomes. They are measured on an interval scale with 0 reflecting states of health equivalent to death and 1

reflecting perfect health (168).

Health utility measures such as EQ-5D have been developed to provide an estimate of patients' preference for different health states. Health utilities can also be established directly using a time trade-off (TTO) or a standard gamble (SG) approach (117). TTO is a method, which in the context of visual health, offers patients to trade some time off in order to have a better visual outcome and quality of life in the remaining expected life. SG as a method offers patients the choice between having a perfect visual outcome and quality of life for their life expectancy and the probability of the worst outcome (death) (169-171). In ophthalmology, those methods have been used in a range of conditions including the dry eye (172), diabetic retinopathy (173, 174), age-related macular degeneration (AMD) (175, 176), glaucoma (177, 178) and uveitis (179, 180).

1.9.3.5.2 HRQoL disease specific measures

Various measures have been developed to assess the impact of vision and eye disease on patient's health status and/or quality of life such as the National Eye Institute Visual Functioning (NEI VFQ-25), the Vision Function (VF-14) and the Impact of Vision Impairment (IVI) (153, 181). However, none of these tools were developed specifically for uveitis (158, 182). In uveitis, the challenge of using HRQoL instrument would be to include both vision and disease-related quality of life measures comprising all components of visual symptoms, ocular surface symptoms, general symptoms, emotional well-being, activity limitation, mobility, convenience, health concerns, social well-being, and economic well-being (183).

The NEI VFQ-25 has 12 subscales: general health, general vision, near activities, distance activities, dependency, driving, role difficulties, mental health, social functioning, colour vision, peripheral vision and ocular pain (184-186). Generally, using a specific vision-related tool such

as NEI VFQ-25 plays a role in evaluating disease status, progression as well as therapy evaluation (184). Although NEI VFQ-25 was not originally designed specifically for uveitis patients, it is a better tool than the generic EQ-5D-5L in capturing vision-related activities (187). Kay and Ferreira found that mapping NEI VFQ-25 scores to EQ-5D utilities provides a low predictive power and may lead to inaccurate utility values that do not represent patients' preferences (188).

Generic measures may be useful to allow comparisons of the impact of disease/treatment with other conditions, useful to inform health policy; whereas disease specific measures may be more appropriate to inform clinical practice, guidelines development and tailor care to individual's needs. The generic HRQoL tools may not be sensitive enough to detect the impact of eye disease and its treatment. This was noted in patients who had significant benefit of cataract surgery at 3 months using vision-related QoL instrument, the Vision Function (VF-14), however, it was not significant using the generic SF-36 (189). In response to the sensitivity issue around the generic HRQoL instruments, disease specific tools have been developed in many areas such as pulmonary hypertension, prostate cancer, but further work is still needed for uveitis (168). PROMs have been used in clinical trials of various subspecialties including medical retina and glaucoma; however, other subspecialties are still lacking the use of PROMs (153).

1.9.3.5.3 What is already known about HRQoL in uveitis

Recently a cohort study of 200 uveitis patients evaluating HRQoL using TTO and SG health utility model, demonstrated a direct relationship between the degree of visual impairment and reduced HRQoL; thus TTO and SG utility values are dependent on the degree of loss of vision. Furthermore, disease complications (cataract, macular scar, retinal detachment, optic neuropathy) were additional predictive factors of reduced HRQoL and are directly related to TTO and SG utility values. Interestingly uveitis duration and flare-up were not significantly

associated with TTO and SG utility values (182). TTO HRQoL associated with poor vision<6/60 in the better-seeing eye, was equivalent as HRQoL in end-stage renal disease in haemodialysis patients (190) or AIDS HRQoL (191).

Furthermore, the study by Niemeyer et al. of 102 uveitis patients, confirmed a positive correlation between worse vision for more than 6 months and reduced HRQoL using TTO. It is worth noting that legally blind patients (≥1.0 LogMAR) in at least one eye, had a lower TTO score and were willing to trade a median of 4.3 years compared to patients who are not legally blind who had a higher TTO score. The differences in the TTO scores were not significant among all the anatomical forms of uveitis. The use of corticosteroids for more than 6 months was associated with low TTO scores regardless of the dosage used. Psychological morbidity especially depression and the use of antidepressant medications were also associated with a lower TTO score and patients were willing to trade more time for healthy eyes. Finally, the level of education was a predictor for TTO activity, therefore patients with a college education are willing to trade off remaining life for healthy eyes compared to those who had no college education (179, 182).

The NEI VFQ-25 scores were significantly lower in uveitis patients in-terms of driving, social functioning and self-care (158, 192). Patients with uveitis reported having a markedly poorer visual functioning and general health, which is worse in patients with severe uveitis compared to milder forms of uveitis. The study by Schiffman et al. of 76 uveitis patients, found that physical health and mental health were significantly lower among patients with uveitis than the general population (158).

Active PSIU patients reported having significantly lower HRQoL scores in-terms of general health, visual function (near vision, peripheral vision, and colour vision), social functioning and mental health compared to those with inactive uveitis (158, 193, 194). However, a current

active flare-up of the disease was not associated with HRQoL scores (182). It is worth noting that patients with poor visual functioning reported worse related HRQoL (184, 194). PSIU patients had significantly lower NEI VFQ-25 scores in-terms of general health, visual function (near vision, peripheral vision, colour vision), and dependency scores compared to patients with anterior uveitis. PSIU tends to cause ocular morbidity e.g. macular oedema, glaucoma that shows a significantly lower general health and visual functioning (158, 193).

A significant correlation was reported between medical comorbidity, ocular comorbidity, and NEI VFQ-25 scores with physical and mental health scores (158). Thus, patients with systemic diseases (e.g. multiple sclerosis, sarcoidosis, and Behcet's syndrome) reported a further impact on uveitis HRQoL scores compared to those who have no systemic diseases. The Schiffman et al. uveitis study found a significant lower general health score, visual function and social functioning in patients with systemic involvement compared to those with ocular involvement only. Thus systemic and ocular comorbidity were significantly associated with low NEI VFQ-25 scores (158). Furthermore, the study by Miserocchi et al. of 100 patients, found that the HRQoL is significantly associated with the disease duration and visual acuity (193).

Uveitis may affect any age group, however, it often affects the younger working generation and has a disproportionately high impact in-terms of duration of potential vision loss (23), needing for long-term therapy (195) and the socioeconomic impact on patients and the healthcare system (181). In the study by Hernei et al., of 619 patients, low quality of life scores were more likely in the working uveitis population than the non-working population (196).

Moreover, it is not only the disease that impacts people's quality of life but also the treatment burden could impact patients' quality of life. Treatment varies based on the severity of uveitis, anatomical involvement and complication (197). Topical treatment would be considered in anterior uveitis, however; this would be insufficient in PSIU as it does not penetrate to reach

the posterior segment of the eye. Therefore, additional treatment would be needed that may require hospitalisation and close observation and always carry some risks and would have a negative impact on quality of life (193).

The adverse effects of corticosteroid were reported as a major burden in PSIU. Further reduction of inflammation and improvement in visual acuity added a significant improvement in HRQoL, but the treatment burden itself can impact patients' HRQoL. Patients report having a lower physical role, body pain, vitality, and social functioning as the intensity of the treatment increases (158, 193), and a further reduction in the HRQoL following exposure to adverse events. The study by Schiffman et al. (76 patients) reported a positive correlation between the intensity of immunosuppressive treatment and a reduction in HRQoL (158).

1.9.4 Reported outcomes in clinical trials of uveitis

Uveitis clinical trials have used a wide range of outcomes and outcome measures to assess the effectiveness of a given treatment. A scoping search of (MEDLINE) identified one systematic review that has been undertaken in 2013 evaluating all reported outcomes and outcomes measures in uveitis trials. Fifteen online clinical trial registries approved by the International Committee of Medical Journal Editors were searched, of which 104 clinical trials were included in the analysis. Included trials were prospective interventional design in PSIU (intermediate, posterior, and panuveitis) (21).

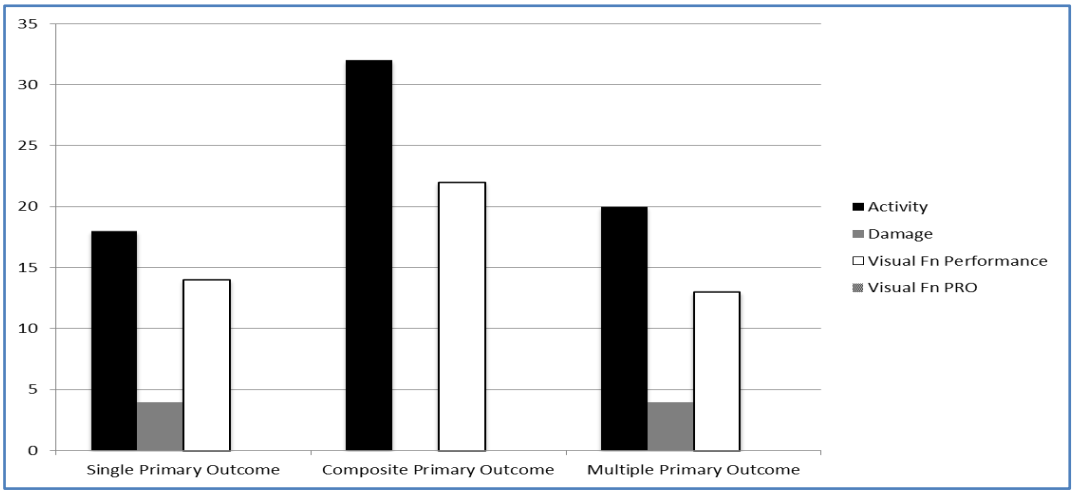
The review identified 14 different items utilised as a primary outcome and used to assess the effectiveness of the treatment in uveitis and UMO. Additionally, multiple outcomes of interest are reported in uveitis clinical trials. The primary outcome was related to treatment efficacy in 90% and treatment safety in 10%; efficacy primary outcomes were single in 38%, Multiple in 19 % and composite in 37%. Additionally, 83% of the efficacy trials used a broad range of uveitis

disorders (intermediate, posterior, and panuveitis), whereas 20% used a single disorder (21).

Disease activity was reported as a primary outcome in 74% of the 94 trials. Numerous measures of disease activity were identified including anterior chamber cells, anterior chamber flare, vitreous haze, vitreous cells, snowballs, macular oedema, chorioretinal inflammatory lesions, retinovascular inflammation, treatment requirement, and uveitis recurrence rate. Approximately 22% of registered trials reported multiple primary outcomes with inadequate definition. None of the included trials used patient reported outcomes as a primary outcome measure (Figure 8) (21).

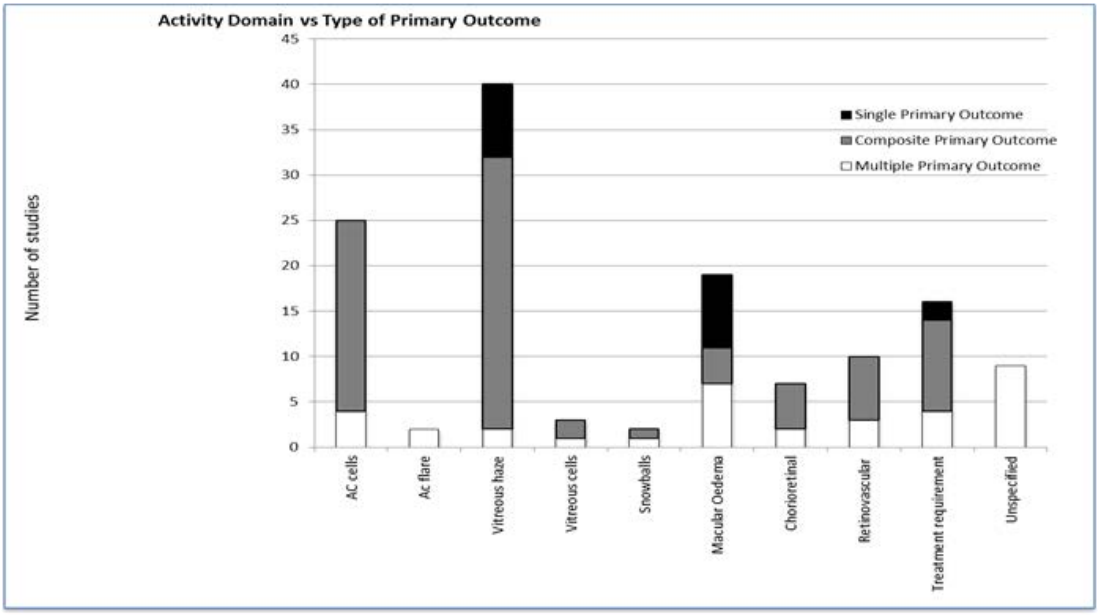
Four outcome categories (domains) were identified in uveitis clinical trials including: (1) disease activity (e.g. anterior chamber cells, anterior chamber flare, vitreous haze, vitreous cells, snowballs, macular oedema, chorioretinal inflammatory lesions, retinovascular inflammation, treatment requirement, and uveitis recurrence rate; (Figure 9); (2) Disease associated tissue damage or complications (e.g. raised intraocular pressure, posterior capsular opacification); (3) Visual function (e.g. distance visual acuity); (4) patients experience (e.g. NEI-VFQ-25) (21).

Figure 8: Type of primary outcomes vs dimensions



This graph was taken from Denniston, et al 2015. Heterogeneity of primary outcome measures used in clinical trials of treatments for intermediate, posterior, and panuveitis. Orphanet journal of rare diseases, 10 , p.97 (21)

Figure 9: Activity domain vs type of primary outcomes



This graph was taken from Denniston, et al 2015. Heterogeneity of primary outcome measures used in clinical trials of treatments for intermediate, posterior, and panuveitis. Orphanet journal of rare diseases, 10 , p.97 (21)

1.9.5 The challenges with outcome assessment

1.9.5.1 Selection of outcomes in clinical trials

Traditionally, outcomes in clinical trials are selected by clinicians and researchers (140). Outcome assessment and reporting in uveitis are based on recommendations of the Standardisation of Uveitis Nomenclature (SUN) workshop in 2005. This was a major step forward in the process of standardising the methods for reporting clinical data in the field of uveitis but it was based on the consensus of clinical experts only (27, 198). The majority of those outcomes are relevant to the disease process but might not be directly relevant to patients and their carers (199).

In most clinical trials selection of outcomes is guided by clinical, statistical and regulatory consideration which may lead to miss outcomes that are important to patients (200) leading to research waste. Research waste is a major concern among clinical trials accounting for more than 85% of research investments (201). Research waste represents a large cost to society,

participants and healthcare resources (202). Several factors contribute to research waste including inadequate methods (wrong research questions are studied), design (poorly designed studies), inaccessible results or unpublished results, quality of research, and reporting bias (201, 202). For example, if trialists decided to report outcomes that are relevant to them rather than to patients or reporting outcomes with positive results can lead to potentially erroneous conclusions with serious consequences for patients (203). Research waste, therefore, could be avoided using a proper methodological and reporting approach and greater involvement of all relevant stakeholders (204).

1.9.5.2 Importance of outcomes to patients as well as other stakeholders

It is important to use outcomes that are relevant to all stakeholders including patients, carers, policy-makers, commissioners as well as clinicians (205). Patients and their carers are a vital part of any clinical trial, and they deserve to receive the best possible treatment for their health condition. Lack of attention to the reported outcomes will impact the relevance and importance of those outcomes to the service user (140, 141).

Literature suggests the importance of outcomes may vary between patients, carers and healthcare professionals and there may be a tendency for clinicians to undervalue a number of outcomes that matter to patients (206, 207). As a result, differences in what patients think are important and what clinicians think are important can lead to discordance between patients' priorities and healthcare professionals' perspectives. In the light of this, the International Consortium for Health Outcomes Measurement (ICHOM) defined outcomes as patients' concerns about the disease and treatment and how this would improve their functionality to live a normal and productive life (208).

In ophthalmology, clinicians may focus on disease activity, but this might not provide details

on the impact of the uveitis and/or treatment on patients' functionality in-terms day-to-day activities, social life, psychological and emotional well-being. Such functional outcomes may be underrepresented compared to clinical and anatomical outcomes that are easier to measure (209).

The World Health Organisation defines quality of life as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment" (210). HRQoL helps clinicians and trialists to understand the impact of the disease and the treatment on patients' lives evaluating physical and social functioning, psychological and emotional well-being (199).

To ensure that clinicians and researchers are collecting outcomes that are important to patients and their carers, there is a need to involve them in identifying those outcomes (140, 141). This would help to provide data for clinical guidelines and shared decision-making supported by clinicians' experience and patient preferences to optimise clinical effectiveness (199). If reported and measured outcomes in clinical trials are not patient-centred, this may lead to increase waste in healthcare resources and research (211).

1.9.5.3 Heterogeneity of outcomes across PSIU clinical trials

Numerous authors have highlighted the paucity of evidence to support treatment decisions in the management of the uveitis blinding disease (212, 213). There are many challenges to undertaking efficacy and effectiveness studies in PSIU such as the heterogeneity of uveitis, scarcity of the individual disease syndromes, and variation in outcomes used by trialists (21).

One of the major blocks identified in this area has been around these outcome measures: the inadequacy of many of the standard outcomes used and inconsistency of the use of these outcomes between trials (93). This makes it difficult to compare those reported outcomes and limits evidence synthesis and meta-analysis in the field. This makes it harder for health authorities and service commissioners to evaluate the effectiveness of different treatments. In consequence, decisions for future licensing and funding are affected (205).

1.9.5.4 Reporting bias

Clinical trials aim to use pre-specified outcomes prior to the start of the study. This is important to ensure consistency in reporting those outcomes. In some instances, trialists may selectively report some outcomes or under-report others (selective reporting bias) (214). If this is the case, trialists should declare the change and justify it (215). Trial registration and publication of a trial protocol are important to specify what outcomes will be measured and reported in the trial. However, the use of numerous outcomes can lead to reporting bias where outcomes are selected based on their statistical significance ('cherry-picking') (93). Transparent reporting of the trial outcomes is important to ensure the validity of the evidence whereas outcome reporting bias contributes to research waste (216).

1.9.6 Standardising Outcomes via Core Outcome Sets (COS)

Inconsistent use and reporting of outcome measures can be addressed through the use of a core outcome set (COS). COS is defined as a minimum set of outcomes that have been agreed to be measured and reported in all trials for a specific clinical area. COS is not restrictive since other data can be collected, but rather ensure that certain key outcomes are always collected in a standardised way (205).

The development of COS is supported by the Core Outcome Measures in Effectiveness Trials

(COMET) initiative. The COMET database requires specification of the clinical area for which outcomes are considered (PSIU), the target population based on the selection criteria (adult patients), the setting used to report those outcomes (clinical trials) and methodology used to aid the development process of COS (141).

The COMET initiative aims to raise awareness around inconsistent reporting of outcomes in clinical trials and aid the process of developing COS, ensuring that patients and the public are involved in the development process. Further, one of the main aims is to liaise with other researchers, and healthcare professionals working on the same COS reduce duplication of effort and provide resources where needed. COMET has a searchable database for all relevant COS that are updated frequently. The involvement of patients and other key stakeholders is an important feature of COS development. COS aims to reduce heterogeneity between trials as agreed set of outcomes would be reported and measured indicating their relevance to all stakeholders and build a robust, repeatable evidence base (141).

1.9.7 The potential value of COS

The development of a COS for PSIU would provide for the first time a standardised set of outcomes to be measured (reduce heterogeneity) that has value to all stakeholders and can be used in all comparative efficacy or effectiveness trials in uveitis (217). This has the potential to ensure that trials do not simply reflect medical perspectives but include those outcomes that matter to other stakeholders (patients, carers) as well as regulators and policy-makers to enable them to make licensing and funding decisions. This has the potential to profoundly enhance evidence synthesis and reduce research waste. COS are increasingly recognised since they are a standardised way to enable comparison (due to the consistent collection of outcomes) and combination of trial results with direct benefits to patients with this sight-threatening disease (218).

1.10 Aims

The aim of this thesis was to: (i) assess the effectiveness of the available pharmacological therapies used in the treatment of UMO; (ii) develop a core outcome set (COS) for efficacy and effectiveness clinical trials in adult patients with non-infectious PSIU, that is suitable for patients with and without the key sight-threatening complication, UMO.

1.10.1 Objectives

There are three specific objectives for the study:

1. To conduct a systematic review to assess the effectiveness of the available pharmacological agents used to treat UMO, the leading reversible cause of sight-loss in PSIU.

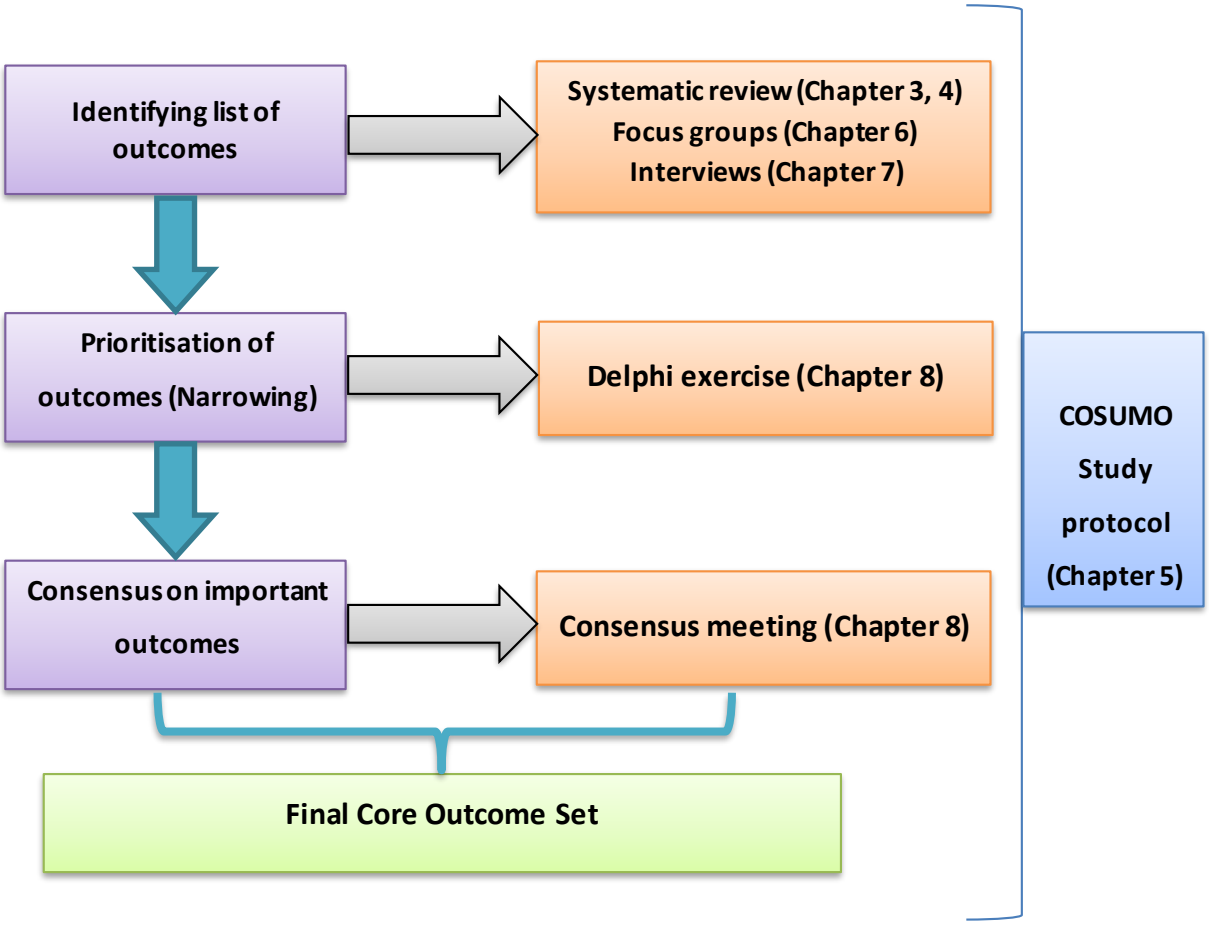
2. To identify a comprehensive list of outcomes based on (a) systematic review of clinical trials in PSIU and (b) findings from key respondent focus groups and interviews (patients, carers, ophthalmologists, nurse practitioners and health policy-makers/commissioners).

3. To prioritise identified outcomes through a consensus process with the key stakeholder groups (patients, carers, ophthalmologists, nurse practitioners and health policy-makers/commissioners) based on (a) a two round Delphi exercise (an online web-based survey) and (b) a face-to-face consensus meeting.

1.11 Chapters overview

Although a number of the component parts of my thesis stand as research projects in their own right, together they describe the creation of the first COS for PSIU. Figure 10 outlines the steps employed in developing the COS reported in my thesis and also indicates within which chapters the methods and findings for each stage are reported.

Figure 10: Stages in Core Outcome Set Development



Defining a COS involves identifying potential outcomes and then through a series of steps narrowing the list to those considered most important. Identifying outcomes can be done by looking at outcomes already used in the context of research on the disease in conjunction with asking key stakeholders (patients, carers, clinician, nurse practitioners and key decision-makers) for their suggested outcomes. This long-list of candidate outcomes can then be narrowed through a staged prioritisation process by the key stakeholders leading to a consensus on a list of outcomes that comprise the COS. This process is described in the chapters as follows:

Chapter 2: General Methods employed in the thesis.

Chapter 3: Protocol for the systematic review (published paper).

Chapter 4: Results of the systematic review (published paper).

Chapter 5: Study protocol for developing our COS (published paper).

Chapter 6: Outcomes identified through focus group discussions with patients and carers (published paper).

Chapter 7: Outcomes identified using interviews with healthcare professionals.

Chapter 8: Delphi exercise, consensus meeting and final core outcome set.

Chapter 9: Discussion and conclusion.

Chapter 2: General Methods

2.1 Introduction

This thesis comprises a number of different studies which ultimately addressed the main aim of the thesis to develop a COS for non-infectious PSIU: a systematic review, a qualitative research method, a Delphi exercise and a consensus meeting. This chapter provides a general overview of the methods used to develop a COS and justifies the approach taken. A detailed protocol is presented in Chapter 5. The Core Outcome Measures in Effectiveness Trials (COMET) initiative has been supporting the development of COS with 966 registered entries on the COMET database (May 2020) (219). The COMET handbook is a useful guide to all COS developers providing details on the development process, implementation and evaluation of COS. Currently, there is no consensus on the optimal method for COS, however, the book gives recommendations on some methods commonly used (141).

2.2 Overall information on COS

2.2.1 Participants involvement in outcomes selection and development of a COS (stakeholders)

Traditionally and before the introduction of the COS there has been a tendency to prioritise views of the clinical and research team over the views of patients and carers, whereas a COS helps to ensure that outcomes that matter to patients and carers are embedded within any clinical trial. However, not all reported COS have included this group in the final development of the COS. By inviting patients and carers to express their opinions, COS enables patients' and carers' priorities to be used alongside those of clinicians and trialists, encouraging their opinion to be recognised and considered at different levels (199). Recognition of patients' and carers' priorities is important in its own right to ensure that the outcomes we evaluate are those that

matter to patients, but also can lead to reduced NHS burden (cost, frequency of hospital visits) and enhanced effective healthcare (220). The representation of stakeholder groups in COS development varies between studies. They are commonly classified as clinical experts, non-clinical experts and public representatives (221, 222). The most recent review on the COMET database has highlighted that clinical experts (clinical research expertise, clinical trialists/members of a clinical trial network and others) were present in 98% of all COS development processes. Non-clinical research experts (researchers, academic research, statisticians, epidemiologists, representatives, methodologists and economists) were present in 38% of all COS development processes (223).

Although public representatives (e.g. patients, carers, patient support group and service users) are important stakeholder groups in the COS development, they had low representation compared to the clinical experts' groups (33%). Furthermore, the health and research authorities (regulatory representatives, governmental agencies, policy-makers, commissioners) were represented in 21% of all COS development (223). The resulting COS should be holistic in nature and have value to all stakeholders: patients, carers, health professionals and other relevant personnel. Involving patients and carers in the development of COS is a key feature of this process. Further details are reported in Table 5.

Additionally, variations have been found between studies in-terms of stakeholder groups and geographical area of recruitment. For example, public representatives are recruited on a national basis, whereas clinical experts are more likely to be recruited on a national and international basis. A good example was seen in Blackwood et al. which included participants representing intensive care survivors, carers, nurses, allied health professionals, critical care physicians; clinical trials groups, trial investigators; and industry. Additionally, the study was set on an international basis and including Europe, North and South America, Australia, Asia,

and Africa (224). Using a wide geographical area and involving a wide range of stakeholder groups ensuring the presence of public involvement alongside health professionals increases the opportunity to use and apply such COS globally in clinical trials and health-related practice. Therefore improve patient's outcomes and reduce the disease burden (221).

Table 5: Participants involvement in outcomes selection and development of a COS

Stakeholder groups	Members of each stakeholder group	Frequency of Participants
Clinical experts	Clinical experts	169 (62)
	Clinical research expertise	114 (42)
	Clinical trialists/ Members of a clinical trial	12 (4)
	Others with assumptions	54 (20)
	Total	**268 (98)**
Public representatives	Patients	89 (33)
	Carers	63(23)
	Patient support group representatives	23 (8)
	Service users	5 (2)
	Total	**89 (33)**
Non-clinical research experts	Researchers	64 (23)
	Statisticians	27 (10)
	Epidemiologists	19 (7)
	Academic research representatives	4 (2)
	Methodologists	16 (6)
	Economist	6 (2)
	Total	**103 (38)**
Authorities	Regulatory agency representatives	43 (16)
	Governmental agencies	18 (7)
	Policy makers	8 (30
	Charities	2 (1)
	Service commissioners	3 (1)
	Total	**59 (22)**
Others	Pharmaceutical industry representatives	42 (15)
	Device manufacturers	4 (2)
	Biotechnology company representatives	1 (<1)
	service providers	4 (2)
	Ethicists	1 (<1)
	Journal editors	5 (2)
	Funding bodies	1 (<1)
	Yoga therapists/ instructors	1 (<1)
	Members of health care transition research consortium	1 (<1)
	Educationalist	1 (<1)
	Nutritionist	1 (<1)
	National professional and academic bodies/ committees	1 (<1)
	Other (besides known participants)	15 (6)
	Others with assumptions	54 (20)
	Total	**84 (31)**

This table was adapted from the systematic review. Gargon, E., et al., 2018. Choosing important health outcomes for comparative effectiveness research: 4th annual update to a systematic review of core outcome sets for research. PloS one, 13(12), p.e0209869.

Our study has used multiple stakeholder groups including patients/carers and healthcare professionals (e.g. ophthalmologists, nurse practitioners, health policy-makers/ commissioners). It is worth noting that the study had an overlap between participants in the qualitative work, Delphi and consensus exercise.

2.2.2 COS development

A wide range of methods has been used to develop COS. Some of those methods were used to identify outcomes, and others were used to reach consensus on those reported outcomes. Our study has used multi methods to define a long-list of outcomes comprising a systematic review and qualitative study followed by a two round Delphi exercise and face-to-face consensus meeting (Chapter 5).

2.2.2.1 Overview of available methods in core outcome set development

Development of a COS is a process of identifying a 'long-list' of outcomes via systematic reviews, and/or qualitative methods such as focus groups or interviews prior to then narrowing this down using consensus methods. Common consensus methods include Delphi surveys, consensus development conferences and nominal group techniques. The consensus approach helps to prioritise and ultimately decide whether to include outcomes in the final COS (225-229).

There has been a variety of methods used to aid the development process of COS; some studies have used a single method while most have used a combined method(s). A scoping search of MEDLINE identified a systematic review, undertaken in January 2014 and updated in March 2018. The review evaluated methods used to develop COS in 307 included studies (221, 230). Eight different methods were used to develop COS. The most common method was semi-structured group discussion (n=62, 20%). Other methods included were unstructured group

discussion (n=18, 6%), systematic reviews (n=25, 8%), Delphi surveys (n=14, 4%), consensus development conferences (n=14, 5%). Less frequent methods used were the nominal group technique (n=1, <1%) and interviews (n=1, <1%) (221, 223).

Multi methods were used in the majority of those studies used to develop COS (n=151, 49%). A combination of a Delphi exercise and another method(s) (n=71, 23%) was the commonest multi methods approach followed by a combination of semi-structured group discussion and another method(s) (n=51, 17%). Less frequent combinations were consensus development conferences and another method(s) (n=8, 3%), and literature/systematic reviews and another method(s) (n=16, 5%), nominal group technique and another method(s) (n=4, 1%), and focus group discussion and another method(s) (n=1, <1%) (221). Interestingly, the majority of COS developed were in the field of cancer, rheumatology, neurology heart and circulation (231). Table 6 summarises the main characteristics of each method used in the development process of COS. Further discussion is provided below.

2.2.2.2 Overview of consensus process in core outcome set development

A consensus is an agreement of participants' opinions on important outcomes that would be part of the COS. This is presented as a proportion of participants agreeing the importance of those outcomes ranging between 50-100% and the threshold is defined prior to the start of the study. Although there have been variations between studies on the consensus proportion, 70% threshold agreement among participants has commonly been used to either include or exclude an outcome from a COS (221).

Not only does the consensus proportion differ between studies, but also different levels of Likert scales have been used to rank the importance of reported outcomes. For example, Gladman et al. 2005 used three ranking levels (1= less important; 2= important; 3= most

important) to assess psoriatic arthritis outcomes on 50% threshold agreement (232). Schmitt et al. 2010 used a 9 point Likert scale (1–3= not important; 4–6= equivocal; and 7–9= important) on 60% threshold agreement (233). Devane et al. 2007 used a 5 point Likert scale (1= no importance; 2= some importance; 3= moderate importance; 4= very important, and 5= extremely important 70% threshold agreement (234), Dent et al. 2008 used a 6 point scale (1=agree strongly, 2= agree moderately, 3= just agree, 4= just disagree, 5= disagree moderately, 6= disagree strongly) 75% threshold agreement (235). Heiligenhaus et al. 2012 used a 5 point Likert scale (1= highest importance and 5= lowest importance) on the agreed proportion of 100% (236).

In this study we have adopted the COMET consensus style using a 9-point Likert scale; (1-3 = less importance; 4-6= important and 7-9= critical) using a 70% threshold agreement. This score is commonly used by the Grading of Recommendation Assessment Development and Evaluation (GRADE) to score the quality of evidence for outcomes in systematic reviews and has been adopted in other core outcome development research groups using Delphi methods (237). Therefore, the term 'Consensus In' is utilised based on an outcome being scored 7-9 by more than 70% participants, and being scored 1-3 by fewer than 25% participants. 'Consensus Out' is based on an outcome being scored 1-3 by more than 70% and being scored 7-9 by less than 25 %. No consensus is based on an outcome where the level of importance was not decided due to uncertainty (238).

Table 6: Characteristics of methods used to develop core outcome sets

Method used to develop COS	Structured, semi or unstructured	Type of method	Sample size	Face- to-face or non-face-to-face (e.g. email, telephone)	Group vs individual interaction	Responses from all participants	Participant anonymity	Cost	Recruitment process
Systematic review	Structured	Review	NA	NA	None	NA	NA	Expensive	NA
Focus group discussion	Semi-structured	Qualitative	6-8 in each FG	Face- to-face	Group interaction		No	Cheap to run	Recruitment might be time consuming; and as a result, a risk of dropout
Interviews	Structured or unstructured or Semi structured	Qualitative	Depends on saturation	Face- to-face	Individual interaction	Achieved	Anonymous	Expensive (depends on the size and the geographical area)	Recruitment is easier for telephone interviews compared to face-to-face interviews
Delphi Technique	Structured	Consensus	No guidelines	Non-face-to-face	NA	Achieved	Anonymous	Cheap to run	Recruitment might be time consuming and the chance of having Low response rate
Consensus development conference	Structured	Consensus	No guidelines	Face- to-face	Group interaction	NA	No	Expensive meeting to run (depends on the size and the geographical area)	Recruitment might be time consuming; and as a result, a risk of dropout
Nominal Group Technique	Structured	Consensus	No guidelines	Face- to-face	Group interaction	Achieved	No	Expensive (depends on how many groups and geographical area)	Recruitment might be time consuming; and as a result, a risk of dropout
Teleconference meeting	Structured	Consensus	No guidelines	Video (e.g. Skype)	Group interaction	NA	No	Cheaper to run, able to have participants from various geographical area)	Recruitment is easier compared to face-to-face meetings
Questionnaire survey	Structured	Quantitative	No rule of thumb to determine the sample size	It can be either	NA	Achieved	Anonymous	Cheap to run	Non-face-to-face survey is easier to recruit compared to face-to-face

2.3 Methods used in COS development

2.3.1 Scope of a COS

2.3.1.1 Defining the research question for the COS

Prior to conducting a COS, it is necessary to ensure whether there is an existing COS in the field. The research question should be carefully defined to reflect the scope of the COS within the intended use, for instance, the breadth of the health condition in which it will be used and any limitations over the types of participants. For example, if you are developing a COS for patients with uveitis, we could choose to develop a COS for 'all uveitis' or 'non-infectious uveitis' or 'non-infectious uveitis affecting the posterior segment' or 'birdshot chorioretinopathy', reflecting an increasingly narrow approach.

Similarly, you might choose to develop a COS just for adults, just for children (or particular age groups of children) or all ages. In some contexts, COS may also be developed for a particular treatment or for all types of treatment for a particular condition such as the COS for treatment of squamous cell carcinoma (e.g. radiotherapy, surgical treatment and chemotherapy) (205).

2.3.1.2 Does a relevant COS exist

There is a need to run a scoping search to answer the COS research question. Once the nature and scope of the COS have been defined, searches are undertaken to identify whether any COS already exists in that area, whether complete or in development and an evaluation of its suitability (which may include the consensus process used, its representation of stakeholders, etc.).

The online COMET registry is the primary source for identifying COS, particularly for those in development, however, searches of the published medical literature are also recommended since not all COS are registered on the COMET website (205).

Assuming that no pre-existing COS is available (or is not fit-for-purpose), then the process of developing a new COS begins in earnest. We can consider this process in the context of the research question within this thesis. First, the intended scope of the COS was defined: Core Outcome Set for Posterior Segment-Involving Uveitis (PSIU) being suitable for adult patients with or without Uveitic Macular Oedema (UMO). Second, searches were undertaken of the COMET database, to identify any COS (complete/in development) in this area. No COS for PSIU was identified. Third, the process was supported by searching MEDLINE (using terms of ophthalmology and core outcomes) to identify any pre-existing COS in this area. Scoping search (February 2016) identified seventy studies that might be relevant. Screening titles and abstracts of identified articles did not show any reported COS in the uveitis field. It is worth however noting the existence of the Standardisation of Uveitis Nomenclature (SUN) recommendations for recording disease activity in uveitis which features heavily in studies from the last decade (chapter 1) (27, 198).

2.3.2 Systematic Review and Meta-analysis

Prior to conducting a systematic review, it is important to establish whether there are any existing reviews on the same question or related questions. Systematic reviews are considered the best method to provide a framework for synthesising evidence across multiple studies. The systematic approach is designed to increase identification of relevant studies, reduction

of reviewer biases (e.g. in the selection of studies and the weight given to those studies), and highlighting the quality (strengths and limitations) of included studies in the final review to support decision-making (239). Systematic reviews help to appraise and synthesise the best available evidence on the research question providing an informative conclusion (240).

In this thesis, a systematic review was undertaken to assess the effectiveness of pharmacological agents for the treatment of Uveitic Macular Oedema (UMO). The review provided a comprehensive overview of the pharmacological agents used to treat UMO and highlights that, for many of these pharmacological agents, there is little evidence for them being effective and safe in UMO (213).

Systematic reviews of clinical trials are also a useful method for identifying a list of outcomes for inclusion in a COS. Our systematic review provided a number of outcomes that contributed to the long-list (213). However, they do not necessarily reflect the priorities of other stakeholders, most importantly, the patient (chapter 4) (241).

2.3.2.1 Systematic review methods

To achieve a reproducible and transparent reporting of the systematic review, the following steps should be considered while conducting the review:

I. Defining the review question

Systematic reviews start with question formulation that guide many aspects of the review process, including eligibility criteria, searching for studies, data collection, analysis and presentation of findings. A systematic review should have a clearly defined question, and the

component depends on the type of question in the review. For example, effectiveness systematic reviews use PICO format (population, intervention, comparator and outcome) (242). These comprise:

- *Population*: describes what type of participants would be included in the search and clinical problem. For example, investigating non-infectious uveitis in adults vs children, or investigating uveitis in Behcet's disease in adults and children.

- *Interventions*: describe the main intervention of interest (e.g. drug administration, surgical intervention, and social or education intervention).

- *Comparisons*: describe what the intervention will be compared to (e.g. studies that compared drugs to no intervention or drug compared to another drug(s), or drugs compared to a surgical intervention). Furthermore, trials testing new drugs (experimental trials) either compared to placebo or standard therapy.

- *Outcomes*: describe the main outcomes of interest that will be assessed in the study (e.g. best corrected visual acuity, quality of life).

- *Study design*: describes what type of studies will be eligible for the systematic review (e.g. randomised/non-randomised and observational). This highlights elements of the question directly informing other parts of the review methodology.

II. Scoping search for available systematic reviews

The scoping search helps to determine the direction of the review, can help refine the research question and direct the search strategy of the review. The scoping search is used as a starting

point to develop the search strategy (243). In brief, and as discussed in more detail in Chapter 3, the search strategy combined index and free text terms for outcomes in the condition (macular oedema) and the disease context (uveitis) where possible (244).

Prior to conducting the systematic review, a scoping search of Cochrane Library and MEDLINE was conducted and identified that only one systematic review of UMO had previously been undertaken (December 1, 2011). The review had a lack of steps to minimise bias in the review process and there are potential concerns over transparency in reporting as the review does not meet PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards. [16]. Therefore, there was a need for a new systematic review in this field. Our new systematic review identified a wide range of reported outcomes among included studies that contributed to the 'long-list' of outcomes for the COS (213).

III. Systematic review protocol

The study protocol is the systematic review guide that defines and explains the search strategy, selection criteria, data extraction, quality assessment and analysis process. The review should be pre-registered, such as on the PROSPERO database (240).

IV. Literature search

A literature search should be conducted throughout the pre-specified databases (e.g. MEDLINE, EMBASE, CINAHL and Cochrane Library). Additionally, a reference management tool can be used to facilitate removal of duplicate records, noting decisions and aid citation and referencing (137). Systematic reviews are being comprehensive in relevant evidence identification to the searching stage.

V. Screening title and abstract, selecting full-text paper

Selection criteria are applied to screen titles and abstracts of the identified articles. Full texts of the potentially relevant articles are retrieved and assessed against the selection criteria (240). This stage adds value to the review and reduces the error of bias by having two authors assessing independently the decision for inclusion (245).

VI. Data extraction and quality assessment

Data extraction should be undertaken to extract data from included studies using data extraction forms, either manual or electronic. Additionally, critical appraisal of included studies should be carried out to identify whether the study authors adhere to the highest possible standards. Adequate risk of bias tool appropriate to the study design assesses the internal validity. For example, the risk of bias tool from the Cochrane Handbook is usually used to assess the quality of RCTs (239, 246). To ensure high quality is achieved throughout the review and reduce the error of bias, two authors independently extract data and assess the quality of included studies (247)

VII. Data analysis and synthesis

Data tabulation and analysis should be undertaken to build up the evidence and provide an interpretation of the data. Analysis of evidence should include a direct comparison of interventions via included head-to-head studies where data are available and the need to consider meta-analysis where possible. Following data extraction and analysis stages, the review is then narratively synthesised highlighting the strengths and limitations, implications and applicability of the research findings (248, 249).

2.3.2.2 Strengths and limitations of a systematic review

The major strengths of systematic reviews include being able to identify, synthesise and assess all available primary research trials in the field in order to generate robust evidence answering the research question. Therefore, a good systematic review leads towards a credible and informative conclusion. Systematic reviews are at the top of the hierarchy of evidence to inform clinical decisions-making, improve outcomes for patients and provide clinical guidelines for ophthalmology practice (137).

Systematic reviews are a scientific exercise that aim to develop new knowledge from existing primary research and present the evidence in an unbiased way as possible using all the steps presented above. Systematic reviews focus on evidence, impact, validity and causality of included studies considering study methods of design and analysis (250). Methods used to minimise bias across defined stages include the use of two reviewers, and specific tools to assess the quality of included studies (250).

Studies considered to have a high risk of bias can overestimate treatment effect and subsequently affect the future clinical decision-making if combined to a low risk of bias (251). It is, therefore, important to use a critical appraisal tool to evaluate the quality of included studies and assess whether contradictory findings between studies reflect differing risks of bias. Failure to include risk of bias in systematic reviews may have serious implications on future evidence to inform clinical guidelines (247).

A systematic review may also allow meta-analysis, where data are combined from several independent primary studies that address the same research question in order to produce a

more precise estimate of treatment effect (increasing power and precision) (243, 252). Meta-analysis should only be undertaken where clinical and methodological homogeneity exists. A number of elements can limit both the review and meta-analysis e.g. selection of studies, heterogeneity, lack of information on important outcomes and lack of information on the subgroup analyses (253).

Systematic reviews can contribute to a COS (as in this thesis) (254), and on the other hand the development of a COS will increase the reliability of the systematic reviews due to consistent reporting of outcomes and ability to perform meta-analysis (255).

Although systematic reviews are a transparent method used to identify data, they can be time-consuming and expensive to run. Furthermore, there is a possibility of missing some studies that were not captured by the search, particularly if the population of interest is a subgroup and was not specified in either title or abstract. Such issues in the study quality e.g. methodology or accuracy of published data are perpetuated in the systematic review and are a common concern when conducting a meta-analysis (239).

In order to determine the effectiveness of the available pharmacological agents used to treat UMO and establish a list of outcomes from those included studies to inform COS, a systematic review was undertaken (protocol Chapter 3; results Chapter 4; informing COS development Chapter 8).

2.3.3 Qualitative research

Qualitative research helps to understand how participants view their social and psychological

world providing enriched data on their lived experience (256). Qualitative research methods can help to answer the question of what it is like to live with uveitis enhancing a better understanding of patients' disease and associated treatment.

Qualitative research attempts to use data collection methods that allow researchers to develop understandings around their topic of interest in a participant-led manner. In other words, the researchers are trying to put themselves in the shoes of the people taking part in the research so that they can understand things from their perspectives. In the context of a COS, it can be used to identify potential outcomes for inclusion, and can be used alone or in combination with a systematic review (141, 257). A variety of data collection methods are utilised in qualitative research (e.g. focus group discussions and interviews) discussed below.

2.3.3.1 Focus groups

Focus group discussions were first introduced in the early 1920s in marketing and business settings before being used in healthcare (258, 259). Focus group discussion is a qualitative data collection method used to gain in-depth understanding of participants' perception and values (260). It is also an effective way to assess participants' experience of disease and the treatment (259). A focus group forms a face-to-face group discussion between participants and interaction is the key feature of the focus group. Usually a focus group contains 6-8 people who meet to discuss specific topic(s) such as a health-related issue (e.g. PSIU). It is, therefore, a good opportunity for the researcher to draw out many aspects of people's lives. In the focus group discussion, the researcher acts as a moderator to facilitate the discussion between participants to enhance people's contribution during the meeting. There are different options

for moderation e.g. one moderator, dual moderation (as in my case with an experienced supervisor helping me moderate groups), or even training members of a target group to help moderate the focus group (respondent moderator) (261).

2.3.3.1.1 Strengths and limitations of focus groups

A focus group is an effective method of gathering information, assessing participants needs and making use of the group dynamic (258). Focus group discussions allow researchers to work face-to-face with a wide range of participants from different demographic groups (262). The effectiveness of data collection is influenced by the researcher's ability to encourage participants to talk, monitor participants' body language and prompt the discussion in appropriate direction to ensure a wide coverage is achieved and enhance the ability of the study to produce useful insights (261). Another key point for a successful focus group discussion is the group composition, clarity of the task and effectiveness of the process (262).

In the context of a COS, the task of the focus group is to have a facilitated discussion allowing participants to build on each other's ideas and experiences regarding the disease and treatment impacts. The researcher in the focus group is able to observe the extent and nature of agreement and disagreement among participants and able to prompt the discussion accordingly (263). Focus group discussions are able to prompt reflection based on the views and experiences of other groups' members, enhancing direct conversation and interaction between participants and researchers which is the key of having a successful focus group discussion. Focus group discussion provides insights into the sources of complex behaviours and motivations exploring participants' ideas that it is not possible for individual interviews to

do (264).

Focus group discussions can be less costly and save time compared to studies that use individual interviews as a data collection method including the same number in the focus group. Furthermore, focus groups can provide a safe environment for people who might find a one-to-one interview intimidating and benefits people who prefer to be in group situations to share their experience and views (259).

Determining the number of focus group discussions needed in a study is a key part of research design, however, recruitment is affected by a number of factors (e.g., budget, personnel, and timescale). In qualitative research, the sample size cannot be determined in advance and estimation of saturation is still debatable (265). Data saturation is achieved when enough data are available to describe and explain the study phenomena, at which point recruitment of further participants and collecting further data will not lead to new outcomes (266). Saturation is a subjective judgment of the researchers (267), however, assessing the code frequency across data and checking the proxy of themes helps to achieve saturation. Guest et al suggested that three focus group discussions are enough to identify the most prevalent themes across the data. Furthermore, the use of 2-3 focus groups is able to identify 80% of themes while 3-6 focus groups are sufficient to identify 90% of themes (268). It is important to note that saturation depends on the details and depth of data collected rather than the amount of data (267). In this study, four focus groups were conducted and data saturation was achieved as no new outcomes were emerged by the last focus group.

Focus groups and similar qualitative approaches are time-burdensome on participants, and as

a result, there can be problems with recruitment and risk of dropouts from the focus group increases on the day of conducting the discussion. This seems a common issue on qualitative research, however, several strategies could be considered to minimise such issues with recruitment including sending recruitment questionnaires, telephone invitation, door to door invitation and email; and recruiting through networks, social media and other available groups such as patients groups (261).

Additionally, participants may be encouraged to take part in the group discussion by giving them incentives. Over-recruitment may be needed to counteract the risk of dropouts from the study (260). Another challenge with focus groups is to facilitate a meaningful group discussion, therefore, the researcher must allow all voices to be heard and recorded. If some participants are allowed to dominate, others lose their opportunity to participate and the outcome becomes skewed (269, 270).

Focus groups have the ability to prompt reflection based on the views and experiences of other groups' members. However, one of the limitations of being unable to have an in-depth exploration of individual participants' own personal contexts and the relationship of that to their views and experiences (261).

In order to promote interaction and discussion to identify outcomes of importance to adult patients of posterior segment-involving uveitis and their carers, focus group discussion was selected. Further details on the methods and results are presented (Chapter 6).

2.3.3.2 Interviews

Interviews are a research data collection method that is widely used to gain in-depth knowledge and understanding of people's perceptions. Three interview styles were identified based on the format and characteristics of used questions (271).

First, *structured interviews* allow researchers to follow a specific set of questions in a pre-determined order with a limited number of response categories. Structured interviews are quantitative methods similar to questionnaires allowing the interviewer to have a high level of control over the discussion and analyse data in a quantitative way (272).

Second, *unstructured interviews* allow researchers to have a conversation founded on story-telling based on events or actions from the perspective of a participant's life experience (273). Interviewees are given a wide room to express their experience by asking them broad questions. Although collected data are rich, however, interpretation, comparison and analysis can be challenging (274).

Third, *semi-structured interviews* allow researchers to have an outline for a wide range of topics that are prepared for discussion. This is the most commonly used style in qualitative health research that allows in-depth discussion and conversation to answer the research question. This forms an interview type between structured and unstructured styles (275).

Semi-structured interview method allows the interviewer to ask multiple questions and then keep the focus of the interview on one or more questions that are directly related to the main theme of the study. The main discussed question(s) would be supported by a number of probes

and prompts to enhance the discussion and dig deeper for further details (274). The process of the interview is based on the interaction between the researcher and the interviewee combining the structure and flexibility. It is important for the researcher to build a good rapport with the interviewee, put the interviewee at ease, create respect and show interest (271). The role of the researcher is to facilitate the discussion enabling the interviewee to talk about their thoughts, feelings, and experiences and managing the interview process ensuring good coverage and sufficient collection of data. It is, therefore, the interviewee's responses that help guide the direction of the interview and the depth of collected data (276).

Interview delivery can also vary, being either face-to-face or by telephone. A face-to-face Interview, discusses topics by which the interviewer and the interviewee are usually undertaken in one place, although interestingly, skype/videophone interviews are also considered as a form of a face-to-face interview (276). The main point of a face-to-face interview is that the interviewer and the interviewee can see each other. Telephone interviews were introduced as a qualitative research method allowing researchers to have access to a wide geographical area and collect rich and in-depth data (271).

2.3.3.2.1 Strengths and limitations of interviews

Both focus groups and interviews are data collection methods that allow researchers to develop understandings around the topic of interest in a participant-led manner; however, interviews give the opportunity to understand individual views and contexts in much more detail than focus groups. Interviews are a highly effective method by which individuals are more dynamic generating a list of domains within the topics than focus groups (277).

Interviews give the opportunity for the interviewer to ask, clarify and discuss in detail all relevant questions. Interviewees are likely to have a better opportunity to express their own views, improving the likelihood of useful coverage of the topic (278).

A topic guide is usually used to run the interview, however, it is not restricted to specific questions and it is the researcher's ability to guide the interview and redirect the discussion as appropriate. Based on this the researcher is able to revise and direct the research framework where new information emerges. This highlights the flexibility of the method in tailoring the order of questions (279). Interviews are able to capture in-depth data about the topic that is often missed by more positivistic enquiries (278). Although gathered data using this method may not be generalised to a larger population, however, they are transferable to another setting with a similar population. The presence of researchers during data collection may affect participants' responses (276).

Another challenge in interviews and focus groups is that they generate huge volumes of data which can be difficult to analyse (280), thus an experienced qualitative researcher would be needed to aid the analysis process for such data. Interviews may have a relative absence of bias compared to focus groups. Interviewees try to articulate their views rather than to impress the interviewer. However, in focus group discussion if a participant starts talking about the negative experience of the NHS for example, this can determine the perception of others who have no experience (279).

Telephone interviews provide interpersonal communication between the interviewee and the researcher without face-to-face meeting that is relatively cost-effective compared to face-to-

face interviews (281, 282). Telephone interviews can be arranged without significant changes to caring arrangements for the interviewee and could also save time for both the interviewee and the researcher through avoiding travel time (273). Telephone interviews give the opportunity for the interviewees to be interviewed in their own environment, which may allow the interviewee to be more comfortable and able to talk frankly. It can also be easier to recruit for telephone interviews compared to face-to-face interviews (283). Telephone interviews are a faster data collection method compared to face-to-face interviews (276).

Although focus groups were considered to elicit outcomes from healthcare professionals in the same ways as patients and carers, this was not possible for pragmatic reasons due to the scheduling of joint meetings around clinical commitments. Therefore, semi-structured telephone interviews were used as reported in chapter 7. Recruitment and practicalities are more convenient using telephone interviews, however, a number of limitations may arise using this technique (277).

In telephone interviews, researchers do not see the interviewees to read their facial expressions, gestures or reactions in order to determine whether they are able to understand the question and some assessment of their frankness and honesty in answering it. Being unable to read body language is a crucial limitation in conducting telephone interviews, however, there is no evidence that telephone interviews provide less quality data compared to face-to-face interviews (276).

Other limitations of telephone interviews include participants' and interviewer capacity to hear clearly over the telephone. Therefore, telephone interviews have less control and limit

the capacity of the researchers to demonstrate their interpersonal skills (276, 284). Additionally, clarity of recorded voices (quality) could be an issue in the telephone interviews due to recorder quality, telephone coverage signal (bad reception) or even if the interview was conducted in an unusual place (e.g. while driving or in the park, etc.) (285). Thus, it is the researcher's responsibility to ensure that the interviewees are sitting in a quiet place prior to the start of the interviews, so that can be heard clearly and equipment for recording the interviews are well-prepared and tested beforehand. Limited telephone or internet coverage in certain areas and low response rate are also disadvantages in telephone interviews (274)

Finally, skype, face-time and other videophone approaches may provide a middle way, with the convenience of a telephone approach but more opportunities to pick up on non-verbal cues. However, not all interviewees have access to this technology (e.g. through not having a smartphone or computer) (286).

2.3.4 Developing an outcome domains framework from the qualitative data

A thematic analysis of content was informed by the framework analytical approach. Qualitative data were coded for outcomes. The focus groups data were coded inductively (from the raw data), without application of any a priori outcome domain framework. For example codes refer to substantive things (e.g. structural changes), emotions (e.g. frustration, anger, sadness, embarrassment) or visual functional (e.g. distance vision, near vision, distinguish colours (colour vision), peripheral vision) or daily activities and housework (e.g. shopping, housework tasks and other daily activities. Whilst this was the case it should be noted that coding of qualitative data was subsequent to the systematic review analysis and the analyst may have

been sensitised to certain concepts and outcomes apparent from this review, and also from their prior clinical experience. Dual coding with one of the PhD supervisors was utilised as a reflexive tool during coding in acknowledgement of this possibility.

During analysis of interview data the domain framework developed from the focus group data was applied to interview data where healthcare professionals discussed similar outcomes and concepts. Where professionals identified novel outcomes and concepts these were added to the existing domain framework.

Initially the researcher creates outcome domains for each outcome to be grouped into and then these were discussed and agreed among the research team. Our outcome domains therefore attempt to provide an essential structure to the conceptualisation of outcomes that are important in non-infectious uveitis affecting the posterior segment of the eye that needs to be measured in PSIU clinical trials.

2.3.5 The Delphi technique

The Delphi technique is a consensus technique used to seek participants' opinions and enhance their decision-making by refining their judgments using a series of survey rounds. This technique gives participants the opportunity to release their feedback and promote further discussion in many more rounds (287). Delphi methodology was first used in the 1950s to address specific military issues investigating the forecast of the group over the forecast of the individuals. Application of Delphi methodology went beyond this and now Delphi approach is widely used in public health, education, communication technology and transportation (288).

An online Delphi study is used to reduce the range of potential outcomes to a smaller core

outcome set (287) as informed by the work of the COMET Initiative (231). Delphi technique usually includes sequential rounds, a minimum of two rounds. However, the way Delphi rounds are presented varies between studies. The most commonly used technique includes two rounds, through which participants' opinions are sought in the first round followed by asking them to add any other-related outcomes which they think should be included. In the second round of the Delphi, feedback is given to participants who are asked to re-evaluate their responses in the light of the newly generated data and responses of other stakeholders. They then re-state their opinions in the light of this feedback. The second round of the Delphi has also been used to obtain agreement on ideas where consensus was not obtained in the first round (148).

Two methods are commonly used to present outcomes in the final round of the Delphi including: (1) All outcomes from previous rounds were presented including additional outcomes identified by participants. Participants are asked to revise their responses and re-rate outcomes (all outcomes including additional ones) on the basis of the available feedback from all the stakeholders' groups; (148); OR (2) Only outcomes that have not achieved consensus in previous rounds are presented, thus outcomes that have reached consensus are removed and participants are asked to re-rate the remaining outcomes (outcomes scored low and the consensus was not achieved) (289). Our study has used the first method presenting all outcomes and the new additional one for participants to re-rate them in the final round.

2.3.5.1 Strengths and limitations of the Delphi technique

Delphi is a method of reaching consensus across multiple domains. A key advantage is how

well it can work across multiple stakeholder groups (290, 291). Delphi technique is a flexible and structured design through an organised group communication process that permits utilising participants' responses in order to reach an agreement. Therefore, the Delphi technique encourages participants to share their knowledge and generate new ideas that apply to the purpose of the study (291). Delphi techniques encourage anonymity and confidentiality of responses allowing participants to have freedom of expression without any pressure [76].

The Delphi technique is cost-effective and fairly rapidly completed; therefore, it is considered a quick method to obtain agreement on collected data. Delphi technique scores well for feasibility, does not require participants to meet in one physical place and it is easy to understand (291). Convenience is an important issue for both the researcher and participants; it is, therefore, an easy communication method between parties in their own time (289).

An important benefit – but also the limitation - of most modern Delphi platforms is that they are electronic. This helps to reach people across the world and extend the sampling process (292). If the Delphi technique is conducted online, the researcher can log in any time to monitor participants' activities and participants are issued with login access to the survey wherever they have internet facilities and allowing participants to complete the survey at their convenient time (293). Delphi groups are able to express their views without pressure or influence made by dominant individuals (288, 291). However, an online Delphi technique may provide barriers to others who have issues with the internet or technology. Based on the telecommunication statistics in 2019, 90% of the households in Great Britain had internet and

89% of the households in Europe had internet access (294). Even for those who in theory have internet access, some groups such as the elderly or participants with visual impairment may struggle with standard electronic platforms, although there are a number of adaptations to assist with this (screen readers, magnifiers, etc.) (295, 296).

Despite the above benefits of the Delphi process, it has been subject to criticism for the lack of guidelines in determining sample size and sampling techniques. There is no agreed definition over the number of rounds and the style of each round. Variations in the number of participants included in Delphi techniques have been found, with 20 being the smallest number of participants and 1018 the largest number of participants (297). It is worth noting that the number of participants in the second round is often less compared to the first round (292).

Recruitment might be time-consuming, and the chance of having a low response rate in the first place is a major concern of Delphi methodology. Delphi technique requires time and commitment from participants to complete the whole process, which might lead to dropping out or low response rates. Withdrawal from the second and the third round of the Delphi survey may mean that the numbers in the final round are too low to provide confidence in the final results due to dropout (298).

The process also has some concerns over time delay between Delphi rounds in data collection. Delphi techniques include sequential rounds, and the time period between rounds could lead to variability in participants' responses due to being unable to remember their scoring. Thus, it is desirable to complete Delphi rounds with a short time gap between them to keep things

fresh in everybody's minds. Additionally, there are some concerns about technique reliability where researchers impose their conceptions in the first round only based on the literature review without having the participants' views using qualitative research methods (292). However, participants should be willing to add their views to the first round without any constraint from the researcher (292).

Finally, low presentation to any of the stakeholder groups may skew results since such stakeholder views may be diluted by the clinical experts' views (299). Furthermore, anonymity is a key feature for Delphi techniques, but may limit the opportunities to ensure accuracy and clarify a respondent's statement (298). Ultimately, however, the Delphi process has been widely used to obtain consensus over which outcomes to include in later stages of COS development processes and is the recommended approach of COMET.

An alternative approach could have been to use Nominal group Techniques and surveys (Refer to Appendix 24). However, the Delphi technique was chosen for this study as per COMET recommendations.

2.3.6 Consensus meeting

The consensus meeting was first used in the United States of America in the early 1970s to address the National Institutes of Health development programme to seek agreement on the safety and efficacy of medical procedures, drugs and devices (300). Consensus development meetings were introduced to the UK health system to discuss healthcare policies and its implementation in clinical practice (301). The consensus meeting is a useful method to evaluate the list of outcomes in the final core outcome set and the need to combine outcomes

if an overlap is noted between components (302). It provides a good opportunity to gain insight on the Delphi process from informed multiple stakeholders' views. It is also a useful method to discuss whether further outcomes should be included and check for redundancy between outcomes and for reaching an agreement through sharing information and knowledge of the stakeholders' groups. The consensus meeting also enhances the critical thinking of the key stakeholders and facilitates joint decision-making of the diverse group (303). Consensus meetings should be run in a comfortable atmosphere to encourage participants to be active in their decisions, putting the interest of the group over their own interest. Communication and cooperation between participants are the keys to reach successful agreement on the items discussed and to enhance implementation (304).

Two methods are commonly used to run the consensus meeting based on the Delphi results and the number of outcomes in the final round of the Delphi: (1) Results from all Delphi rounds are presented, however, the discussion is focused on the final round of the Delphi. Thus, all outcomes achieved consensus via the Delphi exercise are included in the COS and discussion is undertaken on those outcomes where no consensus could be achieved (the 'unsure' group); OR (2) Results from the final round of the Delphi are presented, and discussion is focused only on those outcomes that have achieved consensus, and addresses issues such as how to groups these items into higher domains. In this case, all other outcomes (no consensus and consensus out) are excluded from the discussion. Our study used the second approach.

Two approaches may be considered in how the key stakeholders are distributed within the consensus meeting(s): (1) Hold separate consensus meetings for each major group of

stakeholders. For example, run a meeting for healthcare professionals and another one for public representatives (patients, carers, service users, etc.). Using this style aims to have a homogeneous consensus group meeting by which results are relevant to a specific stakeholder group; OR (2) Run one consensus meeting and includes members of all the key stakeholder groups and the research team. Our study has used this approach which is becoming more widely used aiming to have a heterogeneous group among all stakeholders, thus generalisability of results is improved based on the overall agreement rather than by specific stakeholder groups (137, 305).

The consensus meeting is usually chaired by a facilitator and may have a panel to assess the level of evidence for final decisions. For example, a consensus development meeting was held to discuss the effect of corticosteroids for fetal maturation on perinatal outcomes. The key stakeholder groups included representatives from neonatology, obstetrics, family medicine, behavioural medicine, psychology, biostatistics, and the public. A drafted statement was prepared and presented to the team, and final decisions were made on the basis of pre-defined consensus criteria (306). It should be recognised that there is a lack of guidelines on exactly how the final decisions should be reached during the consensus meeting. The basis for decisions should be reported (307).

Running a successful consensus meeting is a major priority for researchers; therefore certain features have to be considered (308):

- *Background reports are prepared:* the meeting will start with introductions and the presentation of a background report and relevant information that reflect all

participants' feedback from any previous work (e.g. Delphi process).

- *Audience participation is encouraged:* members of the stakeholder groups are encouraged to take part in discussing outcomes of importance for inclusion in the core outcome set and voting on outcomes where consensus was not gained by other consensus methods (e.g. Delphi process). The audience should have the opportunity to ask questions and clarifications if any of the reported information is not clear.
- *Panel to agree the final list of outcomes:* following the voting process, the final list of outcomes should be presented and the team should agree with the final list of outcomes for use and report in clinical trials. The panel team normally includes a panel chair and other members included in the consensus meeting may have the opportunity to discuss the implementation of the research findings nationally and internationally where possible.

2.3.6.1 Strengths and limitations of the consensus meeting

The consensus meeting is an important method of reaching an agreement through sharing information and knowledge with the stakeholder groups. It enhances critical thinking among the key stakeholders and facilitates the joint decision-making of the diverse group. Consensus meetings are run in a comfortable atmosphere to encourage participants to be active in their decision putting the interest of the group over their interest. Thus, the meeting is chaired by a facilitator and may include different stakeholder groups by which all participants are having a chance to take part in the discussion and voting process (304).

Consensus meetings are expensive to run. The cost is usually dependent on the size of the group and the geographical area the researcher is willing to cover. The researcher may have to cover all expenses including travel, accommodation, catering, and venue. Furthermore, including international participants to enhance the validity and generalisability of research findings adds more financial burden to the research (137).

Coordination and logistics can be challenging although this has been enhanced with modern voting platforms (309). As previously mentioned, elderly and visually impaired people may however find the new technology hard to use and this should be addressed to avoid a negative impact on the voting process and skewing the results. Consensus meetings are a significant time-cost for participants, and this may affect recruitment; a low response rate either due to not having enough participants to recruit or due to lack of attendance from a specific stakeholder group on the day of the meeting would compromise the representation and the input of that particular group (137).

2.4 Dissemination of the research finding

Dissemination of the study findings is a key issue for research, and it is an important step to ensure recommendations are well-disseminated to a wide range of people on a national and international basis. Discussion around the dissemination of the research finding could be part of the consensus meeting agenda and the panel would highlight this in its conclusions.

Research findings are disseminated via conferences, workshops and publications. In addition, clinical trialists need to be informed of the research finding so all uveitis clinical trials are

aligned with the new COS recommendations. This is to give the best chance of this ensuring that all reported outcomes are routinely measured in uveitis clinical trials following the final recommendations of the COS. Registration on the COMET database is a key method of enabling the wider community to become aware of the existence of a COS for a particular condition. COS can be revisited and updated as new outcomes become available or if it is suspected that priorities may be changing. Further details on the study dissemination are reported in chapter 9.

2.5 Implementation of research findings

This is to ensure future acceptance of COS findings and implementation in future clinical trials. Implementation of research findings helps to inform health policies and clinical decision-making. In return, better healthcare and effective management are likely to be maximised. Implementation of research findings is a process that may include all aspects of dissemination (e.g. factors affecting implementations, how to promote a wide range of use and sustainability). Nevertheless, the main challenges would be to convince all users (e.g. researchers, clinicians, quality improvement team and policy-makers) about research findings. It is, therefore, a challenge for amending their behaviour to follow the new recommendations and improve the research quality. Thus, users are encouraged to get involved in the research design and the study conduct rather than the dissemination of the research findings only. It is important to recognise that developing a COS is not the end of the process, but is rather the initial step in the standardisation process as this is helping to determine important outcomes and outcome domains. In most cases, there may still be a need to determine the measurement

tool to aid the assessment of those reported outcomes and outcome domains.

Some COS development processes do define the measurement tool at the same time, such as the COS for non-specific low back pain which evaluated the outcomes domain of physical functioning using Oswestry Disability Index version 2.1; a tool and pain outcome domain using Numeric Rating Scale (NRS) for pain intensity tool (310). However, many outcomes defined within a COS may not have a validated tool ready-made for the purpose, and in other cases, there may be multiple tools for which consensus needs to be reached through a subsequent process. It is also worth recognising that the COS may need to be updated in the future as priorities change or new outcomes become available (e.g. instrument-based measures). Outcome measurement instruments (OMIs) such as clinical rating scales, imaging tests, patient surveys, and performance-based tests that define how to measure outcome (i.e. constructs or domains) in the COS. It is important to be consistent in those instruments to enhance comparison and construct evidence synthesis (311). The Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) initiative developed guidelines on how to select OMIs (312).

2.6 Ethics

The researcher (Mohammad Tallouzi) alongside the Chief Investigator (Prof Phil Murray) ensured that the study was conducted in line with the principles of good clinical practice and will conform to: the Department of Health Research Governance Framework, the Declaration of Helsinki and the University of Birmingham's Code of Practice for Research.

2.6.1 Research ethics committee

Ethical approval for the study has been granted by the National Research Ethics Service (NRES) West Midlands – South Birmingham Research Ethics Committee (Reference number 17-LO-0432).

2.6.2. Research governance

The research and development approvals for the COSUMO study are outlined below:

Sandwell and West Birmingham Hospitals NHS Trust – Birmingham and Midland Eye Centre) reference number CPMS 33991

University Hospitals Birmingham Foundation NHS Trust (Queen Elizabeth Hospital), reference number RRK6155.

2.6.3. Informed consent

Eligible participants (patients, carers and healthcare professionals) were contacted (using the participant's preferred method) to answer any questions they may have and ensure they have understood the previously seen information sheet and, should they wish to proceed to the focus group discussion or interviews. The researcher set a convenient date and time for the focus group discussion/ interviews. Written informed consent was taken from all participants on the day of the focus group prior to commencement of the focus group discussion. Verbal consent was obtained from each participant before commencing the interview. Focus group discussion and interviews were audio recorded. For the Delphi study participants were given a unique ID number to gain access to the online Delphi survey and were asked to provide their

consent to proceed with the Delphi survey. Face-to-face consensus meeting participants provided written informed consent before the commencement of the discussion.

2.7 Data Handling and Management

The data from this study were protected by adhering to the data protection act (1998), NHS code of confidentiality (2003) and University of Birmingham code of practice for research (2015-2016). Clinical personal details such as name, email, telephone number were stored on secure encrypted and password protected computers and networks at the University of Birmingham. Personal data were stored and accessed for over three years after the study ended and the research data generated by the study are kept for 10 years. T

The link between identifiers and participants was held in a secure encrypted file on a secure network which was backed up immediately in accordance with Information Security Policy of the University of Birmingham and Data Protection Act Regulations. Digital recordings from the focus groups and interviews were deleted immediately from the recording device after each audio recording was uploaded to a secure encrypted and password protected computers and networks at the University of Birmingham. The transcripts generated from the focus groups and interviews were anonymised and assigned a unique identification number.

2.8 Conclusion

This chapter described a wide range of methods used to aid the process of developing a COS. It also discussed in detail the strengths and limitations of each method and the rationale for their use in the COS development.

There is a significant variation in the methods used to develop a COS, but a multi methods approach is the most frequently used and is supported by the COMET initiative (141, 223). This commonly includes a systematic review and qualitative research followed by a consensus process of Delphi methodology culminating in a consensus meeting. Using multi methods helps to maximise coverage, capturing all reported outcomes in clinical trials through systematic review, augmented by the direct personal experience of patients and carers and professional expertise of healthcare professionals and commissioners, described using qualitative research methods. These help to ensure that the COS is relevant to a diverse group of stakeholders. Using this approach helps provide robust data to strengthen the research findings, enhance generalisability and future applicability of the COS. In doing so if implemented it may help to reduce the burden of conditions such as uveitis, to improve the evaluation of treatment efficacy, and thereby improve patient care.

Chapter 3: The Effectiveness of Pharmacological Agents for the Treatment of Uveitic Macular Oedema (UMO): A Systematic Review Protocol

3.1 Background to chapter 3

Uveitic Macular oedema (UMO) is the accumulation of fluids at the central part of the retina, known as the macula. It is the leading cause of sight-loss in those forms of uveitis which affect the more posterior structures in the eye (PSIU) (23, 313) (described in section 1.5.3). A wide range of treatment options are available for UMO including systemic, local or topical treatment (described in section 1.8). However, there is lack of consensus guidelines to direct treatment options which may lead to uncertainty for patients, clinicians, policy-makers and other healthcare providers (314).

This chapter presents the study protocol for a systematic review that aims to assess the effectiveness of pharmacological agents used to treat UMO. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42015019170) (315)

The protocol was published in full in the peer reviewed journal BMC Systematic Reviews (316). This chapter is comprised of this paper. The findings of this systematic review are presented in chapter 4 (The effectiveness of pharmacological agents for the treatment of Uveitic Macular Oedema (UMO)).

Publication

1. Tallouzi, M.O., Moore, D.J., Calvert, M., Murray, P.I., Bucknall, N. and Denniston, A.K., 2016. The effectiveness of pharmacological agents for the treatment of uveitic macular oedema (UMO): a systematic review protocol. *Systematic reviews, 5*(1), p.29. Available from: https://doi.org/10.1186/s13643-016-0203-

2. Tallouzi, M.O., Moore, D.J., Calvert, M., Murray, P.I., Bucknall, N. and Denniston, A.K. The effectiveness of pharmacological agents for the treatment of Uveitic Macular Oedema (UMO): a systematic review protocol. PROSPERO 2015 CRD42015019170. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42015019170.

3.2 The Systemic Review Protocol.

Tallouzi *et al. Systematic Reviews* (2016) 5:29
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Systematic Reviews

PROTOCOL Open Access

The effectiveness of pharmacological agents for the treatment of uveitic macular oedema (UMO): a systematic review protocol

Mohammad O. Tallouzi[1*], David J. Moore[1], Melanie Calvert[1], Philip I. Murray[2], Nicholas Bucknall[3] and Alastair K. Denniston[4]

Abstract

Background: Macular oedema (MO) describes the accumulation of fluid in the central part of the retina, known as the 'macula' which provides central vision. MO is the leading cause of sight loss in patients with intraocular inflammation (uveitis). There is a lack of consensus over the treatment of uveitic macular oedema (UMO). The proposed systematic review will evaluate the evidence on the effectiveness of pharmacological agents used to treat UMO. All systemic, local, or topical pharmacological agents will be included.

Method/design: Standard systematic review methodology will be employed to identify, select and extract data from comparative studies (randomised/non-randomised trials and observational studies) of the pharmacological interventions in patients with UMO. Searches will be conducted through bibliographic databases (Cochrane Library, MEDLINE, EMBASE and CINAHL) and clinical trials registers. No restriction will be placed on either language or year of publication. Translation of non-English language articles will be undertaken to minimise selection bias. The primary outcome of interest will be best corrected visual acuity and secondary outcomes will be adverse events, health-related quality of life, assessment of UMO using central macular thickness (e.g. by optical coherence topography (OCT)), clinical and angiographic assessment of UMO, clinical estimation of vitreous haze. Risk of bias assessment appropriate to each study design will be undertaken. Data will be grouped by comparison, tabulated and narratively synthesised. Meta-analysis will be undertaken where clinical and methodological homogeneity exists. Subgroup and sensitivity analyses, also network analyses and intra/inter-pharmacological class analyses will be undertaken where deemed appropriate.

Discussion: A number of published studies have investigated the effectiveness of the pharmacological agents used to treat UMO. However, there is no recent systematic review that synthesises this evidence. This systematic review will analyse the effectiveness of systemic, local and topical therapies to treat UMO. The findings will provide important evidence to inform clinical and health policy decision-making for the treatment of UMO.

Systematic review registration: Prospero CRD42015019170

Keywords: Systematic review, Macular oedema, Macular edema, Uveitis, Management, Pharmacological agents, Meta-analysis

* Correspondence: mxt500@bham.ac.uk
[1]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
Full list of author information is available at the end of the article

Background

Uveitis describes a group of disorders characterised by intraocular inflammation. Uveitis is the fifth commonest cause of visual loss in the developed world and accounts for about 10–15 % of total blindness [1, 2] and up to 25 % in the developing world [3, 4]. Although uveitis may affect any age group, it peaks in the working age population with no significant gender difference [5]. The annual incidence of uveitis is estimated at 14–50 per 100,000 with a prevalence of around 38–200 per 100,000 general population [1, 2, 5, 6].

Uveitis has a disproportionately high impact in terms of years of potential vision loss and economic effects because it often strikes at a younger age than common age-related eye disorders such as cataract, age-related macular degeneration and glaucoma [1].

Uveitis may be classified anatomically as anterior uveitis, intermediate uveitis, posterior uveitis or panuveitis [7, 8]. The leading cause of sight loss in patients with uveitis is macular oedema and known in this context as uveitic macular oedema (UMO) [1, 9]. Macular oedema (MO) describes the accumulation of fluid in the retina (the light-sensitive inner-lining of the eye) in the area that provides central vision known as the 'macula' [10]. MO is more common in those forms of uveitis which affect the more posterior structures in the eye, namely intermediate, posterior or panuveitis; collectively, these are sometimes referred to as posterior segment- involving uveitis. MO can also occur in association with anterior uveitis [11].

Macular oedema accounts for 41 % of visual impairment and 29 % of blindness in uveitis [6, 12]. In the Multicentre Uveitis Steroid Treatment (MUST) trial of systemic corticosteroid vs a fluocinolone acetonide implant in non-infectious intermediate, posterior and panuveitis, it was noted that low vision (best corrected visual acuity (BCVA) worse than 20/40) was present in 50 % of recruited patients and legal blindness (BCVA of 20/200 or worse) in 16 %, with cystoid macular oedema being present in 38 % of eyes with similar distribution across intermediate uveitis, posterior uveitis and panuveitis [13].

The impact of UMO on visual acuity is usually assessed using standard distance visual acuity charts, either using a Snellen chart or Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Acuities from Snellen charts are usually reported in metres in the UK and feet in the USA. Acuities from ETDRS charts are usually reported either as 'number of letters read' or converted into a LogMAR fraction. Although certain visual acuities are considered to be equivalent (e.g. 0.0 LogMAR = 6/6 UK Snellen = 20/20 US Snellen), due to intrinsic differences between the charts, it is recognised that these equivalences are approximate [11]. Although the Snellen chart is still widely used in clinical practice, most trials use ETDRS charts due to various methodological advantages. Traditionally, MO has been assessed clinically using stereoscopic slit-lamp fundus bio-microscopy and fluorescein angiography, an invasive procedure requiring intravenous dye and stereo photography imaging testing [14]. More recently, a non-invasive imaging technique, optical coherence tomography (OCT), has become a standard clinical practice in the follow-up of UMO and monitoring treatment response [15, 16]. OCT may be more sensitive than clinical measures in detecting the presence of UMO and provides accurate measures of the structural changes in terms of macular thickness [17].

The treatment of UMO is a major priority in tackling sight loss in uveitis and will be the focus of this study. Corticosteroids are the mainstay of treatment for UMO [10], with alternative routes of administration: systemic (oral, intravenous and intramuscular); local which includes periocular injection (sub-Tenon and orbital floor injection) and intraocular (intra-vitreal injection or implant) [18, 19]. 'Second line' therapies are typically immunomodulatory and include T cell inhibitors (e.g. ciclosporine, tacrolimus), antimetabolites (e.g. azathioprine, methotrexate, mycophenolate Mofetil), alkylating agents (e.g. cyclophosphamide) and biological agents (e.g. interferons, antitumor necrosis factor (anti-tumour necrosis factor (TNF)) agents) [20–23]. Most of these agents are only used systemically (oral, intravenous or subcutaneous), while intra-vitreal use has been reported for both methotrexate and anti-TNF agents [22–25]. Other treatments that have been used in UMO include the oral carbonic anhydrase inhibitor (acetazolamide), and intra-vitreal anti-vascular endothelial growth factor (anti-VEGF) agents [10, 26].

Whilst there have been narrative reviews on the management of UMO, [10] a scoping search of Cochrane library, MEDLINE, identified that only one systematic review has been undertaken [16]. That review aimed to cover all pharmacological interventions for UMO and had fairly comprehensive searches, not restricted by language or year of publication, undertaken up to late 2011. The review only included RCTs of which nine were reviewed. Limitations to this work include a lack of steps to minimise bias in the review process, and there are potential concerns over transparency in reporting as the review does not meet PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses standards). The review highlights the availability of trials across the classes of pharmacological interventions yet meta-analysis was limited by heterogeneity and availability of data. The authors also noted that relevant work was ongoing, with more than 10 clinical trials related to UMO in progress at the time of that review.

Further, scoping work has suggested a role for non-RCT evidence in this field. Scoping searches suggest that RCTS in this field are likely to be small in size and may have shorter periods of follow-up than non-RCTs. Non- RCTs may therefore be more suitable for the detection of adverse events. There is thus value in including the non-RCT body of evidence in any new systematic review.
Although there is a wide range of treatment options available for UMO, there are currently no consensus guidelines to direct treatment in this field. This may lead to uncertainty for patients, clinicians and healthcare pro- viders. It is timely to review the literature in order to evaluate and summarise the available evidence for the pharmacological agents used for the treatment of UMO, which may form the basis of evidence-based clinical rec- ommendations. Identifying the most effective treatment for ocular inflammatory disease is the number one prior- ity for research in inflammatory eye disease [27].

Methods/design

Aim

The aim is to assess the effectiveness of the available pharmacological therapies used in the treatment of UMO. The aim will be achieved by conducting a system- atic review of studies:

- Comparing a pharmacological agent to the non-use of a pharmacological agent.
- Comparing a pharmacological agent to the same or another pharmacological agent.

Standard protocol-driven systematic review methods will be used.
The systematic review protocol has been registered with the international prospective register of systematic reviews (PROSPERO) database ref (CRD42015019170) and has been reported according to the PRISMA-P gui- dlines (see Additional file 1).

Searches

The following sources will be searched.

- Bibliographic databases of published studies
- MEDLINE, MEDLINE in process (Ovid).
- EMBASE (Ovid).
- CINAHL (EBSCO)
- The Cochrane Library (CENTRAL Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database).

The search strategy will combine index and free text terms for the condition (MO) and the disease context

Table 1 MEDLINE sample search strategy for uveitic macular edema

Count	Searches
1	Exp Macular Edema/
2	(macular adj2 edema). ti,ab.
3	(macular adj2 oedema). ti,ab.
4	1 or 2 or 3
5	Exp Uveitis/
6	Uveit$.ti,ab.
7	5 or 6
8	4 and 7

(uveitis) where possible. A sample research strategy from MEDLINE is provided in Table 1, and this strategy will be adapted for the use in each bibliographic database. Identified systematic reviews will be used to check if all relevant primary studies are identified.

- Registers of Clinical trials
- Clinicaltrials.gov. www.clinicaltrials.gov.
- International Standard Randomised Controlled Trials Number (ISRCTN database). www.contolled- trials.com
- WHO International Clinical Trials Registry Platform (ICTRP portal). www.who.int/ictrp/en/.
- UK Clinical Research Network (UKCRN). www.ukcrc.org
- Abstract and conference proceedings
- British Library's ZETOC.
- Conference proceedings Citation Index (Web of Science).
- Dissertations, theses
- British library Ethos
- ProQuest. www.proquest.com
- Grey literature
- OpenGrey. www.opengrey.eu

These sources will be searched in a more iterative way as complex search strategies may not be able to be used; therefore, keywords/phrases based on macular edema/ oedema and uveitis will be employed.
There will be no restriction placed on either lan- guage or year of publication; however, for conference abstracts, only those within 3 years of the search date will be considered. The literature search results will be entered onto EndNote ×7 (Thomson Reuters) to facilitate the removal of duplicate records, study se- lection, recording decisions and references.

Selection criteria

The following criteria will be used to select studies for review:

- Study design
- Randomised controlled trials (RCTs) and other comparative studies where the comparator group is from a concurrent time period (e.g. non-randomised controlled trials, comparative observational studies).
- Participants
- Participants of any age, gender or ethnicity with a diagnosis of UMO.

Studies on a population broader than UMO will only be included if data specific for the UMO subgroup is reported separately.

- Intervention and comparator
- Comparing any pharmacological agent to no use of a pharmacological agent.
- Comparing any pharmacological agent to the same or another pharmacological agent.
- Outcomes
- Outcomes will not be used for study selection. However, clinical- and patient-reported outcomes are considered important for the aims of the review.
- Primary outcome.
- Best corrected visual acuity.
- Secondary outcome
- Adverse events.
- Health-related quality of life.
- Central macular thickness (e.g. by OCT)
- Angiographic assessment of UMO
- Clinical assessment of UMO
- Clinical estimation of vitreous haze
- Clinical estimation of anterior chamber cells

Selection process

The study selection process will be conducted in two stages:

- First, title and abstract of the identified articles will be screened in order to remove irrelevant records. Articles that obviously do not meet the selection criteria will be excluded.
- Second, the full text of the potential relevant articles will be retrieved and assessed against all the selection criteria.

At both stages, two reviewers will independently assess articles with any disagreements resolved by discussion and, if required, referral to a third reviewer. Both stages of the selection process will be piloted and if necessary modified. The study selection processes will be illustrated using a PRISMA flow diagram and details of articles excluded at the full text stage will be recorded along with the reason for exclusion [28].

Translation in part or wholly of non-English language articles will be undertaken to aid study selection and analysis.

Data extraction

Two authors will independently extract data from the included publications. Any discrepancies will be resolved through discussion and referral to a third reviewer if needed. A standardised piloted data extraction form will be used. Study authors may be contacted if further infor- mation is required. For each study, the following infor- mation (but not limited to) will be extracted.

- Study characteristics
- Authors—publication year—title and journal
- Study design
- Setting
- Sample size
- Length of follow-up
- Analysis
- Participant characteristics
- Patient selection/recruitment criteria
- Patients' characteristics (demographic data, number, age, gender, socioeconomic status and ethnicity).
- Type of uveitis (anatomical categorisation, syndrome/aetiological classification)
- Comorbidity
- Co-medication
- Intervention and comparator
- Pharmacological agents
- Regimen (dose, frequency of administration, route of administration)
- Comparator details
- Any difference in underlying care between treatment groups
- Outcomes and findings
- Outcomes measured and results for each outcome including precision and statistical test results.
- Completeness of follow-up for each outcome

Quality assessment

Quality assessment of all included articles will be undertaken by two reviewers independently with disagree- ments resolved by discussion and referral to a third reviewer if required.

The risk of bias tool from the Cochrane Handbook will be used for RCTs [29]. For non-randomised con- trolled trials, the domains in the risk of bias tool for RCTs will be used (accepting that criteria for randomisa- tion and possibly concealment of allocation are not rele- vant). For prospective controlled observational studies, the guidelines outlined in Chapter 13 of the Cochrane Handbook will be followed [29]. The domains in the risk of bias tool for RCTs can be used as a minimum

assessment (again accepting that the studies are not randomised). The most relevant criteria for assessment in this area are likely to relate to how the groups were selected, differences in patient characteristics, loss to follow-up and biases and confounding in outcome assessment. Any case controlled studies/analyses will be assessed based on the Newcastle-Ottawa scale [30].

Analysis

Studies will be grouped by each intervention and comparison, with data tabulated and a narrative synthesis of evidence conducted for each outcome of relevance to the review.

Assessment of clinical and methodological heterogeneity will be employed to determine whether for each comparison for each outcome, studies are sufficiently similar to ensure data pooling by meta-analysis is appropriate and whether a random effect or fixed effect model is the most appropriate [31]. The I^2 statistic (which gives the percentage of the total variability in the data due to between-study heterogeneity) and the tau-squared statistic (which gives an estimate of the between-study variance) will be reported where appropriate. Data from differing study designs will not be pooled together. For each meta-analysis containing 10 or more studies, the likelihood publication bias will be investigated and funnel plot will be constructed [32].

It is expected that multiple time point data will be available within the same study and between studies. Nominally, data will be categorised in each analysis into the following groups based on follow-up period:

≤3 months, >3 and ≤6 months and >6 months post interventions. Within the last category, further division may be considered to assess longer-term data.

Results for some outcomes are likely to be presented using a number of different measure/statistics within the same study and/or between studies. For example, visual acuity may be reported in metres or feet (from Snellen charts), a LogMAR score, number of letters or lines read (from ETDRS charts), and the change in acuity may be reported as a change in any one of these indices or categorised against a threshold, e.g. proportion of subjects with change greater or equal to a specific number of lines/letters read [11]. Visual acuity can therefore be considered as continuous data (e.g. group mean LogMAR score), some as discrete data (e.g. number of lines read) and some as dichotomous data (e.g. proportion of patients reading x lines, or proportion with a LogMAR score greater than *y*). The first and last are likely to be the most common data. Conversion of data between formats to maximise the data available for each analyses will be considered (for example if the type of chart is known, letters might be able to be converted to lines; LogMAR score and letters interchanged; Snellen UK, US and ETDRS data approximated. Any conversion of data will be undertaken with due caution and with regard known issues [11]. The impact of any converted data on findings will be explicitly acknowledged.

Continuous data (e.g. health related quality of life) from the same scale will be pooled using mean differ- ence and from a different scale where tools are consid- ered to be assessing the same underlying features, standardised mean difference will be used. Further, subgroup analysis will be considered where deemed appropriate. Where data allows, such analysis could include grouping by clinical and anatomical classification to the type of uveitis (anterior, intermediate, posterior and pan) and route of administration of the intervention.

Direct comparison of interventions will be undertaken via included head-to-head studies where these are available. For included randomised controlled trials, the potential for network meta-analysis or adjusted indirect comparison will be explored. It may be possible to estimate the relative effect of the different pharmacological agents if sufficient studies exist to inform the network. The ability to undertake network meta-analyses/adjusted indirect treatment comparisons will be dependent on a number of key assumptions (e.g. the homogeneity, similarity and consistency assumptions) [33, 34].

Based on all the above, as the interventions fall into five classes of agent (corticosteroids, T cell inhibitors, antimetabolites, alkylating agents and biological agents) evidence of effect of agents within each class will be discussed to report on the consistency and magnitude of the class effect. Finally, any inference of comparisons be- tween classes will be considered.

Reporting

The review and its findings will be reported in accordance to the PRISMA guidelines [28]. The strengths and weaknesses of the review methods and the available evidence will be discussed in relation to the internal and external validity of the findings. The implications of the review findings will be discussed in the context of current and future clinical practice related to UMO and the future research agenda.

Discussion and potential impact

UMO is a major cause of blindness in the working age population. However, there is a wide variation in treatment reflecting limitations in primary data and a lack of national guidelines or consensus statements. This review will systematically and comprehensively retrieve evidence from a wide range of sources to evaluate the pharmacological treatment of the UMO. Furthermore, this review will provide valuable information regarding the effectiveness of pharmacological agents.

We hope this review will provide a clear reference point for ophthalmologist and decision makers. The re- vealed evidence will aid standardisation of clinical prac- tice on the most effective therapies to improve outcomes for patients and help minimise harm from inappropriate therapies. Furthermore, this review is timely due to the recent availability of novel local therapies which have been approved by UK National Institute for Health and Care Excellence (NICE) for other forms of MO, but whose role in UMO is not yet established.

Additional file

Additional file 1. PRISMA-P 2015 checklist: recommended items to include in a systematic review protocol.[a] (PDF 153 kb

JT

Abbreviations

Anti-VEGF: anti-vascular endothelia growth factor; BCVA: best corrected visual acuity; CENTRAL: Cochrane Central Register of Controlled Trials;

CINAHL: Cumulative Index to Nursing and Allied Health Literature; ETDRS: Early Treatment Diabetic Retinopathy Study; MEDLINE: Medical

Literature Analysis and Retrieval System Online; NICE: National Institute for Health and Care Excellence; OCT: optical coherence topography;

PRISMA: Preferred Reporting Items for Systematic Reviews and

Meta-analyses: TNF: tumour necrosis factor: UMO: uveitic macular

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MT, AD, DM, and MC led the development of the protocol. MT drafted the manuscript. AD and PM provided clinical advice; DM and MC provided methodological advice. NB provided the patient public perspective. All authors read and approved the final manuscript.

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Author details
[1]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. [2]Institute of Immunology and Immunotherapy, College of Medical and
Dental Sciences, University of Birmingham, Birmingham, UK. [3]Birdshot Uveitis Society representative, Birmingham, UK. [4]Department of Ophthalmology, Queen Elizabeth hospital, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham B15 2WB, UK.
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Chapter 4: The Effectiveness of Pharmacological Agents for the Treatment of Uveitic Macular Oedema (UMO): A Systematic Review

4.1 Background to chapter 4

Uveitis describes a group of diseases characterised by intraocular inflammation. Uveitis is the fifth commonest cause of visual loss in the developed world and accounts for about 10–15% of total blindness (23, 24) and up to 25% in the developing world (313, 317). Uveitic Macular oedema (UMO) is a major sight threatening complication which occurs in 29% of uveitis patients. This review focuses on the treatment of UMO which is a substantial priority in tackling sight-loss in patients with uveitis (56). This review summarises the available evidence for the pharmacological agents used for the treatment of UMO.

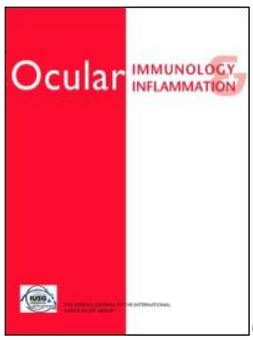
The results of the systematic review assessing the effectiveness of the pharmacological agents used in the treatment of UMO are presented in this chapter in the format of the paper published in the Ocular Immunology and Inflammation Journal (213). Supplementary details accompanying this publication are also included in this chapter.

The outcomes identified in this systematic review were used to support a comprehensive list of outcomes in included uveitis clinical trials to inform core outcome set development (Chapters 6-8).

Publication

1. Tallouzi, M.O., Moore, D.J., Barry, R.J., Calvert, M., Mathers, J., Murray, P.I. and Denniston, A.K., 2019. The effectiveness of pharmacological agents for the treatment of uveitic macular oedema (UMO): A systematic review. *Ocular immunology and inflammation, 27*(4), pp.658-680**.** Available from: https://doi.org/10.1080/09273948.2019.1569243

4.2 The Systematic Review Results



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ORIGINAL ARTICLE

The Effectiveness of Pharmacological Agents for the Treatment of Uveitic Macular Edema (UMO): A Systematic Review

Mohammad O. Tallouzi, MSc[1,2], David J. Moore, PhD[3], Robert J. Barry, PhD[4], Melanie Calvert, PhD[2,3], Jonathan Mathers, PhD[2,3], Philip I. Murray, PhD[4], and Alastair K. Denniston, PhD[2,5]C

[1]Academic Unit of Ophthalmology, Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, [2]Centre for Patient Reported Outcome Research, Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, [3]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, [4]Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, and [5]Department of Ophthalmology, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

ABSTRACT

Purpose: To conduct a systematic review of effectiveness of pharmacological therapies for treatment of Uveitic Macular Edema (UMO).

Method/Design: Comparative studies of pharmacological therapies in patients with UMO were identified in Cochrane CENTRAL/MEDLINE/EMBASE/CINAHL/trials registers (February 2017). PROSPERO registra- tion: CRD42015019170.

Results: Thirty-one studies were included. Corticosteroids were the most frequently studied (n = 20). Corticosteroids (all forms) were consistently of greater/equal efficacy to active comparators; for anti-VEGF (n = 4) improvement, best-corrected visual acuity (BCVA) and central macular thickness (CMT) were mostly less than local corticosteroid injection; for interferon (n = 1) improvement BCVA and CMT were greater than the comparator of methotrexate; for topical indomethacin (n = 1) improvement, BCVA and CMT were greater than placebo. Non-steroidal anti-inflammatory drugs, carbonic anhydrase inhibitors, and vitamin E (n = 5) were not effective for these outcomes.

Conclusion: The review highlights areas where the evidence base is still lacking, and appropriately focused trials are needed to inform best treatment to tackle this sight-threatening condition.

Keywords: Macular edema, management, meta-analysis, pharmacological agents, systematic review, treatment, uveitis

Uveitis describes a group of disorders characterized by intraocular inflammation. Uveitis is the fifth com- monest cause of visual loss in the developed world and accounts for about 10–15% of total blindness[1,2] and up to 25% in the developing world.[3,4] Although uveitis may affect any age group, it peaks in the working-age population with no significant gender difference.[5] The annual incidence of uveitis is esti- mated at 14–50 per 100 000 with a prevalence of around 38–200 per 100 000 general population.[1,2,5,6]

Macular Edema (MO) is a leading cause of sight-loss in uveitis, due to its impact on the "central vision".[1,7]

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Correspondence: Mohammad O. Tallouzi, Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK; Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT. E-mail: mxt500@bham.ac.uk

Uveitis may be classified anatomically as anterior uvei- tis, intermediate uveitis, posterior uveitis, or panuveitis.[8–10] MO is more common in those forms of uveitis that affect the more posterior structures in the eye, namely intermediate, posterior, or panuveitis; collectively these are sometimes referred to as posterior segment-involving uveitis. Less commonly MO occurs in association with anterior uveitis.[11]

The treatment of Uveitic Macular Edema (UMO) is a major priority in tackling sight-loss in uveitis,[10] and is the focus of this study. In current clinical practice, the mainstay of treatment for UMO is corticosteroid, delivered by various routes, including systemic (oral, intravenous, and intramuscular); local, which includes periocular injection (sub-Tenon and orbital floor injection); and intraocular (intravitreal injection or implant).[10,12,13] Other classes of intervention include non-corticosteroid immunomodulatory agents (e.g. T cell inhibitors (e.g. cyclosporine, tacrolimus)), anti-metabolites (e.g. azathioprine, methotrexate, mycophenolate), alkylating agents (e.g. cyclophosphamide), and biological agents (e.g. interferons, antitumor necrosis factor (anti-TNF)).[14–17] Most of these agents are only used systemically (oral, intravenous, or subcutaneous), while intravitreal use has been reported for both methotrexate and anti-TNF agents.[16–19] Other treatments that have been used in UMO include non-steroidal anti- inflammatory drugs (NSAID), anti-vascular endothelial growth factor (anti VEGF), carbonic anhydrase inhibitor (e.g. acetazolamide), and vitamins.[10,20]

Whilst there have been narrative reviews on the management of UMO,[10] one systematic review published in 2011 has been undertaken to date. The review included RCTs only and had some methodo- logical limitations (lack of steps to minimize bias in the review process).[21] Currently, there are no consen- sus guidelines to direct treatment of UMO, therefore, it is timely to review the literature to summarize the available evidence for the pharmacological agents used for the treatment of UMO.

METHOD

Protocol was registered with PROSPERO database ref (CRD42015019170), and published prior to study commencement.[22] The review and its findings are reported in accordance with the PRISMA guidelines.[23]

Search Strategy

MEDLINE, EMBASE, CINAHL, Cochrane Library, and registers of clinical trials were searched from inception to February 2017.[22] Reference lists of included studies and identified reviews were also searched. The search strategy for each bibliographic database is shown Supplementary Table 1. There was no restriction placed on either language or year of publication; however, for conference abstracts, only those within three years of the search date were considered.

Selection Criteria

Studies were included if meeting the following criteria:

Study design: Randomized controlled trials (RCTs) and other comparative studies where the comparator group was from a concurrent time-period (e.g. non- RCTs, comparative observational studies).

Participants: Participants of any age, gender, or ethnicity with a diagnosis of UMO. Studies on a population broader than UMO were only included if data specific for the UMO subgroup was reported separately.

Intervention and comparator: Any pharmacological agent compared to no use of a pharmacological agent or to another pharmacological agent.

Selection Process

Search results were entered onto EndNote x7 (Clarivate Analytics). Duplicate entries were removed. Titles and abstracts were screened to remove irrelevant records based on the study design, population and intervention. Full texts were retrieved for the remain- ing potentially relevant studies and assessed against the selection criteria. Details of articles excluded at the full text selection stage were recorded along with the reason for exclusion. Translation in part or wholly of non-English language articles was undertaken to aid selection and reviewing.

Two reviewers independently selected, appraised, and extracted data from included articles, with disagreements resolved by discussion and referral to a third reviewer if required. Attempts were made to contact authors for missing information.

Data Extraction

The following data were extracted using standardized forms:

Study characteristics: authors, publication year, journal, study design, setting, sample size, length of follow-up analysis.

Participant's characteristics: patient's selection/recruit- ment criteria, demographic data, type of uveitis

(anatomical categorization, syndrome/aetiological classification), comorbidity, and co-medication.

Intervention and comparator: type, dose, frequency and route of administration, underlying care.

Outcomes: Best-corrected visual acuity (BCVA) (the pri- mary outcome of this review) adverse events, health- related quality of life (QoL), central macular thickness (CMT), assessment of UMO leakage using Fundus fluorescein angiographic (FFA), clinical assessment of UMO, vitreous haze, and anterior chamber cells.

Quality Assessment

The Cochrane risk of bias tool was used to guide appraisal of all studies.[55] For randomized crossover studies, additional criteria such as washout period and carry over treatment effect were used. For con- trolled observational studies, the domains in the risk of bias tool for RCTs were used as a minimum assess- ment (again accepting that the studies were not ran- domized), and noting that the most relevant criteria for assessment in this area relate to how the groups were selected: differences in patient characteristics, loss to follow-up, and biases and confounding in out- come assessment.[55]

Analysis

Data were grouped together from the same study design and by each intervention and comparison, with data tabulated and a narrative synthesis of evi- dence conducted for each outcome of relevance to the review.

Multiple time point data were available within the same study and between studies and considerd in the ranges ≤3 months, >3 and ≤6 months, and >6 months at the end of interventions. The potential for meta- analysis was considered where there was more than one study of the same design in the same population for the same comparison presenting the same type and time point of data for each outcome. No meta- analysis was deemed feasible.

RESULTS

Database searches identified 3891 records, of which 1151 were duplicates. After screening titles and abstracts, full selection criteria were applied to 81 articles which yielded 31 included studies[13,24–54]; of these two studies[28,32] were identified through cross-checking bibliographies of recent reviews[10,21] and two studies through screening references of included studies.[29,39] The study selection process is shown in details of excluded studies are shown in Figure 1. Details of excluded studies are shown in Supplementary Table 2.

Of the 31 included studies, there were 23 rando- mized control trials,[13,25–31,33,36,37,40–50,54]

three randomized crossover trials,[51–53] one intern- ally randomized controlled study (by eye within an individual),[34] and four retrospective cohort studies.[35,38,39,41] Eighteen studies enrolled UMO patients[13,27,29,33–42,48–52] and 13 studies had UMO as a subgroup of all enrolled patients.[24,26,28,30–32,42–47,49] The most frequently encountered class was cortico- steroids agents (n = 20), followed by immunomodula- tory agent (n = 8), anti VEGF (n = 4), NSAIDs (n = 3), carbonic anhydrase inhibitor (n = 3), and vitamins (n = 1). Study characteristics, presented by compari- son, and outcomes measured are shown in Table 1.

Quality Assessment

Quality assessment revealed concerns over allocation concealment for RCTs, and masking for both partici- pants and outcome assessors in observational studies. Summary for Cochrane risk of bias are shown in Figures 2 and Figure 3, Supplementary Table 3 (RCTs), Supplementary Table 4 (crossover RCTs), and Supplementary Table 5 (observational studies).

Types of Studies and Reported Outcomes

The efficacy of intervention for the outcomes of importance for this review (BCVA, CMT, macular leakage) is provided in Table 2 and safety data in Table 3. In addition, any comparisons between inter- ventions (where reported) are highlighted in the text below, and any comparison for each intervention ver- sus baseline (where reported) is provided in the Supplementary Documents.

Corticosteroid

Corticosteroid versus no pharmacological agent. Three RCTs[24–27] compared intravitreal corticosteroid injec- tions to sham, two of which did not report specifically on a UMO subgroup. The remaining RCT, by Shin et al., reported no significant difference between cor- ticosteroid and sham for BCVA, CMT or area of macular leakage at any time point.[27]

Corticosteroid versus different corticosteroid. Two RCTs compared fluocinolone implant to systemic prednisolone.[28,29] Tomkins et al. reported no signifi- cant difference between interventions for BCVA and CMT.[29] In the one study by Pavesio et al. that reported macular leakage, there was a significantl

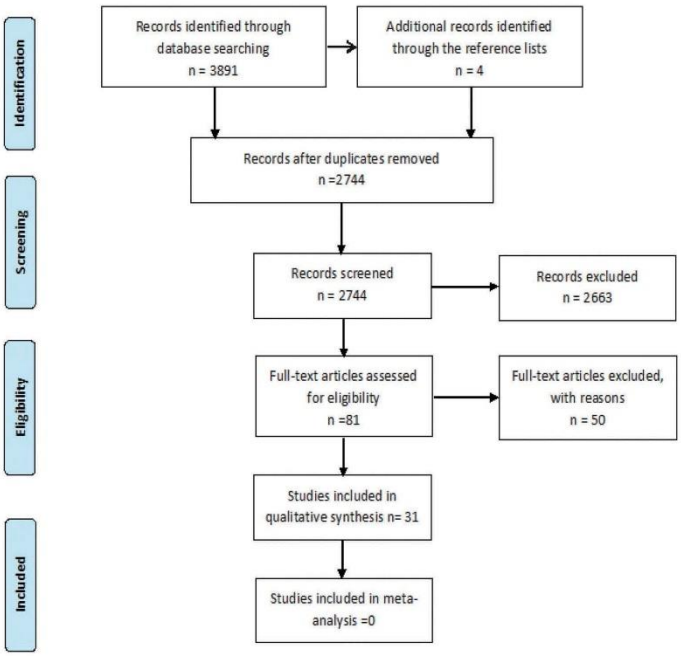

FIGURE 1. PRISMA flow diagram.

greater improvement in intravitreal fluocinolone compared to sytemic prednisolone.[28]

Corticosteroids versus same corticosteroids (Same route but different doses). Three RCTs compared two different doses of fluocinolone implant with limited UMO-specific subgroup data given.[30–32] All studies reported no significant difference between implants for macular leakage at all time points.[30–32]

Same dose and different routes of administration (Corticosteroids versus same Corticosteroids). Two RCTs compared triamcinolone in different routes of administration including subtenon, orbital floor, intravitreal, and subconjunctival routes. Venkatesh reported no significant difference between subtenon and orbital floor method for BCVA and CMT at any time point.[13] However, Chen and Liang reported a significant difference between interventions, for BCVA and CMT favoring subconjunctival group compared to intravitreal triamcinolone.[33]

Corticosteroids versus same corticosteroids (Different route and different dose). Two studies compared triamcinolone administered via intravitreal route to either subtenon route or orbital floor injection at different doses. In comparison between interventions, there was no significant difference at any time point for BCVA in either trial.[34,35] In the one study that reported macular leakage, there was a significantly greater improvement in intravitreal triamcinolone compared to the orbital floor.[35]

Corticosteroids versus anti VEGF. Four studies compared intravitreal triamcinolone to bevacizumab; in the two RCTs, there was no significant difference at any time point for BCVA in either trial.[36,37] Similar findings were noted in the two retrospective cohort studies of the same comparison.[38,39] For CMT, only one study showed a significant difference between interventions, favoring intravitreal triamcinolone. There was reduction in CMT versus baseline in all interventions in all studies, with a potential trend favoring greater benefit with intravitreal triamcinolone compared to anti-VEGF.[36] In the one study by Soheilian et al. that reported macular leakage, there was no-significant difference between interventions.[37]

Corticosteroids versus NSAID. A single RCT compared intravitreal corticosteroid to intravitreal NSAID. In comparison between interventions, there was no

TABLE 1. Study characterisitics, presented by comparison, and outcomes measured.

	Author/year	Design	Population	Intervention	Comparator	Outcomes
Corticosteroids	1. **Corticosteroids vs. Placebo (UMO subgroup no details)**					
	Kuppermann 2007 Williams 2009[24,25]	RCT	CRVO, Irvine-Gass syndrome and DMO	Dexamethasone 350 µg or 700 µg implant (DDS)	Observation	*The proportion of patients achieving 10 letters improvement in BCVA at the day 90 of follow up (ETDRS). The proportion of patients achieved 15 letters improvement in BCVA, the proportion of patients achieved 2 and 3 grade levels of improvement in fluorescein angiogram leakage. Adverse events
	Lowder 2011[26]	RCT	Uveitis/UMO	Dexamethasone 350 µg or 700 µg implant (DDS)	Sham	*BCVA (Snellen chart), CMT, Safety measures, IOP and cataract progression
	Shin 2015[27]	RCT	UMO	Intravitreal Triamcinolone a Acetonide 4 mg	Sham	*BCVA (ETDRS), CMT, IOP and cataract progression
	2. **Corticosteroids vs. Corticosteroids**					
	Pavesio 2010[28]	RCT	Uveitis/UMO	Fluocinolone Acetonide implant 0.59	Standard of Care	*Uveitis recurrence rate, BCVA (LogMAR), macular leakage Safety outcomes (IOP, Lens opacity and adverse events)
	Tomkins-Netzer 2015[29]	RCT	UMO	Systemic prednisolone (1 mg/kg/day up to 60 mg/day)	Fluocinolone Acetonide implant 0.59 mg	*CMO resolution and macula leakage (FFA)/BCVA (Snellen chart)
	3. **Corticosteroids vs. same Corticosteroids different dosing or routes (UMO subgroup no details**					
	Sangwan 2015[30]	RCT	Uveitis/UMO	Fluocinolone Acetonide implant 0.59 mg	Fluocinolone Acetonide implant 2.1 mg	*Change in uveitis occurrence rate pre-implantation and 3 years' post implantation. Evaluating the non-implanted eye anterior chamber activity, vitreous activity BCVA (LogMAR) and rate to post implantation reoccurrence of uveitis, change in BCVA and area of macular edema on FFA. Proportion of eyes requiring systemic therapy or periocular injection. Safety measures (IOP, lens opacity, visual field, ocular adverse events (any IOP<6 mmHg, any loss of ≥3 lines visual acuity from baseline or in the last visit, and retinal tears).
	Callanan 2008[31]	RCT	Uveitis/UMO	Fluocinolone Acetonide implant 0.59 mg	Fluocinolone Acetonide implant 2.1 mg	
	Jaffe 2006[32]	RCT	Uveitis/UMO	Fluocinolone Acetonide implant 0.59 mg	Fluocinolone Acetonide implant 2.1 mg	*Recurrence rate in the implanted eye from the 34 weeks before implantation to the 34 weeks after implantation. BCVA (LogMAR), need for adjunctive therapy, and safety measures.

(*Continued*)

TABLE 1. (Continued)

Author/year	Design	Population	Intervention	Comparator	Outcomes
Venkatesh 2008[13]	RCT	UMO	Triamcinolone Acetonide 20 mg (0.5 ml) cannula method	Triamcinolone 20 mg (0.5 ml) Smith and Nozik method and orbital floor method	*BCVA (LogMAR), anatomical macular changes (OCT), adverse events, and raised IOP
Chen and Liang 2016[33]	RCT	UMO	Triamcinolone Acetonide (0.1 ml) subconjunctival	Triamcinolone (0.1 ml) intravitreal	*BCVA (LogMAR), anatomical macular changes (OCT), adverse events including IOP
Choudhry and Ghosh 2007[34]	RCT (internally randomized within the individual)	UMO	Triamcinolone Acetonide intravitreal 4 mg	Triamcinolone Acetonide subtenon 20 mg	*BCVA (LogMAR), anatomical macular changes (FFA), adverse events including cataract progression and raised IOP
Roesel 2008[35]	Retrospective cohort	UMO	Triamcinolone Acetonide 4 mg intravitreal	Triamcinolone Acetonide 40 mg orbital floor	*BCVA (LogMAR), macular leakage (FFA), adverse events including cataract progression and raised IOP
4. **Corticosteroids vs. other drugs (UMO subgroup no details)**					
a. **Corticosteroids vs. anti VEGF**					
Rahimi 2012[36]	RCT	UMO	Bevacizumab 1.25 mg intravitreal	Triamcinolone Acetonide 4 mg intravitreal	BCVA (LogMAR)/CMT (OCT), AC activity, vitreous activity/adverse events,raised IOPI, and cataract progression
Soheilian 2010[37]	RCT	UMO	Bevacizumab 1.25 mg Intravitreal	Triamcinolone Acetonide 2 mg intravitreal	BCVA (LogMAR), CMT (OCT), macular leakage (FFA), adverse events, IOP, and lens opacity
Lasave 2009[38]	Retrospective Cohort	UMO	Bevacizumab 2.5 mg intravitreal	Triamcinolone Acetonide 4 mg intravitreal	BCVA (LogMAR)/CMT (OCT)/adverse events, IOP, and lens opacity
Bae 2011[39]	Retrospective cohort	UMO	Bevacizumab 1.25 mg intravitreal	Triamcinolone Acetonide 4 mg intravitreal or Triamcinolone Acetonide 40 mg subtenon	BCVA (LogMAR), IOP, CMT, adverse events, IOP, and lens opacity
b. **Corticosteroids vs. NSAID**					
Soheilian 2013[40]	RCT	UMO	Diclofenac 500 mcg/ 0.1 ml Intravitreal	Triamcinolone 2 mg/0.05 m Intravitreal	BCVA (Snellen chat) and (LogMAR), CMT, adverse events, IOP, and lens opacity
Radwan 2013[41]	Retrospective cohort	UMO	Bromfenac (drops)	Bromfenac with either intravitreal Triamcinolone 4 mg or Bevacizumab intravitreal 25 mg/ml	BCVA (LogMAR) and CMT
c. **Corticosteroids vs. anti TNF**					
Markomichelakis 2010[42]	Prospective cohort	Uveitis/UMO	Infliximab intravenous infusion 5 mg/kg	Methylprednisolone 1 g/ day or intravitreal Triamcinolone 4 mg	BCVA (LogMAR), anterior chamber cell activity, vitreous cell activity, degree of inflammation to the posterior segment (retinal vasculitis, retinitis, macular edema, and papilitis)
d. **Corticosteroids vs. T cell inhibitor**					
Nussenbalatt 1991[43]	RCT	Uveitis/UMO	Cyclosporine 10 mg/ Kg oral	Prednisolone 64 mg or 42 mg oral	BCVA ≥ 15 letters (ETDRS), Vitreous haze ≥2 increments and anterior chamber activity

Immunomodulatory	**Imunnomodulatory vs. placebo**					
	Nguyen 2016a[44]	RCT	Uveitis/UMO	Adalimumab (loading dose 80 mg followed by fortnightly 40 mg) subcutaneous	Placebo	(LogMAR), proportion of CMT change, change in AC activity, vitreous haze score, BCVA
	Jaffe 2016[45]	RCT	Uveitis/UMO	Adalimumab (loading dose 80 mg followed by fortnightly 40 mg) subcutaneous	Placebo	BCVA (LogMAR), time to evidence of UMO on OCT, efficacy, and time treatment failure and safety
	Immunomodulatory vs. immunomodulatory					
	Nguyen 2016b[46]	RCT	Uveitis/UMO	Sirolimus 44 µg intravitreal	Sirolimus 440 µg or 880 µg intravitreal	BVCA, *the proportion of eyes with vitreous haze score of 0.5 at 5 months without the use of rescue therapy, the proportion of eyes with vitreous haze score of 0 at 5 months, and adverse events
	Nguyen 2016c[47]	RCT	Uveitis/UMO	Sirolimus 440 µg, intravitreal	Sirolimus 880 µg intravitreal	*BCVA (EDTRS), CMT, vitreous cells, and AC cells safety parameters (adverse events, serious adverse events)
	Mackensen 2013[48]	RCT	UMO	Interferon beta 44 µg subcutaneous three times a day	Methotrexate 20 mg subcutaneous once a week	*BCVA (LogMAR), CMT (OCT), QoL (NEI VFQ-25), Vitreous haze, Ac activity, and adverse events
	Rathinam 2014[49]	RCT	Uveitis/UMO	Methotrexate 25 mg weekly (oral)	Mycophenolate 1 g twice daily (oral)	Change in BCVA, adverse events, and resolution of UMO, *treatment success
NSAID	1. **NSAID vs. Placebo**					
	Allgeri 2014[50]	RCT	UMO	Indomethacin 0.5% drops four times a day	Artificial tears of methyl-hydroxy-propyl-cellulose four times a day	*BCVA (LogMAR) and CFT (central foveal thickness (OCT))
	2. **NSAID vs. anti VEGF**					
	Radwan 2013[41]	Retrospective cohort	UMO	Bromfenac (drops)	Bromfenac with either intravitreal Triamcinolone 4 mg or Bevacizumab intravitreal **	*BCV (LogMAR) and CMT (OCT)
Carbonic Anhydrase inhibitor	**Acetazolamide vs. Placebo**					
	Lashay 2003[51]	Randomized crossover	UMO	Acetazolamide 250 mg orally twice daily	Placebo (multivitamin) PO	BCVA (LogMAR), CMO changes (FFA)
	Whitcup 1996[52]	Randomized crossover	UMO	Acetazolamide 500 mg orally twice daily	Placebo (multivitamin)	CMO grading (FFA), BCVA (Snellen chart) number of letters read, and adverse reaction
	Farber 1994[53]	Randomized crossover	UMO	Acetazolamide 250 mg orally slow release twice daily	Placebo	BCVA (LogMAR), posterior vitreous penetration ratio (PVP, mid vitreous penetration ratio (MVPR), and clinical chemistry)
Vitamin	**Vitamin E**					
	Nussenblatt 2006[54]	RCT	UMO	Vitamin E 1600IU daily (oral)	Placebo (oral)	BCVA (ETDRS) and CMT (OCT)

* The primary reported outcome in the included study- Absence of the star indicates unspecified outcomes in terms of primary or secondary.**Dosage of Bevacizumab was not reported.

FIGURE 2. Risk of bias summary for RCTs.

significant difference at any time point for BCVA and CMT.[40]

Corticosteroids vs immunomodulatory. Two studies compared corticosteroid to immunomodulatory agents[42,43]; one of which did not report specifically on a UMO subgroup. The remaining RCT with UMO subgroup, by Nussenblatt et al., did not report any data on the difference between interventions; however, a complete resolution of macular leakage was reported in both interventions.[43]

Immunomodulatory

Biological agent (Anti-TNF) versus placebo. Two RCTs, (VISUAL I) and (VISUAL II), compared anti-TNF to placebo. UMO was a subgroup of the study population, with no UMO-specific subgroup data given, and no further evaluation was possible.[44,45]

Antimetabolites versus antimetabolites. A single RCT compared methotrexate to mycophenolate. In comparison between interventions, there was no significant difference for UMO resolution at any time point.[49]

T-cell inhibitor versus T-cell inhibitor. Two RCTs by Nguyen et al. compared three different doses of intravitreal sirolimus.[46,47] Limited UMO subgroup data was provided, with no reported statistical comparisons either to baseline or between interventions for CMT or BCVA and macular leakage.

Biological agent versus antimetabolites. A single RCT compared Interferon beta to methotrexate, with a significant difference between interventions favoring interferon beta for BCVA and CMT.[48]

Anti VEGF

Anti-VEGF agents were compared to corticosteroids and are addressed earlier in section Corticosteroids vs anti VEGF.

NSAID

NSAID versus placebo. A single RCT compared indomethacin 0.5% to methyl-hydroxy-propyl-cellulose. In comparison between interventions, there was no significant difference for BCVA and CMT.[50]

NSAID versus (NSAID and corticosteroid (triamcinolone) or NSAID) and anti VEGF. A retrospective cohort study compared a NSAID to a combination of the same NSAID with either intravitreal anti VEGF or intravitreal corticosteroid. There was no significant difference between interventions for BCVA and CMT, despite the statistical significance from baseline in dual therapy groups.[41]

Carbonic anhydrase inhibitor

Carbonic Anhydrase inhibitor (Acetazolamide) versus placebo. Three randomized crossover studies compared carbonic anhydrase inhibitor (acetazolamide) to placebo. All studies reported no significant benefit of acetazolamide on BCVA.[51–53] In the one study by Whitcup et al., acetazolamide was associated with significantly greater reduction in macular leakage compared to placebo.[52]

Vitamins

Vitamin E vs placebo. A single RCT compared vitamin E to placebo. The study reported no significant

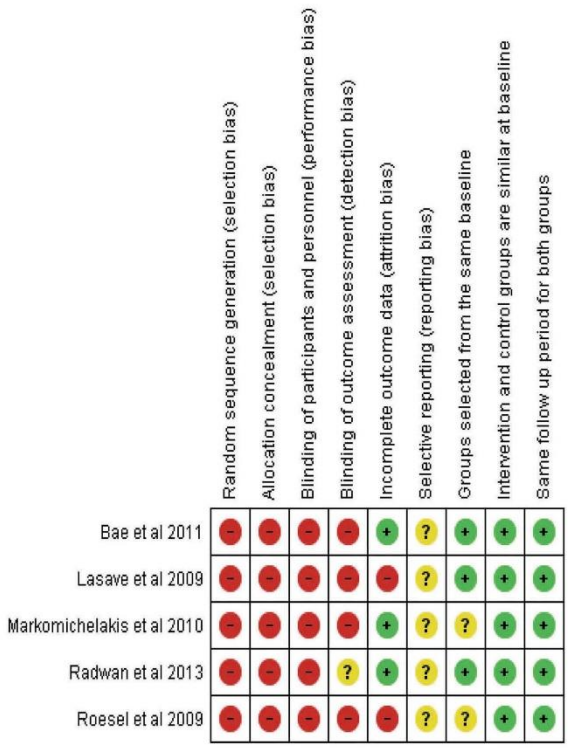

FIGURE 3. Risk of bias summary for observational studies.

difference between groups for BCVA, CMT, and macular leakage.[54]

Adverse Events (AEs)

Corticosteroids

Raised intra-ocular pressure (IOP) and cataract progression were the most commonly reported adverse events in studies using corticosteroid, especially after local administration. Elevated IOP (from baseline) was reported in 8 studies, the proportion of participants with raised IOP being 10–40% occurring over 4–12 weeks follow-up, including different routes of administration (six intravitreal, one subtenon, one subconjunctival, and one orbital floor). Only four of these studies reported additional use of medical IOP-lowering treatment for IOP>22 mmHg (range of 10–16%)[27,34,35,39] and one study reported one patient requiring glaucoma surgery (representing 5% of those who had had intravitreal triamcinolone in that study).[38]

Cataract progression was reported in five studies after local injection of triamcinolone, the proportion of participants was ranging from 5% to 68% (intravitreal 14–68%, orbital floor 27%, subconjunctival 15%) between 6 and 12 months of follow-up.[27,35,37,38,40] There were no studies that provided UMO subgroup–specific data for AE in systemic versus local corticosteroid therapy.

Other reported ocular adverse events occurred predominantly after local therapies of corticosteroid injections comprised subconjunctival hemorrhage (5–10%),[33] vitreous opacity, requirement for vitrectomy, and vitreous hemorrhage that resolved spontaneously.[36] Blepharoptosis was also reported in one patient following subtenon corticosteroid injection which resolved spontaneously.[39]

Immunomodulatory

Flu-like symptoms (46%) were the most common AEs in interferon beta; with one further serious AE (hypertensive crisis in a patient with known systemic hypertension) (11%) was reported.[48] However, nausea

TABLE 2. Mean BCVA, CMT and area of macular leakage.

Study	Interventions	BCVA (Baseline)	BCVA ≤3months	BCVA >3 and ≤6 months	BCVA >6 months	CMT (Baseline)	CMT ≤ 3 months	CMT >3 and ≤6 months	CMT >6 months	Mean area of UMO at baseline	Mean area of macular leakage/Proportion of resolved leakage
1. Corticosteroids											
I. Corticosteroids vs. Placebo											
Shin 2015[27]	IVTA	69 ± 9.6 (EDTRS)	70(EDTRS)	74(EDTRS)		337 ± 83 μm	270 μm $P = 0.014$	245 μm		2.3 ± 1.91	0.95 ($P = 0.025$) –3 month 0.85 (S) 6 months
	Sham	70 ± 9.0 (EDTRS)	73(EDTRS)	69 (EDTRS)		312 ± 59 μm	280 μm ($P = 0.02$)	270 μm		3.6 ± 4.99	3.6 (NS) 0.75 (S) –6 months
	Intergroup comparison		NS	NS			NS	NS			NS from month 4 onward
I. Corticosteroids vs. Corticosteroids											
Pavesio (2010)[28]	0.59 mg fluocinolone implant										87% 2 years (NR)
	Standard of care										74% 2 years (NR)
	Intergroup comparison										$P = 0.003$ favoring implanted eyes
Tomkins-	Netzer 2015[29]	0.59 mg		68% (NR)2 years Resolution 77% (NR) 2 years	fluocinolone implant Improvement	62 58%. (NR) –2 years	(EDTRS) median			68 (EDTRS) median (NR) 2 years	
	Systemic prednisolone	63 (EDTRS) median			67 (EDTRS) median (NR) 2 years					52% (NR) 2 years Resolution 65% (NR) 2 years Improvement	31% (NR) –2 years
Intergroup	comparison				$P = 0.86$				$P = 0.28$ $P = 0.20$		$P = 0.12$–2 years
Sangwan 2015[30]	0.59 mg fluocinolone implant									38.0mm^2	9 mm^2 (NR) –34 weeks 6 mm^2 (NR) 3 years
	2.1 mg fluocinolone implant									46 mm^2	5 mm^2 (NR) –34 15 mm^2 (NR) –3 years
	Intergroup comparison										$P < 0.0001$ favoring implanted eyes at both visits

Callanan 2008[31]	0.59 mg fluocinolone implant						33mm^2		7 mm^2 ($P < 0.01$)- 1 year 6 mm^2 ($P < 0.01$)-3 years
	Non-implanted eyes of 0.59 mg						25mm^2		26 mm^2) ($P = 0.91$) –1 year 25 mm^2 ($P = 0.80$) 3 years S favoring 0.59mg fluocinolone implant
	2.1 mg fluocinolone implant						30 mm^2		5 mm^2 $P < .01$) 1 year 23 mm^2 ($P = 0.44$) (3 years
	Non-implanted eyes of 2.1 mg						18 mm^2		15 mm^2 ($P = 0.23$) 1 year 19 mm^2 ($P = 0.39$) 3 years S favoring 2.1 mg fluocinolone implant at 1 year only NR between implants
	Intergroup comparison								
Jaffe 2006[32]	0.59 mg fluocinolone implant and 2.1 mg i fluocinolone mplant (combind)				25% achieved 3 or more line of BCVA on LogMAR		36 mm^2		7 mm^2 ($P < 0.05$) 34 weeks
	Non-implanted eyes				5.3% achieved 3 or more line of BCVA on LogMAR		42 mm^2		29 mm^2 (NS) 34 weeks
	Intergroup comparison				NR				$P < 0.0001$ favoring implanted eyes
Venkatesh[13]	PSTA (Cannula method)	0.65 LogMAR	0.15 LogMAR ($P = 00$)			382 ± 174 µm	214 ± 35 µm ($P = 00$)		
	PSTA (Smith and Nozik)	0.60 LogMAR	0.14 LogMAR ($P = 00$)			310 ± 85 µm	208 ± 29 µm ($P = 00$)		
	OFTA	0.65 LogMAR	0.19 LogMAR ($P = 00$)			373 ± 101 µm	262 ± 74µm ($P = 003$)		
	Intergroup comparison		$P = 0.759$				$P = 0.83$		
Chen & Liang 2016[33]	IVTA	2.9 ± 1.1 (SWR)	4 ± 1.4 (NR)			493 ± 99 µm	256 ± 85 µm (NR)		
	Sub conj (TA)	3.0 ± 1.2 (SWR)	4.8 ± 1.3(NR)			485 ± 101 µm	214 ± 66 µm (NR)		
	Intergroup comparison		$P < 0.05$ favoring Sub conj (TA)				$P < 0.05$ favoring Sub conj (TA)		

(*Continued*)

TABLE 2. (Continued)

Study	Interventions	BCVA (Baseline)	BCVA ≤3months	BCVA >3 and ≤6 months	BCVA >6 months	CMT (Baseline)	CMT ≤ 3 months	CMT >3 and ≤6 months	CMT >6 months	Mean area of UMO at baseline	Mean area of macular leakage/Proportion of resolved leakage
Choudhury & Ghosh 2007 [34]	IVTA	0.67 ± 0.10 LogMAR	0.22 ± 0.15 LogMAR (NR)	0.22 ± 0.10 LogMAR (NR)							78% (NR) –3 months 89% (NR) –6 months
	PSTA	0.69 ± 0.14 LogMAR	0.28 ± 0.21 LogMAR (NR)	0.22 ± 0.15 (NR)							56% (NR) –3 months 78% (NR) –6 months
	Intergroup comparison		$P = 0.74$	$P = 0.99$							$P = 0.32$ –3 months $P = 0.53$ –6 months
Roesel 2009 [35]	IVTA	0.61 ± 0.35 LogMAR	0.47 ± 0.31 LogMAR ($P = 0.02$)	0.62 ± 0.33 LogMAR (NR)	0.67 ± 0.33 LogMAR (NR)	NA					100% -(S)-1 and 3 months 75% -(NR) 6 months 42% (NR)-12 months
	OFTA	0.58 ± 0.39 LogMAR	0.46 ± 0.38 LogMAR ($P = 0.03$)	0.47 ± 0.38 LogMAR (NR)	0.44 ± 0.31 LogMAR (NR)	NA					76%(NR)-1 month 20% (NR)-3, 6 and 9 months
	Intergroup comparison		$P = 0.86$	0.10	0.018						$P = 0.36$ (1 months) $P < 0.05$ (3 months) $P = 0.1$ (6 months) $P = 0.56$ (12 months)
I. Corticosteroids vs. other drugs											
a. Corticosteroids vs. anti VEGF											
Rahimi 2012 [36]	IVTA	0.48 ± 0.22 LogMAR	0.07 ± 0.06 LogMAR ($P < 0.001$)	0.03 ± 0.04 LogMAR ($P < 0.001$)	NA	296 ± 33 µm	218 ± 29.0 µm ($P < 0.001$)	199 ± 28 µm ($P < 0.001$)	NA		
	IVB	0.47 ± 18 LogMAR	0.06 ± 0.06 LogMAR ($P < 0.001$)	0.03 ± 0.04 LogMAR ($P < 0.001$)	NA	310 ± 52 µm	234 ± 13 µm ($P < 0.001$)	221 ± 12 µm ($P < 0.001$)	NA		
	Intergroup comparison		$P = 0.772$	$P = 0.326$			$P = 0.010$ favoring IVTA	$P < 0.001$ favoring IVTA			

Soheilian 2010[37]	IVTA	0.85 ± 0.34 LogMAR	Δ –	Δ –	Δ −0.32 ± 0.32 LogMAR (P = 0.001)	361 ± 138 μm	Δ −56 ± 76μm (P = 0.016)	Δ –	Δ –		60% (P = 0.005)	
			0.14 ± 0.30 LogMAR (P = 0.95)	0.29 ± 0.32 LogMAR (P = 0.004)				69 ± 86μm (P = 0.010)	75 ± 106μm (P = 0.03)		12 weeks 65.8% (P = 0.002) 24 weeks 78.6%(P = 0.003) 36 weeks	
	IVB	0.95 ± 0.38 LogMAR	Δ –	Δ –	Δ −0.35 ± 0.45 LogMAR P = 0.016	387 ± 184 μm	Δ −57 ± 111 μm (P = 0.091)	Δ 1 ± 143μm (P = 0.985)	Δ −42 ± 171 μm (P = 0.483)		38.5%(P = 0.206)- 12 weeks 57.1% (P = 0.089) –24 weeks (69.2% P = 0.031) –36 weeks	
			0.19 ± 0.21 LogMAR (P = 0.005)	0.29 ± 0.25 LogMAR (P = 0.004)								
	Intergroup comparison		P = 0.775	P = 0.770	P = 0.936		P = 0.894	P = 0.077	P = 0.338		P = 0.098 –12 weeks P = 0.176 –24 week P = 0.359 –36 weeks	
Lasave 2009[38]	IVTA	1.1 ± 0.2 LogMAR (P < 0.001)	0.7 ± 0.4 (P < 0.001)	0.7 ± 0.3 (P < 0.001)		455 ± 239 μm	289 ± 141 μm (P < 0.0001)	296 ± 134 μm (P = 0.001)				
	IVB	1.2 ± 0.4 LogMAR (P = 0.006)	1 ± 0.3 LogMAR (P = 0.031)	0.8 ± 0.4 LogMAR (P = 0.031)		401 ± 142 μm	323 ± 105 μm (P = 0.012)	345 ± 135 μm (P 0.056)				
	Intergroup comparison		NR	NR			NR	NR				
Bae 2011[39]	IVTA	0.73 ± 0.33 LogMAR (P < 0.001)	0.43 LogMAR (P < 0.001)			594 ± 151 μm	Δ −325 ± 233 μm (P < 0.001)					
	PSTA	0.71 ± 0.23 LogMAR (P < 0.001)	0.58 LogMAR (P < 0.001)			582 ± 146 μm	Δ −166 ± 227 μm (P < 0.001)					
	IVB	0.73 ± 0.41 LogMAR (P < 0.011)	0.56 LogMAR (P < 0.011)			537 ± 214 μm	Δ −167 ± 154 μm (P < 0.001)					
	Intergroup comparison		P = 0.869				P = 0.636					
a. Corticosteroids vs. NSAID												
Soheilian 2013[40]	IVTA	0.75 ± 0.49 LogMAR (P = 0.043)	0.63 ± 0.48 LogMAR (P = 0.043)	0.48 ± 0.49 LogMAR (P = 0.043)	0.58 ± 0.39 LogMAR (P = 0.80)	642 ± 289 μm	335 ± 109 μm (P = 0.018)	407 ± 92 μm (P = 0.028)	510 ± 194μm (P = 0.398)			
	IVDS	0.67 ± 0.22 LogMAR (P > 0.99)	0.69 ± 0.39 LogMAR (0.786)	0.70 ± 0.37 LogMAR	0.64 ± 0.35 LogMAR (0.779)	488 ± 104 μm	439 ± 161 μm (P = 0.123)	404 ± 196 μm (P = 0.161)	403 ± 132μM (P = 0.123)			
	Intergroup comparison		P = 0.779	P = 0.281	P = 0.463		P = 0.281	P = 0.955	P = 0.613			
a. Corticosteroids vs. T cell inhibitor												
Nussenblatt 1991[43]	Cyclosporine										47%	
	Prednisolone										63%	
	Intergroup comparison										P = 0.376	

(Continued)

TABLE 2. (Continued)

Study	Interventions	BCVA (Baseline)	BCVA ≤3months	BCVA >3 and ≤6 months	BCVA >6 months	CMT (Baseline)	CMT ≤ 3 months	CMT >3 and ≤6 months	CMT >6 months	Mean area of UMO at baseline	Mean area of macular leakage/Proportion of resolved leakage
1. Immunomodulatory Agents											
I. Immunomodulatory vs. immunomodulatory											
Nguyen 2016[47]	Sirolimus 44 μg implant							46% (NR) 5 months			
	Sirolimus 440 μg implant							55% (NR) 5 months			
	Sirolimus 880 μg implant									49%(NR) 5months	
Nguyen 2016[46]	Sirolimus440 μg implant					461 ± 139 μm	403 ± 148 μm (NS)	419 ± 160 μm (NS)			57% (NS) –3months
	Sirolimus880 μg implant					375 ± 89 μm	313 ± 66 μm (NS)	457 ± 204 μm (NS)			28% (NS)-6months 83% (NS)-3 months
	Intergroup comparison						NS	NS			67% (NS)-6 months
Mackensen 2013[48]	Interferon beta	0.48 LogMAR	0.16 LogMAR		(P = 0.0039)			430 μm	228 μm (P = 0.0039)		NS
	Methotrexate	0.34 LogMAR	0.25 LogMAR		(P = 0.1309)			371 μm	409 μm (P = 0.781)		
Intergroup	comparison		P = 0.0435 favoring interferon			P < 0.0001 favoring	interferon				
Rathinam 2014[49]	Methotrexate										77% (NR)-5 months
	Mycophenolate mofetil										54% (NR)- 5 months
	Intergroup comparison										P = 0.31
1. Anti VEGF											
Anti-VEGF agents were compared to corticosteroids and are addressed above											
1. NSAID											
I. NSAID vs. Placebo											
Allgeri 2014[50]	Indomethacin 0.5%	0.4 average in decimal	0.47 average in decimal (P < 0.001)	0.56 average in decimal	(P < 0.0001)		446 ± 149 μm	360 μm (P < 0.001)	280 μm (P < 0.001)		
	Placebo	0.52 average in decimal	0.5 average in decimal NS	0.55 average in decimal NS		390 ± 162 μm	405 μm (NS)	410 μm (NS)			
Intergroup	comparison		P < 0.001	P < 0.001			P < 0.001	P < 0.001			
I. NSAID vs. anti VEGF											

Radwan 2013[41]	Bromfenac	0.39 ± 0.25 LogMAR	0.31 ± 0.27 LogMAR (P = 0.911)			354 ± 97 μm	302 ± 63 μm (P = 0.145)						
	IVB+ Bromfenac	0.55 ± 0.24 LogMAR	0.35 ± 0.23 LogMAR (P = 0.001)			459 ± 155 μm	288 ± 81 μm (P = 0.002)						
	IVTA + Bromfenac	0.52 ± 0.50 LogMAR	0.33 ± 0.55 LogMAR (P = 0.017)			423 ± 175 μm	260 ± 46 μm (P = 0.009)						
	Intergroup comparison		P = 0.928				P = 0.279						
1. Carbonic Anhydrase inhibitor (Acetazolamide)													
1. Acetazolamide vs. placebo													
Whitcup 1996[52]	Acetazolamide	48(EDTRS) (20/100–2 Range 15–70	48(EDTRS) (20/100–2) Range 8–72							2.1 Range 0.0–20.0	1.5 Range 0.0–5.0		
	Placebo	49(EDTRS) 20/100–1) Range 8–76	51 (EDTRS) (20/ 100 + 1) Range15–78							2 Range 0.2–20.0 2.1	2.0 Range 0.0–20.0		
	Intergroup comparison		NS								P = 0.01		
Lashay 2003[51]	Acetazolamide	0.537 LogMAR Range 0.1–1.5	0.448 LogMAR Range 0.1–1.5							1.892 Range 0–4	1.678 Range 0–4 (P = 0.99)		
	Placebo	0.430 LogMAR Range 0.1–1.5	0.430 LogMAR Range 0.1–1.5					Range 0–4		1.643 Range 0–4	1.714 Range 0–4		
	Intergroup comparison		NS									NS	
Farber 1994[53]	Acetazolamide	0.57LogMAR	0.49 LogMAR P = 0.01							DNA	DNA	DNA	
	Placebo	0.51 LogMAR	0.50 LogMAR							NR	NR	NR	
	Intergroup comparison		NS							NR	NR	NR	
1. Vitamin													
Vitamin E vs. placebo													
Nussenblatt 2006[54]	Vitamin E	59 ± 5 (EDTRS) SWR	54 ± 5 (EDTRS) 4 months			232 ± 47 μm		367 ± 59 μm 4 months					
	Placebo	57 ± 6 (EDTRS) SWR		56 ± 6 (EDTRS) (NS) 4 months			467 ± 124 μm		392 ± 119 μm (NS) 4 months				
	Intergroup comparison							NS					

(*Continued*)

NS

PSIU: Posterior Segment Involving Uveitis,
IVTA: Intravitreal triamcinolone acetonide,
PSTA: Posterior subtenon triamcinolone acetonide,
OFTA: Orbital floor triamcinolone acetonide,
VB: Intravitreal bevacizumab, IVDS: Intravitreal diclofenac sodium,
NS: Non-significant change from baseline with no reported *P* value.
P value in brackets represents the comparison to the baseline
S: Reported as significant from baseline but no *P* value
NR: Not reported as significant or non-significant and no *P* value
SWR: Scale was not reported.
AP value without brackets represents the group comparison
Δ Represent the mean change from baseline CMT values were rounded to the nearest value
NB: Data in the above table represent the latest available data within the follow-up in the given time points (e.g. ≤3months would include 3months data).

(19%) and headache (20%) were the most common AEs in methotrexate and mycophenolate.[48,49]

Non-steroidal anti-inflammatory drugs (NSAID)

Posterior subcapsular cataract was the only reported AE following intravitreal injection of diclofenac sodium (13%).[40]

Anti VEGF

Hypopyon (a visible layer of inflammatory cells in the anterior chamber) was the only reported AE following bevacizumab injection (7%).[37]

Carbonic Anhydrase inhibitor (Acetazolamide)

In the two studies that reported AEs with acetazolamide, non-serious AEs include paraesthesia, nausea, drowsiness, weight loss, fatigue, allergic reaction, mild nausea, pins and needles.[52,53] In the one study by Farber et al., severe AEs were reported including severe allergic reaction, severe diuresis, and hematuria.[53]

Vitamins

No AEs were reported.[43]

DISCUSSION

This systematic review provides a comprehensive overview of the pharmacological agents used to treat UMO. Of the 31 included studies, most were RCTs (70%), the remainder being randomized crossover trials (10%), prospective cohort studies (6%), and retrospective cohort studies (13%). A critical distinction was between those which enrolled UMO patients (65%) and those studies that enrolled UMO as a subgroup of all enrolled patients (35%). There were, therefore, relatively few studies that met the ideal scenario of being a well-designed RCT specifically enrolling UMO patients (35%). Our study, therefore, highlights that for many of these pharmacological agents, there is little evidence for them being effective and safe in UMO.

The relative scarcity of RCT data for these agents in UMO is highlighted by the fact that there were no agents for which there were sufficient homogenous trials for a meta-analysis. It is worth noting that a previous systematic review by Karim et al.[21] did undertake a meta-analysis of acetazolamide, based on the three trials which we also identified.[51–53] In our opinion, the different doses and formulations of acetazolamide used across these three studies precluded a meta-analysis, so we have simply presented this data in narrative format.

Of the agents considered within this review, the most commonly used are corticosteroids. Increasingly these are being given locally, including

TABLE 3. List of adverse events.

Study	Raised IOP from baseline	Cataract progression	Other Ocular AEs	Systemic AEs
1. Corticosteroids				
1. *Corticosteroids vs. corticosteroids*				
Shin 2015[27]	A higher mean change from baseline in IVTA group vs. sham at 1,2, and 3 months. *No further data reported.*	25% (IVTA) and 15% (sham) at 6 months (IVTA) phakic patients are 64% (Placebo) phakic patients are 55%	No other ocular adverse event related to the study groups	No systemic AEs
Chen 2016[33]	41% (IVTA) 29% (SConjTA) Time point and definition of raised IOP was not reported	Not reported	*Subconjunctival hemorrhage:* 5% (IVTA) and 5% (SConjTA) *Inflammation:* 10% (IVTA) and 2% (SConjTA) *Recurrence of UMO:* 22% (IVTA) and 5% (SConjTA) *Retinal detachment* 2% (IVTA) and 0% (SConjTA)	Not reported
Venkatesh 2008[13]	30% (Cannula PSTA) 40% (Smith and Nozik PSTA) 10% (OFTA). At 1 week	Not reported	Other adverse events such as ptosis, fat prolapse and fat necrosis were not noted in the study	No systemic AEs
Choudhry & Ghosh 2007[34]	10% IVTA (at 1 week); contralateral eye was therefore not given the intended PSTA	No corticosteroid related cataract progression	No other ocular AEs	No systemic AEs
1. *Corticosteroids vs. anti-VEGF*				
Roesel 2008[35]	20% (IVTA) and 0% (OFTA) at 1 month	68% (IVTA) 27% (OFTA) At 12months	No other AEs related	No systemic AEs
Rahimi 2012[36]	Higher from baseline to 20.0 mmHg (IVTA)) vs. 17.8 mmHg (IVB). Time point not reported and no data on baseline IOP	No cataract progression	No other ocular AEs	No systemic AEs
Soheilian 2010[37]	No cases of raised IOP	31% (IVTA), cataract surgery was performed in one patient (20%) No cataract progression in IVB	*Hypopyon* 7% (IVB) and 0% (IVTA) *Vitreous opacity* 7% (IVB) and 0% (IVTA) *Vitreous hemorrhage* 6% (IVTA) and 0% (IVB)	No systemic AEs

(*Continued*)

TABLE 3. (Continued)

Study	Raised IOP from baseline	Cataract progression	Other Ocular AEs	Systemic AEs
Lasave 2009[38]	*Baseline to 3 months:* 15.1 mmHg to 21.5mmHg (IVTA) 15.4 mmHg to 16.6mmHg (IVB) *Surgical glaucoma treatment:* 5% (IVTA) and 0% (IVB)	5% (IVTA) 0% (IVB) At 12 months	No other ocular AEs	No systemic AEs
Bae 2011[39]	*Baseline to follow-up (time point not reported):* 12.4 mmHg to 19.6 mmHg(IVTA) 11.6 mmHg to 13.4mmHg (IVB) 12.1 mmHg to 17.3 mmHg(PSTA) *Surgical glaucoma treatment:* *9% (IVTA), 0% (PSTA) and 0% (IVB)* *Percentage of eyes with increased IOP>5 mmHg (Time point not reported)* *45.5% (IVTA, 40% (PSTA) and 10% (IVB)*	No cataract progression in any of the study group	*Blepharoptosis* 10% (PSTA) 0% (IVTA and IVB)	No systemic AEs
Soheilian 2013[40]	No episodes of increased IOP	14% (IVTA)	No other ocular AEs	No systemic AEs
1. Immunomodulatory agents				
Mackensen 2013[48]	No reported episodes of increased IOP	No reported cataract progression in the study groups	No reported ocular AEs e	SAE: Hypertensive crisis (INF) in 11% required hospitalization. *Most common AEs 46% in INF was flu-like symptoms and most common AEs 19% in MTX were nausea and infections (pharyngitis, urinary tract infection)* *Infection site injection (INF 17%, MXT 15%)* *Tiredness (INF 2%, MXT 11%)* *Thrombophlebitis (INF 2%, MXT 0%)* *Muscle cramps (INF 21%, MXT 19%)* *Nausea (INF 4%, MXT 19%)*

Rathinam[49]	10% (MXT) 5% (MM)	12%(MXT) 8% (MM)	*Vitreous hemorrhage* 2% (MXT) 0% (MM) *Hypotony* 0% (MXT) 2% (MM) *Acute catarrhal* 2% (MXT) 0% (MM)	Non-serious adverse events were reported in 80% of the MXT and 82% of the MM. *Headache was the most common AE 20% in MXTand 31% in* MM *Fever for 12 hours (MXT 5%,* MM 23%) *Nausea (MXT 15%,* MM 5%) *Systemic infection (MXT 10%,* MM 7%) *Vomiting (MXT 7%, MM 5%)* *Diarrhoea and fatigue (MXT 10%,* MM *10%)* *Dyspnoea, mood changes and cardiac dysfunction was reported in 3% of the* MM *and non-in MXT group*
1. NSAIDs				
Soheilian 2013[40]	No reported episode of increased IOP	PCO (12.5%) (diclofenac sodium)	No other ocular AEs	No systemic AEs
1. Anti VEGF Anti-VEGF agents are addressed earlier				
1. Carbonic Anhydrase inhibitor (Acetazolamide)				
Farber 1994[53]	No reported episodes of increased IOP	No reported cataract progression in the study groups	No reported ocular AEs	Acetazolamide: Severe allergic reaction, severe diuresis, hematuria, severe fatigue, muscle cramps, body rash, excessive paraesthesia in extremities, nausea, drowsiness, weight loss and chronic fatigue
Lashay 2003[51]	No reported episodes of increase IOP	No reported cataract progression in the study groups	No reported ocular AEs	Acetazolamide: six non-compliant patients to acetazolamide. No further details reported
Whitcup 1996[52]	No reported episodes of increase IOP	No reported cataract progression in the study groups	No reported ocular AEs	92% (acetazolamide), 14% (placebo). Instances of paraesthesia, nausea, drowsiness, weight loss, chronic fatigue, cutaneous allergic reaction, mild nausea, pins, and needles
1. Vitamin No reported adverse events				

PSIU: Posterior Segment Involving Uveitis, *IVTA*: Intravitreal triamcinolone acetonide, *PSTA*: Posterior subtenon triamcinolone acetonide, *OFTA*: Orbital floor triamcinolone acetonide, *IVB*: Intravitreal bevacizumab, *IVDS*: Intravitreal diclofenac sodium, *TA*: Triamcinolone acetonide, *MXT*: Methotrexate, *MM*: Mycophenolate Mofetil, *PCO*: Posterior Capsular Opacification.

via intravitreal slow-release implants. Our review highlights the potential value of these being effective in reducing UMO and avoiding systemic side-effects. It also underlines the significant rates of ocular adverse events, notably secondary IOP elevation (leading on to glaucoma) and cataract of all local corticosteroid therapies, regardless the route of administration. Another drug of current interest is the anti-TNF agent, adalimumab. The high-profile VISUAL studies have led to its licensing for the treatment of posterior segment involving non-infectious uveitis,[44] but the lack of UMO-specific subgroup data means that we cannot yet evaluate its potential role in the treatment of UMO. A significant number of other immunomodulatory agents have been trialled in UMO, but relatively few in a study design that allows firm conclusions as to relative benefit. It is perhaps worth highlighting that the study by Mackensen's et al found methotrexate to be significantly less effective in the treatment of UMO than interferon beta.[48] In most uveitis centers in the USA and the UK, it is more common to use methotrexate (or in recent years' mycophenolate mofetil) whereas interferon beta is rarely used. Mackensen argues that interferon should be the treatment of choice for UMO.[48] There are however two caveats: first, the drug-related morbidity is significantly higher with interferon (particularly low mood)[48]; and second, this is only a single study.

The major strengths of this review are that it provides the most comprehensive literature review of the treatment of UMO to date. Studies were selected, assessed, and extracted following the pre-specified published protocol[22] and according to PRISMA guidelines.[23] The index and free text terms for the condition (MO) and the disease context (uveitis) were used to broaden the search and capture all the available records. All measures were taken to avoid missing records including: checking the reference lists of the included reviews/studies; seeking opinions of experts of existing knowledge in the field of uveitis and UMO and contacting authors to provide missing or unclear data; and avoiding language or date restrictions.

An additional strength of this systematic reviewwas that it included non-randomized, as well as randomized studies. Whilst we acknowledge the potential allocation bias in not randomizing, the inclusion of such studies can provide useful additional evidence; particularly as such studies often have longer follow-up periods and may identify adverse events that would not be identified through RCTs, which may comprise far fewer patient-years of follow-up.

The major limitation lies in the reporting of the primary studies and the likely gap between the volume of UMO-specific data assessed here, and the much larger volume of data that will have been collected patients with UMO as part of studies on posterior segment involving uveitis (PSIU). The primary reason for this gap is that studies with broad PSIU inclusion criteria (e.g. the VISUAL studies) often include a significant proportion of patients with UMO, and yet many do not report the data relating to these patients as a separate subgroup. It is interesting to note that in some of these studies CMT is reported for the whole group even without specific discussion of the diagnosis of UMO. In this context, a reduction in CMO, often accompanied by an improvement in visual acuity, does provide indirect evidence that an intervention is effective in UMO. Our pre-specified protocol, however, excluded such data since such studies do not specifically report the UMO group (or subgroup), and thus no firm conclusion can be drawn as to an intervention's effect in this group.

In terms of evaluating the comprehensiveness of the searches, as with any systematic review, there is always the concern as to whether searches retrieved all appropriate literature. This is more likely where the population of interest is a subgroup of a study. It is possible that some relevant articles may have been missed due to indexing, such as where UMO was a subgroup and was not specified in the title or abstract.

Overall, the greatest challenges here are the paucity of evidence on which to base an assessment of the effectiveness of the pharmacological agents in the treatment of UMO, and the variable methods of reporting including time points. Our review highlights priority areas for future RCTs, for example, the need for head-to-head studies for many of the major immunomodulatory drugs, and the need to conduct studies which are either exclusive to UMO or are designed to include stratification according to presence or absence of UMO and report the UMO-subgroup data. This is needed if we are to define the relative efficacy and safety of these agents and define their place in treatment pathways. For example, the VISUAL studies have resulted in the licensing of adalimumab for PSIU in the USA and Europe, but it is not clear the extent to which adalimumab would be of value for those patients where UMO would be the primary sign of uveitis activity.

We have discussed elsewhere the challenges of designing and delivering clinical trials in uveitis,[56] but UMO itself should be relatively amenable to clinical trial evaluation, having the advantage of a sensitive objective instrument-based measure.[57] Furthermore, of all the indicators of disease activity in uveitis, UMO is the sign most closely associated with an effect on visual function.[58] In light of this, it is surprising that there are so few high quality RCTs evaluating the major interventions in UMO. This may in part be due to the desire of the major pharmaceutical companies to secure as broad a license as

possible e.g. "posterior segment involving uveitis rather than the narrower 'UMO'". Our review high- lights the need for more well-designed, adequately powered UMO-specific RCTs.

In summary, this systematic review provides a comprehensive overview of the pharmacological agents used to treat UMO. It is the largest systematic review in the field to date and is particularly relevant in the context of the changing landscape of uveitis treatment in which new therapies, such as the dexa-methasone implant (Ozurdex) and adalimumab now being licensed for the treatment of posterior segment- involving uveitis. Whilst this review presents the available evidence to support pharmacological inter- vention in UMO for a range of drugs and routes of administration, it also highlights areas where the evi- dence base is still lacking, and where appropriately focused trials are needed to guide best practice for treating this sight-threatening condition.

ABBREVIATIONS

AE Adverse Events
Anti-TNF Anti-Tumor Necrosis Factor
Anti-VEGF Anti Vascular Endothelia Growth Factor
BCVA Best Corrected Visual Acuity
CM Central Macular Thickness
CENTRAL Cochrane Central Register of Controlled Trials
CINAHL Cumulative Index to Nursing and Allied Health Literature.
ETDR Early Treatment Diabetic Retinopathy Study
FFA Fluorescein Fundus Angiogram
IVB Intravitreal Bevacizumab
IVDS Intravitreal Diclofenac Sodium
IVT Intravitreal Triamcinolone Acetonide
OCT Optical Coherence Topography
OFTA Orbital Floor triamcinolone Acetonide
PSIU Posterior Segment-Involving Uveitis
PSTA Posterior Subtenon Triamcinolone Acetonide
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TNF Tumour Necrosis Factor
UMO Uveitic Macular Edema

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AUTHORS' CONTRIBUTIONS

MT is an NIHR clinical research fellow and he is involved in all stages of the systematic review includ- ing identifying, selecting, extracting and appraising data. MT drafted the manuscript. MT, DM and AD, led the development and structuring of systematic review. AD and PM provided clinical input; MC made substantial contributions to the systematic review version. RB was involved in screening, extract- ing and appraising the collected data. MC, JM, AD, DM and PM provided supervisory support, inputted to the design of the study, commented on the draft manuscript. All authors have read and approved the final manuscript.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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SUPPLEMENTARY MATERIAL

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ORCID

Mohammad O. Tallouzi http:// http://orcid.org/0000-0002-1356-9381

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4.3 Supplementary Document

The online material from the paper is available from:

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Supplementary Results: Full efficacy data, containing extended details of intervention, and efficacy between interventions and against baseline for all time points

1. Corticosteroid

Twenty studies evaluated corticosteroid comparing to placebo, to a comparator within the class, or to an alternative agent across classes. Alternative routes of administration included oral (n=3), intravitreal (n=14), subtenon (n=3) orbital floor (n=2) and subconjunctival (n=1).

1.1 Corticosteroid versus no pharmacological agent

Three RCTs (4 publications) (95, 318-320) compared intravitreal corticosteroid (Dexamethasone 350µg or 700µg) injections to sham (2 RCT) (319, 320) or observation (1 RCT) (95, 318).

Shin et al (2015) evaluated intravitreal triamcinolone (4mg) vs sham injection in 50 eyes (n=25 in each group) in an open-label design. Shin et al (2015) reported slight improvement in BCVA from 69 to 70 letters (EDTRS) in the intravitreal group and from 70 to 73 letters (EDTRS) in the sham group at 3 months with similar results at 6 months follow-up. There was a non-significant difference between groups and comparison to baseline was not provided. CMT showed a significant reduction in both groups from 337 microns to 270 microns in the intravitreal triamcinolone and from 312 microns to 280 microns in the sham group with no significant difference between the groups at 3 months follow-up. Those results were maintained at 6 months follow-up (320). Reduction of macular leakage (defined by a decrease of leakage to < 1 Disc area on FFA) was significantly greater in the triamcinolone group from baseline at 3 and 6 months, and vs sham at 3 months only.

Lowder's et al (2011) reported a significant improvement in CMT at 8 weeks from 344 microns to 245 microns in the 700µg, from 338 microns to 248 microns in the 350µg group, while a non-significant change was reported in the sham group from 324 microns to 312 microns. Nevertheless, the change in CMT was not significant at 26 weeks in all groups. Additionally, there was a significant difference between groups favouring implanted eyes at 8 weeks while a non-significant difference between the groups at 26 weeks (319). No further details were provided. In the other RCT, UMO was a subgroup of the study population, with inadequate UMO-specific subgroup data given to enable further evaluation (95, 318).

1.2 Corticosteroid versus different corticosteroid

Two studies compared fluocinolone acetonide implant 0.59mg to systemic prednisolone, either alone (321) or as part of a standard of care (defined as systemic corticosteroid supplemented if necessary by one or more immunosuppressant at the discretion of the physician) (322). Tomkins-Netzer (2015) conducted a secondary analysis of the double-masked MUST trial and randomisation was not stratified by UMO status. The study compared intravitreal fluocinolone acetonide 0.59mg implant vs systemic prednisolone (1mg/kg/d or $\leq$60mg/d). In 134 eyes of 108 patients who had UMO at baseline and completed two years follow-up, there was no significant difference in the mean improvement in BCVA between the intravitreal corticosteroid group (median 68 letters) and the systemic therapy group (median 67 letters). CMT itself is not reported, but the authors report the proportion of patients who showed improvement of CMT (77% in the intravitreal group vs 65% in the systemic group) and OCT resolution of UMO (68% intravitreal, and 52% in the systemic group); there was no significant difference between the groups. The study reported the proportion of eyes without a leakage in 58% in intravitreal and 31% in the systemic group, with no significant difference between the groups. There were no other data available (321).

In the study by Pavesio et al, UMO was a subgroup of the study population with limited data on the subgroup. The only available data were the area of macular leakage (defined by reduction to the area of leakage of more 1mm^2 on FFA) at two years follow-up, which was higher in the intravitreal fluocinolone acetonide implant group (87%) compared to standard of care group (74%) and the difference between the groups was statistically significant favouring the intravitreal group (322).

1.3 Corticosteroids versus same corticosteroids (Same route but different doses)

Three studies compared two different doses of intravitreal fluocinolone acetonide implant (0.59mg vs 2.1mg in all cases). In all three studies, UMO was a subgroup of the study population, with limited UMO-specific subgroup data given (94, 323, 324). Significant reduction of macular leakage was observed in both implanted groups compared to the non-implanted groups at 34weeks (324) and one-year follow-up (94, 323).

Callanan's et al (2008) reported a significant improvement in the area of macular leakage at one year follow-up from 33mm^2 to 7mm^2 in 0.59mg implant and from 30mm^2 to 5mm^2 in the 2.1mg implant. This continued to be significant at three years follow up in 0.59mg implant only (323).

Sangwan's et al (2015) reported a significant improvement in the area of macular leakage at 34 weeks follow-up from 38mm^2 to 9mm^2 in 0.59mg implant and from 46mm^2 to 5mm^2 in the 2.1mg implant. Similarly, this was maintained at three years follow-up in 0.59mg implant only (94).

Jaffe et al. (2006) reported a significant improvement in the area of macular leakage at 34 weeks follow-up from 36mm^2 to 7mm^2 adding 6 letters gain in 0.59mg implant and from 42mm^2 to 29mm^2 in 2.1mg implant and associated with one letter loss. Additionally, 25% of implanted eyes and 5.3% in non-implanted eyes achieved three or more lines of BCVA on a

LogMAR scale, significantly favouring implanted group. There were no other data available (324).

1.4 Same dose and different routes of administration (Corticosteroids versus same Corticosteroids)

Two RCTs compared triamcinolone acetonide in different routes of administration including subtenon, orbital floor, intravitreal and subconjunctival routes. Venkatesh (2008) evaluated three different methods of periocular administration of 20mg triamcinolone comparing cannula method of subtenon's injection (n=10 eyes), Smith & Nozik method of subtenon's injection (n=10 eyes), and orbital floor injection (n=10 eyes) in an open label RCT. BCVA significantly improved in all groups at 3 months with mean LogMAR improving from: 0.65 to 0.15 in the cannula group, 0.6 to 0.14 in the Smith & Noziak group and 0.65 to 0.19 in the orbital floor group (no significant difference between the groups). CMT showed significant improvement in all groups at 3 months with mean CMT improving from: 382 microns to 214 microns in the cannula group, 310 microns to 208 microns in the Smith & Noziak group and 373 microns to 262 microns in the orbital floor group (no significant difference between the groups) (97) No further results were available.

Chen and Liang (2015) compared subconjunctival triamcinolone (n=41 eyes) to intravitreal triamcinolone (n=41 eyes); no dose is specified although 0.1ml triamcinolone was given in all cases, which would equate to 4mg triamcinolone if a standard preparation was used. BCVA showed no difference between groups at baseline, but that subconjunctival triamcinolone was associated with a significantly higher BCVA (gain of 1.8 lines) compared to intravitreal (gain 1.1 lines) at 3 months follow-up (scale was not reported); similarly, the subconjunctival triamcinolone was associated with a significantly thinner CMT at 3 months follow-up with a mean CMT improving from 485 microns to 214 microns compared to intravitreal triamcinolone

group from 493 microns to 256 microns (325). Statistical comparison was not reported to the baseline.

1.5 Corticosteroids versus same corticosteroids (Different route and different dose)

Two studies compared triamcinolone administered via intravitreal route to either subtenon route or orbital floor injection at different doses. An internally randomised controlled study, Choudhury and Ghosh (2007) compared 4mg intravitreal triamcinolone (n=10 eyes) vs 20mg subtenon triamcinolone (n=10 eyes). BCVA improved in both groups at 3 months follow-up with a mean LogMAR improving from: 0.67 to 0.22 for intravitreal and 0.69 to 0.28 for subtenon route, which was maintained at 6 months follow-up, with no significant difference between the groups at either time point. Statistical comparison to baseline was not reported. Resolution of macular oedema was achieved in intravitreal and subtenon triamcinolone groups at 3 months (78% vs 56%) and 6 months (89% vs 78%) with no significant difference between the groups at either follow-up (326).

A retrospective cohort study, Roesel et al (2008) compared 4mg intravitreal triamcinolone (n=48 eyes) vs 40mg orbital floor triamcinolone (n=49 eyes). BCVA significantly improved in both groups with a mean LogMAR improving from: 0.61 to 0.47 for intravitreal and 0.58 to 0.46 for orbital floor, improvement declined at 6 months. There was no significant difference between groups at 3 and 6 months. CMT was not reported.

Significant resolution of macular oedema was reported in intravitreal triamcinolone compared to baseline and orbital floor at 3 months (100% vs 20%) and was maintained at 6 months in intravitreal group vs orbital floor (75% vs 20%). We have noted that about 25% of patients lost to follow up/ not assessed and have not been included in the analyses at 3 months follow-up (327).

1.6 Corticosteroids vs anti VEGF

Four studies compared intravitreal triamcinolone acetonide (2mg or 4mg) to intravitreal bevacizumab injection (1.25mg or 2.5mg): two RCTs, Rahimi (2012) and Soheilian (2010) (328, 329), and two cohort studies, Lasave (2009) and Bae (2011) (198, 330), were identified. The sample size of the included studies ranged from 31-60 eyes.

In the RCTs, Rahimi compared 1.25mg bevacizumab (n=31 eyes) vs 4mg triamcinolone acetonide (n=29 eyes). BCVA significantly improved at 3 months follow-up in both groups, with a mean LogMAR improving from: 0.47 to 0.06 for intravitreal bevacizumab and 0.48 to 0.07 for intravitreal triamcinolone, the improvement was maintained at 6 months, with no significant difference between the groups on both follow-ups. CMT showed significant improvement in both groups from: 310 microns to 234 microns for intravitreal bevacizumab and 296 microns to 218 microns for intravitreal triamcinolone; this was maintained at 6 months follow-up. Despite the significance in both groups from the baseline, the difference between the groups was statistically significant favouring triamcinolone. Angiographic macular leakage was not reported in Rahimi et al's study (328).

In the RCTs, Soheilian compared 1.25mg bevacizumab (n=15 eyes) vs 2mg triamcinolone acetonide (n=16 eyes). BCVA significantly improved in Bevacizumab groups at 3 months follow-up with a mean LogMAR improving from 0.95 to 0.76; however, it was not significant in the intravitreal triamcinolone group from 0.85 to 0.71. Additionally, BCVA significantly improved in both groups at 6 and 9 months follow-ups with no significant difference between the groups at any of the given follow-up time points. CMT showed no significant improvement for intravitreal bevacizumab group at 3 months follow-up with a mean CMT change from 387 microns to 330 microns; however, this was significant for the intravitreal triamcinolone group from 361 microns to 305 microns. This change was maintained at 6 and 9 months follow-up, with no statistically significant difference between the groups on any of the follow-up time

points. Soheilian el al (2010) reported a statistically significant reduction in the area of macular leakage in intravitreal triamcinolone group at 3, 6 and 9 months, while this reduction was statistically significant at 9 months only for the intravitreal bevacizumab, no significant difference was found between the groups at any of the follow-ups. One patient from the bevacizumab group was lost to follow-up and was excluded from the study at all follow-ups (329).

A retrospective cohort study, Lasave et al compared 2.5mg bevacizumab (n=16 eyes) vs 4mg triamcinolone acetonide (n=20 eyes). BCVA improved in both groups at 3 months follow-up with a mean LogMAR improving from: 1.2 to 1.0 for intravitreal bevacizumab and 1.1 to 0.7 for intravitreal triamcinolone but only significant in the intravitreal triamcinolone group. Further BCVA improvements were significant at 6 months follow-up in both groups.

CMT showed significant improvement in both groups at 3 months, from: 401 microns to 323 microns for intravitreal bevacizumab and 455 microns to 289 microns for intravitreal triamcinolone. Significant improvement of CMT was only maintained in the triamcinolone group at 6 months follow-up. Comparison between the groups was not reported (330).

A retrospective cohort study, Bae et al compared 1.25mg bevacizumab (n=10 eyes) vs 4mg triamcinolone acetonide (n=11 eyes) and 40mg subtenon triamcinolone acetonide (n=10 eyes). BCVA significantly improved in all groups at 3 months follow-up with a mean LogMAR improving from: 0.73 to 0.56 for intravitreal bevacizumab, 0.73 to 0.43 for intravitreal triamcinolone, and 0.71 to 0.58 for subtenon group. CMT showed significant improvement at 3 months follow-up in all groups from: 537 microns to 370 microns for intravitreal bevacizumab, 594 microns to 266 microns for intravitreal triamcinolone, and 582 microns to 416 microns in the subtenon group. There was no statistically significant difference between the groups in either BCVA or CMT (198). There were no other data available.

1.7 Corticosteroids versus NSAID

A single RCT compared intravitreal corticosteroid to intravitreal NSAID. Soheilian et al (2013) compared to 2mg triamcinolone (n=7 eyes) vs 500µg diclofenac (n=8 eyes). BCVA significantly improved at 3 months follow-up with a mean LogMAR from 0.75 to 0.63 in the intravitreal triamcinolone group and maintained at 6 months follow-up, whereas BCVA worsened in the diclofenac group from 0.67 to 0.69 at 3 months with slight non-significant improvement at 6 months follow-ups. CMT showed significant improvement from 642 microns to 335 microns for intravitreal triamcinolone at 3 months and maintained at 6 months, while a non-significant change was noted in the diclofenac group from 488 microns to 439 microns at 3 months and maintained at 6 months follow-ups. The difference between the groups was not statistically significant at any visit for both BCVA and CMT (331).

1.8 Corticosteroids vs immunomodulatory

Two studies compared corticosteroid to immunomodulatory agents: one RCT, Nussenbalatt (1991), and one cohort study, Markomichelakis (2011) (332, 333). In both studies, UMO was a subgroup of the study population, with limited data available on the UMO subgroup.

A single RCT by Nussenbalatt et al (1991) compared three months course of oral prednisolone (80mg for patients weighed 70kg or more and 60mg for patients weighted less than 70kg) to oral cyclosporine 10mg/Kg/day in patients with endogenous uveitis. Nussenbalatt et al (1991) reported the proportion of eyes achieving a complete resolution of macular leakage at 3 months follow-up in 47% of eyes treated with cyclosporine and 63% of eyes treated with prednisolone with no data on the difference between the groups (333). In Markomichelakis et al's study no further evaluation was possible.

2. Immunomodulatory

Eight comparisons were identified for Immunomodulatory agents in the treatment of UMO, with different routes of administration including oral (n=3) intravitreal (n=1), subcutaneous (n=3) and intravenous (n=1). Immunomodulatory agents considered here comprises T-cell inhibitors (cyclosporine, sirolimus) (333-335), anti-metabolites (methotrexate, mycophenolate mofetil) (128, 336) and biological agents (e.g. interferons and the anti-tumour necrosis factor (anti TNF) agents infliximab, adalimumab) (128, 332, 337, 338). Comparisons were to placebo, to a comparator within the drug class, or across the classes.

2.1 Antimetabolites versus antimetabolites

A single RCT by Raithinam et al (2014) compared 25mg oral methotrexate weekly to 1g oral mycophenolate mofetil twice daily in uveitis patients. UMO was a subgroup of the study population, with limited UMO-specific subgroup data given. Raithinam et al (2014) reported the proportions of eyes with a resolution of UMO at 5 months follow-up in 77% of eyes in the methotrexate group and 54% of eyes in the mycophenolate group, with no statistically significant difference between the groups (336).

2.2 T-cell inhibitor versus T-cell inhibitor

Two RCTs by Nguyen et al (2016) compared three different doses (44µg, 440µg or 880µg) of intravitreal sirolimus. UMO was a subgroup of the study population, with limited UMO-specific subgroup data are available (334, 335). Nguyen et al (2016)b reported improvement in CMT at 3 months from 461 microns to 403 microns for the sirolimus 440µg group and maintained at 6 months. However, in the sirolimus 880µg group CMT reduced from 375 microns to 313 microns at 3 months and worsened at 6 months. There was no reported statistical comparison to either to the baseline or between the groups (335). Further, Nguyen et al (2016)b reported a non-significant improvement in the area of macular leakage at 3 and 6 months follow-up. Additionally, Nguyen et al.(2016)c reported the proportion of eyes with CMT reduction

(≥50µm) at 5 months which was 49% in the 880µg group, 55% in the 440µg group and 46% 44µg group, with no other statistical data available (334).

1.3 Biological agent (Anti-TNF) versus placebo

Two RCTs by Jaffe et al (VISUAL I; 2016) and Nguyen et al (VISUAL II; 2016) compared subcutaneous adalimumab (loading dose 80mg followed by fortnightly 40mg) to placebo in posterior uveitis. In both studies, UMO was a subgroup of the study population, with no UMO-specific subgroup data given, and no further evaluation was possible (337, 338).

2.4 Biological agent (interferon) versus antimetabolites

A single RCT by Mackensen et al (2013) compared 44µg subcutaneous Interferon beta three times a week (n=9 eyes) to 20mg subcutaneous methotrexate once a week (n=10 eyes) in UMO. BCVA significantly improved at 3 months follow-up in the interferon group with a mean LogMAR improving from 0.48 to 0.16, however, this was not significant in the methotrexate from 0.34 to 0.25, and the difference between the groups was statistically significant favouring interferon group. CMT showed significant improvement in the interferon group from 430 microns to 228 microns, while CMT increased from 371 microns to 409 microns for methotrexate group; significant statistical difference in CMT at 3 months favouring interferon group (128). No further data were available.

3. Anti VEGF

Intravitreal anti-VEGF was compared to corticosteroid (n=4) (198, 328-330), and not against any other comparator; these studies are addressed earlier.

4. NSAID

NSAIDs were compared to placebo (n=1) (339) corticosteroid (n=1) (331), or combined NSAID and corticosteroid or combined NSAID and anti VEGF (n=1) (340).

4.1 NSAID versus placebo

A single RCT by Allegri et al (2014) compared the use of topical indomethacin 0.5% (n=16 eyes) to topical artificial tears of methyl-hydroxy-propyl-cellulose (n=15 eyes). BCVA significantly improved at 3 months follow-up for indomethacin group from 0.4 to 0.47 in decimal scale while the change of BCVA in the placebo group was not significantly improved (from 0.52 to 0.50 in decimal scales); there were no data available on the statistical difference from baseline while there was statistical significant difference between groups favouring triamcinolone. CMT showed significant improvement for the indomethacin group from 446 microns to 360 microns, while CMT worsened in placebo from 390 microns to 405 microns. There were no other data available (339). Reported data indicate a baseline imbalance for both BCVA and CMT and the effect on the results is unclear.

4.2 NSAID vs corticosteroid and anti VEGF

A retrospective cohort study by Radwan et al (2013) compared topical NSAID to a combination of the same topical NSAID combined with either intravitreal anti VEGF or intravitreal corticosteroid. The authors compared topical bromfenac (n-=34 eyes) to bromfenac/bevacizumab (no dosage recorded) (n=21 eyes) or bromfenac/triamcinolone 4mg (n=12 eyes). There was no significant improvement in BCVA for the bromfenac group from 0.39 to 0.31 LogMAR, while, BCVA significantly improved in both groups of the dual therapies with a mean LogMAR improving (bevacizumab/bromfenac from 0.55 to 0.35 and triamcinolone/bromfenac from 0.52 to 0.33). Despite the statistical significance from baseline in dual therapy groups, the difference between the groups was not significant. CMT showed no significant improvement in bromfenac group from 354 microns to 302 microns and a significant improvement in the dual therapies groups (bevacizumab/bromfenac from 459 microns to 288 microns and for triamcinolone/bromfenac from 423 microns to 260 microns. Despite the significant change in the dual therapy from baseline, the difference between the groups was not statistically significant between the groups at 3 months follow-up (340).

Reported data indicated a significant baseline difference where the more active therapies are in groups with initially worse disease (BCVA/CMT).

5. Carbonic anhydrase inhibitor

5.1 Carbonic Anhydrase inhibitor (Acetazolamide) versus placebo

Three randomised crossover studies compared carbonic anhydrase inhibitor (acetazolamide) to placebo for the treatment of UMO. Farber et al (1994) compared oral acetazolamide slow release 500mg daily (250mg twice a day, one after breakfast and one before bedtime) for a month against placebo (341). Lashay et al (2003) compared oral acetazolamide 250mg twice a day for four weeks compared to the placebo (342). Whitcup et al (1996) compared oral acetazolamide 500mg twice a day for four weeks to placebo (343). All studies used a four weeks' wash-out period then received four weeks course of the reverse study medication. The sample size ranged from 30-40 patients.

All studies reported no significant effect of the acetazolamide on BCVA (341-343). Whitcup et al (1996) suggested a change in BCVA of 2 letters worse to 3 letters gain over a month compared to placebo (CI -2-3, 95%). Lashay's et al (2003) reported no significant effect of acetazolamide on BCVA, although 57% of the acetazolamide group and 40% of the placebo group reported a subjective improvement in their BCVA. Fraber et al (1994) reported no significant improvement of BCVA in 14% of the acetazolamide group compared to 2% of the placebo group with no significant difference between the groups.

CMT was not performed, and thus CMT data was not available. Macular leakage was measured in all studies with variable results: Whitcup et al (1996) reported a significant reduction in macular leakage in acetazolamide compared to placebo (95%, CI -0.59-1). As a result, reduction of macular leakage was reported in 45% of the acetazolamide group compared to 5% of

placebo (343). Further, Lashay's et al (2003) reported improvement of macular leakage in 44% in acetazolamide compared to 19% in placebo, however, there was no statistically significant effect of acetazolamide on UMO on both the time and carryover effect. difference between the groups (342). Additionally, Fraber et al (1994) used vitreous fluorophotometry measurement to judge uveitis resolution at four weeks follow-up, which was statistically significant in acetazolamide compared to baseline; however, this was not significant in the placebo at the same follow-up period compared to the baseline. This test was not performed in 5 patients due to poor dilatation and in patients who underwent cataract extraction (341).

6. Vitamins

6.1 Vitamin E against Placebo

A single RCT by Nussenblatt et al (2006) compared oral vitamin E at a dose of 1600IU (n=9 patients) to placebo (n=8 patients). The study reported no significant improvement in BCVA and CMT at 4 months follow-up in both groups. BCVA is worsened from 57 letters to 56 letters in the placebo and from 59 letters to 54 letters in vitamin E. Although there was a slight reduction in CMT in placebo from 467 microns to 392 microns, it has increased in vitamin E from 232 microns to 367 microns (344). There were no other data available.

4.4 Supplementary tables

Supplementary Table 1: Search strategy.

Medline	
#1	Exp Macular Edema/
#2	(macular adj2 edema). ti,ab.
#3	(macular adj2 oedema). ti,ab.
#4	1 or 2 or 3
#5	Exp Uveitis/
#6	Uveit$.ti,ab.
#7	5 or 6
#8	4 and 7
Embase	
#1	Exp Macular Edema/
#2	(macular adj2 (edema or oedema). ti,ab.
#3	#1 or #2
#4	Exp Uveitis/
#5	Uveit$.ti,ab.
#6	#4 or #5
#7	#3 and #6
Cochrane Library	
#1	Macular near/2 edema
#2	Macular near/2 oedema
#3	Mesh descriptor:(macular edema] explode all trees
#4	#1 or #2 or #3
#5	MeSH descriptor: [uveitis] explode all trees
#6	Uveit*
#7	#5 or #6
#8	#4 and #7
CINAHL	
#1	Macular edema
#2	Macular oedema
#3	#1 or #2
#4	Uveitis (MH)
#5	Uveit*
#6	#4 or #5
#7	#3 or #6

Supplementary Table 2: List of excluded studies and reason for Exclusion

No	References	Reason for exclusion
1.	Adán et al 2013. **Tocilizumab treatment for recalcitrant uveitic macular edema**. Graefe's Archive for Clinical and Experimental Ophthalmology, 251(9), p.2249.	Study design: non-comparative
2.	Antcliff et al 2001. **Intravitreal triamcinolone for uveitic cystoid macular edema: an optical coherence tomography study.** Ophthalmology, 108(4), pp.765-772.	Study design: non-comparative
3.	Bleriot, A., Couret, C., Le Meur, G., Lebranchu, P. and Weber, M., 2014. **Efficacité et tolérance des injections sous-onjonctivales de triamcinolone dans la prise en charge des œdèmes maculaires uvéitiques: étude rétrospective sur trente et un cas**. *Journal Français d'Ophtalmologie*, *37*(8), pp.599-604.	Study design: non-comparative
4.	Butler et al 2012. **Interferon alpha 2b in the treatment of uveitic cystoid macular edema**. Ocular immunology and inflammation, 20(2), pp.86-90.	Study design: non-comparative
5.	Cox, S.N., Hay, E. and Bird, A.C., 1988. Treatment of chronic macular edema with acetazolamide. Archives of Ophthalmology, 106(9), pp.1190-1195.	Study design: non-comparative
6.	Dhir, L. and Prasad, S.D., 2006. **Psoriatic uveitis-associated cystoid macular oedema treated with intravitreal triamcinolone acetonide.** Acta Ophthalmologica Scandinavica, 84(3), pp.436-436.	Study design: non-comparative
7.	Doycheva, D., Zierhut, M., Blumenstock, G., Stuebiger, N. and Deuter, C., 2012. **Mycophenolate Mofetil in the Therapy of Uveitic Macular Edema—Long-term Results**. Ocular immunology and inflammation	Study design: non-comparative
8.	Gaudio, P.A., 2009. **Ranibizumab for uveitic macular edema: why**?American journal of ophthalmology, 148(2), pp.179-180. ammation, 20(3), pp.203-211.	Study design: non-comparative
9.	Grosso, A. and Panico, C., 2009. **Intravitreal Steroids for Macular Edema**. Survey of ophthalmology, 54(3), p.426.	Study design: non-comparative

No	References	Reason for exclusion
10.	Heiligenhaus et al 2014. [**Statement of the German Ophthalmological Society, the Retina Society and the Professional Association of German Ophthalmologists for intravitreal treatment of macular edema in uveitis** (as of 02. 07. 2014)(342). Klinische Monatsblatter fur Augenheilkunde, 231(9), pp.929-936.	Study design: non-comparative
11.	Kim, S.J., Doherty, T.J. and Cherney, E.F., 2012. Intravitreal ketorolac for chronic uveitis and macular edema: a pilot study. Archives of Ophthalmology, 130(4), pp.456-460.	Study design: non-comparative
12.	Kumar, A., 2008. **Bevacizumab and Macular Edema**. Ophthalmology, 115(3), p.585	Study design: non-comparative
13.	Larsson, J., Hvarfner, C. and Skarin, A., 2005. Intravitreal triamcinolone in two patients with refractory macular oedema in sarcoid uveitis. Acta Ophthalmologica Scandinavica, 83(5), pp.618-619.	Study design: non-comparative
14.	Leder et al 2011. **Periocular triamcinolone acetonide injections for cystoid macular edema complicating non-infectious uveitis.** American Journal of ophthalmology, 152(3), pp.441-448.	Study design: non-comparative
15.	Lobo et al 2003. **Visual loss in sarcoid-related uveitis**. Clinical & experimental ophthalmology, 31(4), pp.310-316.	Population: non UMO
16.	Mackensen et al 2008. Intravitreal bevacizumab (avastin) as a treatment for refractory macular edema in patients with uveitis: a pilot study. Retina, 28(1), pp.41-45.	Study design: non-comparative
17.	Markomichelakis et al 2007. **Course of macular edema in uveitis under medical treatment**. Ocular immunology and inflammation, 15(2), pp.71-79	Study design: non-comparative
18.	Mercante et al 2007. **Cystoid Macular Edema in Non-Infectious Uveitis Treated With Fluocinolone Acetonide Intravitreal Implant: 3-Year Results of a Multi-Center Clinical Tria**l. Investigative Ophthalmology & Visual Science, 48(13), pp.280-280.	Study design: non-comparative
19.	Mesquida et al 2014. **Long-term effects of tocilizumab therapy for refractory uveitis-related macular edema.** Ophthalmology, 121(12), pp.2380-2386.	Study design: non-comparative

No	References	Reason for exclusion
20.	National Institutes of Health Clinical Centre (2009). **Efalizumab to Treat Uveitis.** https://clinicaltrials.gov/ct2/show/NCT00280826	Study design: non-comparative
21.	National Eye I, National Institutes of Health Clinical C (2012). **Topical Interferon Gamma for Macular Edema Secondary to Uveitis.**	Study design: non-comparative
22.	Pavesio, C., Zierhut, M., Bairi, K., Comstock, T.L., Usner, D.W. and Fluocinolone Acetonide Study Group, 2010. **Evaluation of an intravitreal Fluocinolone acetonide implant versus standard systemic therapy in non-infectious posterior uveitis.** Ophthalmology, 117(3), pp.567-575.	Population: non UMO
23.	University of California SF, Genentech I (2009). **Lucentis for Inflammatory Macular Edema Trial**	Study design: non-comparative
24.	University of Miami, Genentech I (2012). **Pilot Study of Ranibizumab (Lucentis) for Uveitic Cystoid Macular Edema.**	Study design: non-comparative
25.	Rathinam et al 2014. **A randomized clinical trial comparing methotrexate and mycophenolate mofetil for non-infectious uveitis**. Ophthalmology, 121(10), pp.1863-1870.	Population: non UMO
26.	Rho, D 1996. **Acetazolamide treatment of CME in patients with uveitis**. Ophthalmology, 103(11), pp.1717.	Study design: non-comparative
27.	Rojas et al 2000. **Medical treatment of macular edema in patients with uveitis. In Macular** Edema (pp. 195-203). Springer Netherlands	Study design: non-comparative
28.	Sallam et al 2011. **Review and update of intraocular therapy in non-infectious uveitis**. Current opinion in ophthalmology, 22(6), pp.517-522.	Study design: non-comparative
29.	Schaap-Fogler et al 2014. **Anti-TNF-α agents for refractory cystoid macular edema associated with non-infectious uveitis**. Graefe's Archive for Clinical and Experimental Ophthalmology, 252(4), pp.633-640.	Study design: non-comparative

No	References	Reason for exclusion
30.	Schilling, H., Heiligenhaus, A., Laube, T., Bornfeld, N. and Jurklies, B., 2005. **Long-term effect of acetazolamide treatment of patients with uveitic chronic cystoid macular edema is limited by persisting inflammation**. Retina, 25(2), pp.182-188.	Study design: non-comparative
31.	Tao, Y. and Jonas, J.B., 2010. **Intravitreal triamcinolone**. Ophthalmologica, 225(1), pp.1-20.	Study design: non-comparative
32.	Taylor et al 2012. **The impact of macular edema on visual function in intermediate, posterior, and panuveitis**. Ocular immunology and inflammation, 20(3), pp.171-181.	Study design: non-comparative
33.	Taylor et al 2009. **Intraocular methotrexate in the treatment of uveitis and uveitic cystoid macular edema.** Ophthalmology, 116(4), pp.797-801.	Study design: non-comparative
34.	Tehrani et al 2000. **Deep intramuscular methylprednisolone for the treatment of cystoid macular oedema in uveitis**. Eye, 14(5), pp.691-694.	Study design: non-comparative
35.	Tomkins-Netzer et al 2014. **Long-term clinical outcome and causes of vision loss in patients with uveitis. Ophthalmology**, 121(12), pp.2387-2392.	Study design: non-comparative
36.	Van Kooij et al 2006. **The pros and cons of intravitreal triamcinolone injections for uveitis and inflammatory cystoid macular edema.** Ocular immunology and inflammation, 14(2), pp.73-85.	Study design: non-comparative)
37.	Vallet et al 2015. **Efficacy of anti-TNF alpha in severe and/or refractory Behçet's disease**: Multicenter study of 124 patients. Journal of autoimmunity, 62, pp.67-74.	Study design: non-comparative
38.	Wake Forest U, Wake Forest School of M (2011). Pegaptanib Therapy in Non-Infectious Uveitic Cystoid Macular Edema.	Study design: non-comparative
39.	Weiss et al 2009. **Intravitreal VEGF levels in uveitis patients and treatment of uveitic macular oedema with intravitreal bevacizumab.** Eye, 23(9), pp.1812-1818	Study design: non-comparative

No	References	Reason for exclusion
40.	Yap, Y.C., Papathomas, T. and Kamal, A., 2015. **Results of intravitreal dexamethasone implant 0.7 mg (Ozurdex®) in non-infectious posterior uveitis**. International journal of ophthalmology, 8(4), p.835.	Study design: non-comparative
41.	Younan, C. and McCluskey, P., 2009. **Treatment of chronic uveitic cystoid macular oedema**. Clinical & experimental ophthalmology, 37(4), pp.333-334.	Study design: non-comparative
42.	Zannin et al 2013. **Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis:** 1-year follow up data from the Italian Registry. The Journal of rheumatology, 40(1), pp.74-79.	Population: non UMO
43.	Santos-Gómez, M., Calvo-Río, V., Blanco, R., Beltrán, E., Mesquida, M., Adán, A., Cordero-Coma, M., García-Aparicio, Á.M., Pascual, E.V., Martínez-Costa, L. and Hernández, M., 2016. **The effect of biologic therapy different from infliximab or adalimumab in patients with refractory uveitis due to Behçet's disease**: results of a multicentre open-label study. *Clin Exp Rheumatol*	Population: non UMO
44.	Beltrán-Catalán, E., Fernandez, C., Blanco, R., Calvo-Río, V., Hernandez, M., Mesquida, M., Adan, A., Hernandez, V., Diaz, D., Diaz, G. and Calvo, I., 2016. FRI0486 **Tocilizumab Treatment for Uveitic Cystoid Macular Edema Refractory to Other Synthetic and biological Immunosuppressive Drugs**. Multicentre Study of 23 Patients. *Annals of the Rheumatic Diseases*, *75*(Suppl 2), pp.614-615.	Study design: non-comparative
45.	Lam, W.C., Albiani, D.A., Yoganathan, P., Chen, J.C., Kherani, A., Maberley, D.A., Oliver, A., Rabinovitch, T., Sheidow, T.G., Tourville, E. and Wittenberg, L.A., 2015. **Real-world assessment of intravitreal dexamethasone implant (0.7 mg) in patients with macular edema: the CHROME study**. Clinical Ophthalmology (Auckland, NZ), 9, p.1255.	Study design: non-comparative
46.	Ferrante, P., Ramsey, A., Bunce, C. and Lightman, S., 2004. **Clinical trial to compare efficacy and side-effects of injection of posterior sub-Tenon triamcinolone versus orbital floor methylprednisolone in the management of posterior uveitis.** Clinical & experimental ophthalmology, 32(6), pp.563-568.	Population: non UMO

No	References	Reason for exclusion
47.	Santos-Gómez, M., Calvo-Río, V., Blanco, R., Beltrán, E., Mesquida, M., Adán, A., Cordero-Coma, M., García-Aparicio, Á.M., Pascual, E.V., Martínez-Costa, L. and Hernández, M., 2016. **The effect of biologic therapy different from infliximab or adalimumab in patients with refractory uveitis due to Behçet's disease: results of a multicentre open-label study** Clinical and Experimental Rheumatology	Population: non UMO
48.	Lee, D.J., 2015. **Intraocular implants for the treatment of autoimmune uveitis**. Journal of Functional Biomaterials, 6(3), pp.650-666.	Study design: non-comparative
49.	Preble, J. and Foster, C.S., 2015. **Uveitic macular edema: a stepladder treatment paradigm**. Clin Investigation, 5(6), pp.509-17.	Study design: non-comparative
50.	Fabiani, C., Vitale, A., Emmi, G., Vannozzi, L., Lopalco, G., Guerriero, S., Orlando, I., Franceschini, R., Bacherini, D., Ci mino, L. and Soriano, A., 2017. **Efficacy and safety of adalimumab in Behçet's disease-related uveitis:** a multicenter retrospective observational study. *Clinical Rheumatology*, *36*(1), pp.183-189.	Study design: non-comparative

Supplementary Table 3: Quality assessment for RCTs

Study	Risk of bias domains							
	Selection Bias Random sequence generation	Selection Bias Allocation concealment	Performance bias Blinding of participants and personnel+	Detection bias Blinding of outcome assessment	Attrition bias Incomplete outcome data	Reporting Bias Selective outcome reporting	Were groups similar at baseline?	Was inclusion criteria clearly defined
Williams 2009, Kuppermann 2007	Not reported how list was generated	Not reported how allocation administered. Described as randomised" but with no further details	Yes. Both participants and personnel. No further details	No details whether effective measures were used to blind outcome assessors	No drop out or loss of follow up	No access to the protocol or trail registry	Yes. All baseline characteristics appeared similar	Yes
Lowder 2011	Not reported how list was generated	Central centre (interactive voice/web response system)	Clearly stated that participants and personnel not aware of which treatment received	Clearly stated that outcome assessors were not aware of which treatment participants received	No drop out or loss of follow up	Protocol was accessed via clinicaltrial.gov	Yes. All baseline characteristics appeared similar	Yes
Shin 2015	Yes, web-based randomisation	Yes, web based	Double masked. No further details	Double masked. No further details	No drop out or loss of follow up	No access to the protocol or trail registry	Yes. All baseline characteristics appeared similar	Yes
Tomkins-Netzer 2015	Yes. Computer generated list	Not reported how allocation administered. Described as randomised" but	Clearly stated that participants and personnel not aware of which treatment received	BCVA examiner, visual field reporters and fundus photographs reporters) were masked	No drop out or loss of follow up	No access to the protocol or trail registry	Yes. All baseline characteristics appeared similar	Yes

Study	Risk of bias domains							
	Selection Bias Random sequence generation	Selection Bias Allocation concealment	Performance bias Blinding of participants and personnel+	Detection bias Blinding of outcome assessment	Attrition bias Incomplete outcome data	Reporting Bias Selective outcome reporting	Were groups similar at baseline?	Was inclusion criteria clearly defined
		with no further details						
Pavesio 2010	Not reported how list was generated	Not reported how allocation administered. Described as randomised" but with no further details.	Clearly stated that participants and personnel not aware of which treatment received	No details whether effective measures were used to blind outcome assessors	No drop out or loss of follow up	No access to the protocol or trail registry	Yes. All baseline characteristics appeared similar	Yes
Sangwan 2015	Yes. Computer generated list	Not reported how allocation administered. Described as randomised" but with no further details	Double masked. No further details	Double masked. No further details	No drop out or loss of follow up	No access to the protocol or trail registry	Yes. All baseline characteristics appeared similar	Yes
Callanan 2008	Not reported how list was generated	Described as randomised" but with no further details	Double masked. No further details	Double masked. No further details	No drop out or loss of follow up	Unclear. No access to the study protocol	Yes. All baseline characteristics appeared similar	Yes

Study	Risk of bias domains							
	Selection Bias Random sequence generation	Selection Bias Allocation concealment	Performance bias Blinding of participants and personnel+	Detection bias Blinding of outcome assessment	Attrition bias Incomplete outcome data	Reporting Bias Selective outcome reporting	Were groups similar at baseline?	Was inclusion criteria clearly defined
Jaffe 2006	Yes. Computer generated list	Not reported how allocation administered. Described as "randomised" but with no further details not.	Yes. Clearly stated that participants and personnel not aware of which treatment received	Clearly stated that outcome assessors were masked	No drop out or loss of follow up	Unclear. No access to the study protocol	Yes. All baseline characteristics appear to be similar	Yes
Venkatesh 2008	Selection was generated randomly using a lottery	Not reported how allocation administered. Described as "randomised" but with no further details	No information whether blinding of participants or personnel was performed or not	No information whether blinding of outcomes assessors was performed or not	No drop out or loss of follow up	No access to the protocol or trail registry	Yes. All baseline characteristics appear to be similar	Yes
Chen and Liang 20016	Not reported how the list was generated. Described as "randomised" but with no further details	Not reported how allocation administered. Described as "randomised" but with no further details	No information whether blinding of participants or personnel was performed or not described	No information whether blinding of outcomes assessors was performed or not.	No loss to follow-up/drop-outs.	No access to the protocol or trail registry	Yes. All baseline characteristics appear to be similar	Yes

Study	Risk of bias domains							
	Selection Bias Random sequence generation	Selection Bias Allocation concealment	Performance bias Blinding of participants and personnel+	Detection bias Blinding of outcome assessment	Attrition bias Incomplete outcome data	Reporting Bias Selective outcome reporting	Were groups similar at baseline?	Was inclusion criteria clearly defined
Rahimi 2002	Not reported how list was generated	Not reported how allocation administered. Described as "randomised" but with no further details not.	Blinding for both participants and personnel was not stated	Yes. Measurement of BCVA and OCT were performed with examiners who were not informed of previous findings and randomisation.	No drop out or loss of follow up	Unclear. No access to the protocol	Yes. All baseline characteristics appear to be similar	Yes
Soheilian 2010	Yes. Computer generated list	Yes. No further details	No. The study has mentioned the inability to mask patients completely	Yes. BCVA, OCT and FFA were performed and interpreted by masked examiners both to the randomisation and previous findings	No loss to follow-up/drop-outs.	Macular leakage was reported for some patients and no reasons were given.	Yes. All baseline characteristics appear to be similar	Yes
Soheilian 2013	Yes. Computer generated list	Yes. No further details given	Unclear. Details of the series were unknown to the study investigators**. Not sure if this to do with allocation concealment or blinding**	Yes. BCVA and OCT and FFA were performed and interpreted by masked examiners both to the randomisation and to the previous findings and measurements pre-and post-intervention	No loss to follow-up/drop-outs.	Unclear. No access to the protocol	Yes. All baseline characteristics appear to be similar	Yes

Study	Risk of bias domains							
	Selection Bias Random sequence generation	Selection Bias Allocation concealment	Performance bias Blinding of participants and personnel+	Detection bias Blinding of outcome assessment	Attrition bias Incomplete outcome data	Reporting Bias Selective outcome reporting	Were groups similar at baseline?	Was inclusion criteria clearly defined
Nussenblatt 1991	Not reported how list was generated	No information whether allocation was concealed or not.	Unclear. Mentioned double mask but no further details	Unclear. Mentioned double mask but no further details	No loss to follow-up/drop-outs.	Unclear. No access to the protocol	Yes. All baseline characteristics appear to be similar	Yes
Nussenblatt 2006	Not reported how list was generated.	No information whether allocation was concealed or not	Unclear. Mentioned double mask but no further details	Unclear. Mentioned double mask but no further details	No loss to follow-up/drop-outs.	No access to the protocol	Yes. All baseline characteristics appear to be similar	Yes
Jaffe 2016	Yes. Computer generated list	Web response	Clearly stated that participants and personnel not aware of which treatment received	Clearly stated that outcome assessors were masked	16% in the adalimumab and 6% from the placebo	No access to the protocol	Yes. All baseline characteristics appear to be similar	Yes
Nguyen 2016a	Described as "randomised" but with no further details	Interactive web response	Clearly stated that participants and personnel not aware of which treatment received	Clearly stated that outcome assessors were masked.	16% withdraw form placebo and 12% from the intervention group	No access to the protocol	Yes. All baseline characteristics appear to be similar	Yes
Nguyen 2016b	Described as "randomised" but with no further details	Described as "randomised" but with no further details	Open label or no information on masking. We assume that in absence of reporting on this	Open label or no information on masking. We assume that in absence of reporting on this outcome assessors were not masked	No loss to follow-up/drop-outs.	No access to the protocol	Yes. All baseline characteristics appear to be similar	Yes

Study	Risk of bias domains							
	Selection Bias Random sequence generation	Selection Bias Allocation concealment	Performance bias Blinding of participants and personnel+	Detection bias Blinding of outcome assessment	Attrition bias Incomplete outcome data	Reporting Bias Selective outcome reporting	Were groups similar at baseline?	Was inclusion criteria clearly defined
			patient and personnel were not masked.					
Nguyen 2016c	Described as "randomised" but with no further details	Described as "randomised" but with no further details	Unclear. Mentioned double mask but no further details	Unclear. Mentioned double mask but no further details	3.5% in 440µg, 4% in 880µg and 7% in 44µg	Outcomes were not specified in the trial registry	Yes. All baseline characteristics appear to be similar	Yes
Mackensen 2013	Not reported how list was generated	No information whether allocation was concealed or not.	No information whether blinding of participants or personnel was performed or not	No information whether blinding of outcomes assessors was performed or not	2 patients withdraw before 3 months one due to adverse event and worsening symptoms and one non-compliance. 6 patients decided to switch treatment arms. 2 patients did not wish to stay in the study	No access to the protocol	Yes. All baseline characteristics appear to be similar	Yes
Rathinam 2014	Yes. Computer generated list	No information whether allocation was concealed or not	No. The study stated that patients were unmasked	Clearly stated that outcome assessors were masked	No loss to follow-up/drop-outs.	No apparent selective reporting bias	Yes. All baseline characteristics	Yes

Study	Risk of bias domains							
	Selection Bias Random sequence generation	Selection Bias Allocation concealment	Performance bias Blinding of participants and personnel+	Detection bias Blinding of outcome assessment	Attrition bias Incomplete outcome data	Reporting Bias Selective outcome reporting	Were groups similar at baseline?	Was inclusion criteria clearly defined
							appear to be similar	
Allgeri 2014	Not reported how list was generated	Yes. Allocation of therapy was determined But no further details	Unclear. Mentioned double mask but no further details	Unclear. Mentioned double mask but no further details	No loss to follow-up/drop-outs.	Unclear. No access to the protocol	No Reported data indicate a baseline imbalance for both BCVA and CMT and the effect on the results is unclear	Yes
Choudhry and Ghosh 2007	Yes. No further details (Internally randomised within the individuals)	Yes: Sealed envelop	No information whether blinding of participants or personnel was performed or not	No information whether blinding of outcome assessors was performed or not	Yes. Raised IOP was recorded in one eye at week 1 follow-up and was dropped out of the study	Unclear. No access to the protocol	Yes. All baseline characteristics appear to be similar	Yes

Supplementary Table 4: Quality assessment for Crossover trials

Study	Risk of bias domains								
	Selection Bias ***Random sequence generation***	**Selection Bias** ***Allocation concealment***	**Performance bias** ***Blinding of participants and personnel***	**Detection bias** ***Blinding of outcome assessment***	**Attrition bias** ***Incomplete outcome data***	**Reporting Bias** ***Selective outcome reporting***	**Is it clear that the order of receiving treatments was randomised**	**Are data available from both treatment periods? Is it clear mentioned wash out period?**	**Can it be assumed that the trial was not biased from carry-over effects**
Lashay 2003	Yes. No further details given	No information whether allocation was concealed or not.	Yes. Both participants and personnel. No further details	Yes. All investigators were blinded to the randomisation accept one ophthalmologist who monitored patients' compliance and drug-adverse reactions was not masked.	No drop out	Unclear. No access to the protocol	Yes	Yes. 4 weeks wash out period stated	**Yes**
Whitcup 1996	Yes. No further details given	No information whether allocation was concealed or not.	Yes. Both participants and personnel. No further details	Yes. All investigators were blinded to the randomisation	2 participants dropped out the study, one after randomisation and the second one few days after treatment due to worsening depression	Unclear. No access to the protocol	Yes	Yes. 4 weeks wash out period stated	**Yes**
Farber 1994	Yes. No further details given	No information whether allocation was concealed or not.	Yes. Both participants and personnel except one of the study investigators who knew which patient receive which drug	BCVA examiner, visual field and fundus photographs reporters) were masked	Seven patients discontinued the treatment. And dropped the study due to adverse events	Unclear. No access to the protocol	Yes	Yes.one wash out period stated	**Yes**

Supplementary Table 5: Quality assessment for observational studies

Study	Risk of bias domains									
	Selection Bias *Random sequence generation*	**Selection Bias** *Allocation concealment*	**Performance bias** *Blinding of participants/ personnel*	**Detection bias** *Blinding of outcome assessment*	**Attrition bias** *Incomplete outcome data*	**Reporting Bias** *Selective outcome reporting*	**Groups selected** ***(e.g. from the same source &time)***	**Intervention and control groups similar at baseline**	**Same Follow-up time in both groups?**	**Inclusion criteria clearly defined**
Roesel 2009	Not applicable	Not applicable	No blinding to participants or personnel	No information whether blinding of outcome assessors was performed or not	Yes. Data were missed for some participants in both groups and outcomes data were not reported	Unclear. No access to the protocol	No information given.	Yes. All baseline characteristics appear to be similar	Yes. Both groups followed up for 12 months	Yes
Lasave 2009	Not applicable	Not applicable	No information whether blinding of participants or personnel was performed or not	No information whether blinding of outcome assessors was performed or not	No demographic data for one patient. No details on bilateral eyes in the IVT group	Unclear. No access to the protocol	Yes. Patients who have received injections between May 2007 and May 2008.	Yes. All baseline characteristics appear to be similar	Yes. Both groups were followed up for 6 months	Yes

Study	Risk of bias domains									
	Selection Bias *Random sequence generation*	**Selection Bias** *Allocation concealment*	**Performance bias** *Blinding of participants/ personnel*	**Detection bias** *Blinding of outcome assessment*	**Attrition bias** *Incomplete outcome data*	**Reporting Bias** *Selective outcome reporting*	**Groups selected** ***(e.g. from the same source &time)***	**Intervention and control groups similar at baseline**	**Same Follow-up time in both groups?**	**Inclusion criteria clearly defined**
Bae 2011	Not applicable	Not applicable	No information whether blinding of participants or personnel was performed or not	No information whether blinding of outcome assessors was performed or not	No loss of follow-up	Unclear. No access to the protocol	Yes. All patients' groups who have received injection in the severance Eye Hospital from May 2006 to August 2008	Yes. All baseline characteristics Yes. All appeared to be similar	Yes. Both groups were followed up for 12 weeks	Yes
Markomichelaki 2010	No information whether randomisation was done or not.	No information whether there was allocation concealment or not.	No information whether blinding of participants or personnel was performed or not	No information whether blinding of outcomes assessors was done or not	No apparent incomplete data	Unclear. No access to the protocol	No information given	Yes. All baseline characteristics appear to be similar	Yes. Both groups were followed up for 29 days	Yes

Study	Risk of bias domains									
	Selection Bias *Random sequence generation*	**Selection Bias** *Allocation concealment*	**Performance bias** *Blinding of participants/ personnel*	**Detection bias** *Blinding of outcome assessment*	**Attrition bias** *Incomplete outcome data*	**Reporting Bias** *Selective outcome reporting*	**Groups selected** ***(e.g. from the same source &time)***	**Intervention and control groups similar at baseline**	**Same Follow-up time in both groups?**	**Inclusion criteria clearly defined**
Radwan 2013	Not applicable	Not applicable	No information whether blinding of participants or personnel was performed or not	No information whether blinding of outcome assessors was performed or not	No apparent incomplete data	Unclear. No access to the protocol	Yes. All patients are selected from same time period at the Massachusetts eye hospital from Jan 2005-2011	Significant baseline difference where the more active therapies are in groups with initially worse disease	Yes. Both groups were followed up for 3 months	Yes

Chapter 5: Development of a Core Outcome Set for Efficacy and Effectiveness Trials in Posterior Segment-Involving Uveitis: Study Protocol

5.1 Background to chapter 5

Numerous outcomes have been used in clinical trials evaluating treatment effectiveness for posterior segment-involving uveitis (PSIU). This hinders systematic review and meta-analysis. This chapter presents the protocol for the study that aimed to develop a Core Outcome Set (COS) for PSIU for use in effectiveness trials in adult patients. The development of COS for uveitis provides an agreed standardised set of outcomes that has value to all stakeholder groups (patients, carers, healthcare professionals) which can be used to inform clinical guidelines and health policy.

This chapter presents the protocol for the study that aims to develop a core outcome set for efficacy and effectiveness trials in posterior segment-involving uveitis. The protocol describes the process of defining a comprehensive list of potential outcomes based on a systematic review of comparative PSIU studies; the results of which were presented in chapter 4; qualitative research with public representative stakeholders (e.g. patients with PSIU and their carers) presented in chapter 6; qualitative research with healthcare professionals (e.g. ophthalmologists, nurse practitioners, policy-makers and commissioners who are actively involved in decision-making of uveitis) presented in chapter 7. This was followed by a

consensus process using an online Delphi survey that aims to reduce the long-list of outcomes and a consensus meeting with the key stakeholders groups to ratify the final list of COS.

The protocol was published in the peer reviewed Trials Journal. This chapter is comprised of this paper (244). The findings of this study (final COS) are presented in Chapter 8 (Development of a Core Outcome Set for Clinical Trials in non-infectious Posterior Segment-Involving Uveitis).

Publication:

1. Tallouzi, M.O., Mathers, J.M., Moore, D.J., Murray, P.I., Bucknall, N., Blazeby, J.M., Calvert, M. and Denniston, A.K., 2017. COSUMO: study protocol for the development of a core outcome set for efficacy and effectiveness trials in posterior segment-involving uveitis. *Trials, 18*(1), p.576. Available form: https://doi.org/10.1186/s13063-017-2294-8

2. Tallouzi, M.O., Mathers, J.M., Moore, D.J., Murray, P.I., Bucknall, N., Blazeby, J.M., Calvert, M. and Denniston, A.K. Development of a core outcome set for efficacy and effectiveness trials in adult patients with posterior segment-involving uveitis. COMET database 2015. Available from http://www.comet-initiative.org/Studies/Details/640

5.2 The Core Outcome Set study Protocol

Trials

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STUDY PROTOCOL OPEN

COSUMO: study protocol for the development of a core outcome set for efficacy and effectiveness trials in posterior segment-involving uveitis

Mohammad O. Tallouzi[1,5*], Jonathan M. Mathers[1], David J. Moore[1], Philip I. Murray[2], Nicholas Bucknall[3], Jane M. Blazeby[4], Melanie Calvert[1,5] and Alastair K. Denniston[2,5,6,7]

Abstract

Background: Uveitis, a group of disorders characterised by intraocular inflammation, causes 10–15% of total blindness in the developed world. The most sight-threatening uveitis affects the posterior segment of the eye (posterior-segment involving uveitis (PSIU)). Numerous different outcomes have been used in clinical trials evaluating alternative treatments for uveitis, limiting inter-trial comparison and aggregation of data. We aim to develop a core outcome set (COS) that would provide a standardised set of outcomes to be measured and reported in all effectiveness trials for PSIU.

Methods: A three-phase design will be used informed by recommendations from the Core Outcome Measures in Effectiveness Trials (COMET) initiative. Phase 1: a comprehensive list of outcomes will be identified through both a systematic review of effectiveness trials of PSIU and qualitative research with stakeholders. The qualitative study will comprise focus groups with patients and their carers in parallel with one-to-one telephone interviews with health professionals and policy-makers. In the focus groups, patients will be grouped according to whether or not their uveitis is complicated by the sight-threatening condition uveitic macular oedema (UMO) since it is hypothesised that the presence of UMO may significantly impact on patient experience of PSIU. Phase 2: Delphi methodology will be used to reduce the range of potential outcomes for the core set. Up to three Delphi rounds will be used through an online survey. Participants will be asked to rate the importance of each outcome on a 9-point Likert scale where 9 is most important. Phase 3: a consensus meeting will be held with key stakeholders to discuss the Delphi results and ratify the final outcomes to be included in the COS.

Discussion: The development of an agreed COS for PSIU would help ensure that outcomes which matter to key stakeholders are captured and reported in a consistent way. A COS for PSIU would allow greater comparison and aggregation of data across trials for the better evaluation of established and emerging therapies through evidence synthesis and meta-analysis to inform clinical guidelines and health policy.

Trial registration: COMET. http://comet-initiative.org/studies/details/640. August 2015.

Keywords: Uveitis, Core outcome set, Macular oedema, Domain, Delphi, Interviews, Focus group, Consensus method, Clinical trials, Key stakeholders

* Correspondence: mxt500@bham.ac.uk

[1]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, dgbaston, Birmingham B15 2TT, UK [5]Centre for Patient Reported Outcome Research, Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK Full list of author information is available at the end of the article

Background

Uveitis describes a group of disorders characterised by intraocular inflammation responsible for 10–15% of total blindness in the developed world and up to 25% of blindness in the developing world [1–9]. Although uveitis may affect any age group, it peaks in the working-age population and has a disproportionately high impact in terms of years of potential vision loss [1] and need for long-term therapy with its socioeconomic impact being estimated to be at least as significant as that of diabetic retinopathy [9].

The most sight-threatening uveitis affects the more posterior structures of the eye, classified anatomically as intermediate, posterior and panuveitis [10, 11]. In clinical trials, these uveitic diseases are often grouped together as posterior segment-involving uveitis (PSIU) because of a number of shared features including their higher risk of sight-threatening complications and their requirement for systemic or local injection-based ther- apy. One of the most important complications in uveitis is uveitic macular oedema (UMO) which affects around one-third of patients with PSIU [1, 12–14]. UMO is a leading causes of sight loss in these patients and, due to its impact on the 'central vision' essential for reading, driving or recognising people's faces, may be hypothe- sised to have a distinct impact on patients with PSIU.

There is currently a major unmet need in the treat- ment of PSIU with a paucity of high-level evidence to allow evaluation and licensing of therapies by regulatory authorities [15] and to inform treatment decisions by clinical experts and patients [16]. One of the major blocks identified in this area has been around 'outcome measures': the inadequacy of many of the standard out- comes used and inconsistency of the use of these out- comes between trials [15]. A systematic search of clinical trial registries noted that in 104 clinical trials of PSIU 14 different outcomes were used as a primary outcome, the most common being 'visual acuity', 'vitreous haze' or 'macular oedema'. Even where the same domain was used there was often variation in the way it was mea- sured, analysed and reported [17]. This has seriously limited coherent evidence synthesis and meta-analysis in the field.

Inconsistent use and reporting of outcome measures can be addressed through the use of the core outcome set (COS). The COS is a standardised set of outcomes that have been scientifically agreed and are measured and reported in all trials for a specific clinical area [18]. The COS is not restrictive since other data can be collected, but rather ensures that certain key outcomes are always collected in a standardised way. This may profoundly enhance evidence synthesis by enabling com- parison (due to the consistent collection of outcomes), reducing outcome-reporting bias (as the whole COS is reported) and improving the statistical power of any meta-analysis (more studies can be included). Develop- ment of the COS is supported by a number of initiatives such as the Core Outcome Measures in Effectiveness Trials (COMET) initiative [18] and has been endorsed by Cochrane and the World Health Organisation [19].

The development of a COS for PSIU would provide for the first time a standardised set of outcomes to be mea- sured that has value to all stakeholders and can be used in all comparative efficacy or effectiveness trials in uveitis [20]. This has the potential to profoundly enhance evi- dence synthesis and reduce research waste [19, 21] with direct benefits to patients with sight-threatening uveitis.

Aims and objectives

Aims

The aim of this study is to define a COS for PSIU for use in effectiveness trials in adult patients. In addition, we will evaluate any difference in priorities that arise from the presence or absence of the key sight-threatening compli- cation, UMO.

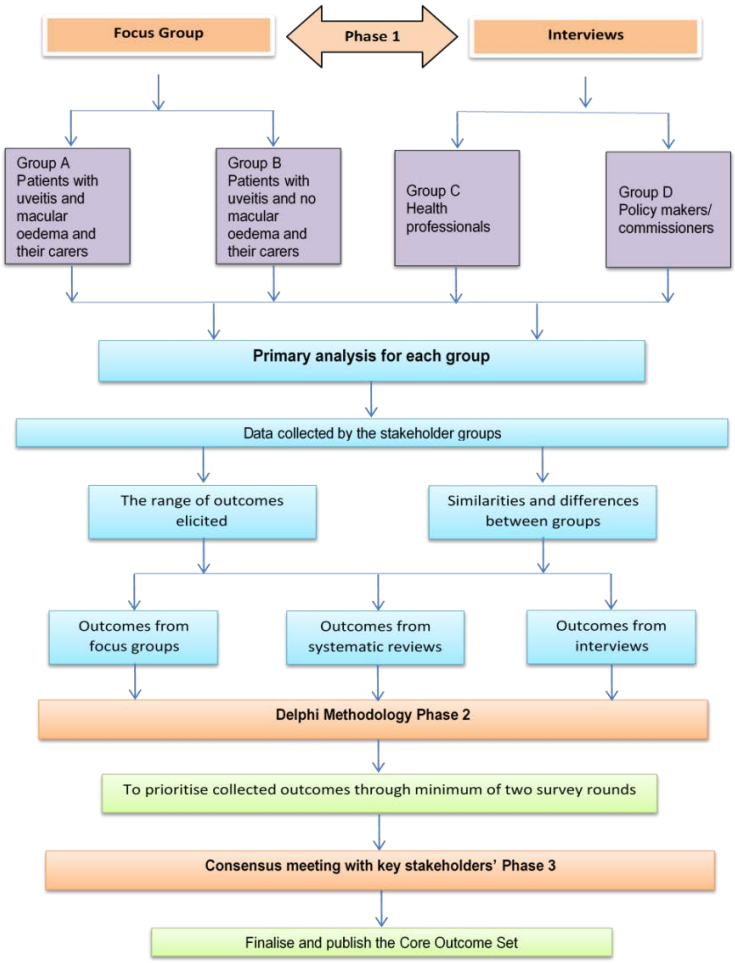
Objectives

There are three specific objectives for the study:

1. To identify a comprehensive list of potential outcomes based on (a) systematic review of clinical trials in PSIU and (b) findings from key respondent focus groups and interviews (patients, carers, health professionals, health policy-makers).
2. To prioritise outcomes through a Delphi process, and to evaluate any potential impact of the presence or absence of UMO.
3. To discuss the Delphi results and finalise the COS for PSIU through a consensus meeting with the key stakeholder groups (patients, carers, clinicians, policy-makers).

Methods

A three-phase approach will be used to develop a com- prehensive COS, in which any relevant outcome identi- fied by any stakeholder will be considered. This may therefore include clinical parameters: patient-reported function, quality of life and health-economic factors, among others. First, a comprehensive list of outcomes will be identified through a review of outcomes reported in existing trials (systematic review) and qualitative re- search with stakeholders. Second, a Delphi process will be used, asking the stakeholders to prioritise outcomes for relevance through an online survey. Third, a consen- sus meeting will be held with key stakeholders to discuss the Delphi results and confirm the final outcomes to be included in the COS [22]. The study design is illustrated in Fig. 1.



Phase 1: identifying a comprehensive list of potential outcomes to be included in the COS

Systematic reviews

A systematic review will be conducted on the effectiveness of pharmacological agents for PSIU (including PSIU with UMO) and potential outcomes will be identified for inclusion in the COS. The identified outcomes from the systematic review will be used to supplement the list of outcomes identified in the qualitative research. The combined list will be reviewed to make sure they provide clear meaning and no duplication [23].

Standard systematic review methodology will be employed to identify, select and extract data from comparative studies (randomised/non-randomised and observational studies) of pharmacological interventions in patients with UMO. Searches will be conducted through bibliographic databases (Cochrane Library, MEDLINE, EMBASE and CINAHL) and clinical trials registers. No restriction will be placed on either language or year of publication. Translation of non-English language articles will be undertaken to minimise selection bias. Data extraction will include the following: basic trial information and name, investigator names, year of study, primary outcome, secondary outcomes, method of measurement and analysis for all outcomes [23].

Qualitative research

Potential outcomes to be included in the COS will be identified through focus groups with patients and carers, and one-to-one telephone interviews with health professionals, health policy-makers and commissioners.

Focus groups with patients and carers

Participants Participants are patients with PSIU and their carers. To be included as a 'Patient Participant', the individual must: have a confirmed diagnosis of uveitis involving the posterior segment of the eye (intermediate uveitis, posterior uveitis or panuveitis) with or without macular oedema; have active follow-up for their PSIU; be at least 18 years of age; have the capacity to read and write the English language as well as good spoken English; and have the capacity to give written consent. Patient participants will be allocated to either the PSIU with UMO group or the PSIU without UMO group based on whether they have had UMO within the last 2 years. For inclusion as a 'Carer Participant', a carer is defined as a person at least 18 years of age (e.g. friend, family member or spouse) who provides unpaid and informal care to the patient during his/her illness and treatment journey for uveitis and UMO. Carers will attend the same focus group as the patient they are accompanying.

Patients will not be included if: they have purely anterior uveitis; or they have other unrelated ocular co-morbidities such as age-related macular degeneration, or diabetic retinopathy that might have significant impact on their vision and experience of uveitis. The presence of uveitis complications such as glaucoma, cataract, retinal vasculitis and choroidal neovascularisation are not exclusion criteria, but will be recorded and reported; these complications are not expected to segregate with either the UMO or non-UMO group and therefore should be approximately equally distributed. Nevertheless, if it was clinically felt that any of these complications was the main cause of vision impairment, those patients would be excluded. Peak central macular thickness will be reported for all patients in which OCT has been undertaken as part of their clinical care. Most recent best corrected visual acuity will be reported in all cases.

Recruitment Patients will be recruited from the NHS Uveitis Clinics at the Birmingham and Midland Eye Centre (Sandwell and West Birmingham Hospitals NHS Trust) and University Hospitals Birmingham NHS Foundation Trust. Eligible participants (patients and their carers) meeting the inclusion criteria will be identified by ophthalmologists (PIM and AKD). A recruitment pack will be distributed and include an invitation letter and a participant information sheet. Written consent will be taken on the day of the focus group. The recruitment process and the consent pathway are illustrated in Fig. 1.

Sampling To ensure a maximum range of views and opinions are collected [24], patients will be purposively sampled according to the following key characteristics: patients with uveitis with vs without UMO; patients with currently active vs inactive disease; age; and gender. We will aim to recruit approximately six participants per focus group, with a total number of participants for this stage anticipated to be between 24 and 30. Initially, four focus groups will be conducted, two each of PSIU with and without UMO, although further groups may be convened depending on judgements of data saturation [25].

Data collection (focus groups)

Focus groups will seek to identify outcomes that are important to patients and their carers. Whilst a variety of approaches will be utilised in order to understand participant perspectives, key areas for discussion will include the experience of uveitis and the impact on patients' and carers' lives; their hopes and expectations for treatment and life with uveitis; as well as discussion about outcomes that they would prioritise. A topic guide will be used to facilitate the focus group discussion. The focus group discussions will be audio-recorded.

One-to-one telephone interviews with health professionals, policy-makers and commissioners

Participants Participants will include health professionals who are involved in caring for patients with PSIU, health policy-makers and commissioners with an influence on uveitis care. The use of telephone interviews facilitates wide geographical coverage and is felt to be more practicable for these participants [26, 27].

Recruitment Recruitment of health professionals, health policy-makers and health commissioners will be via UK and international clinical, research and health service networks. Potential participants will be contacted via email containing an invitation letter and study information sheet, with a single reminder 2 weeks later. For those who agree to participate, a reminder will be sent 2 days prior to the interview date.

Sampling The aim is to recruit approximately 15–20 interviewees (depending on judgements of data saturation) to include clinical, policy and commissioning perspectives.

Data collection (interviews)

One-to-one telephone interviews will be conducted to identify outcomes that are important to clinical and policy participants. A topic guide broadly equivalent to that used in the patient and carer focus groups will be used as a basis for discussion. Interviews will be audio-recorded with oral consent obtained at the start of each interview.

Data analysis

Focus groups and interviews will be transcribed clean verbatim for analysis. A thematic analysis of content will be informed by the framework analytical approach [28]. Analysis will be conducted with reference to recordings,

transcripts and field notes taken at the time of data collection. Following initial familiarisation, data will be coded and then indexed prior to establishing thematic frameworks. These frameworks will enable comparative analysis of outcomes identified between key groups, including evaluating whether the presence of UMO affects the outcomes identified by patients with PSIU. Data collection and analysis will run concurrently.

Synthesis of comprehensive outcome list

The results of the literature review and the qualitative study will be merged to form a single comprehensive list of outcomes. These will be finalised through discussion with representatives of stakeholder groups who will help ensure standardisation and appropriate phrasing for ease of understanding for all groups.

Phase 2: Delphi methodology

An online Delphi study will be used to reduce the range of potential outcomes to a smaller core set [29]. A Delphi approach informed by work of the COMET Initiative will be used [18], including sequential rounds through which the participants' opinions are sought and fed back anonymously. Additionally, participants are encouraged to re-evaluate their responses in the light of these new data [30]. There will be no direct contact between participants, but participants will be asked to participate in sequential questionnaires that constitute different rounds [29, 31]. A recruitment pack that includes an invitation to the study alongside participant information sheet will be sent to the eligible participants. A key part of COS philosophy is to ensure wide stakeholder engagement such that patients, carers, physicians and other health staff contribute to COS development. The Delphi technique has been and will continue to be an important data collection methodology with a wide variety of applications and uses for people who want to gather information from those who are immersed and embedded in the topic of interest and can provide real-time and real-world knowledge [22].

Recruitment

A broader group of participants representing the key stakeholder groups will be approached, via local and national patient groups and clinical and research networks, and invited to participate in the survey. Additionally, participants from the focus groups and interviews will also be invited to take part in the Delphi study. Clinicians will be invited through international expert groups while nurse practitioners will be invited via the International Ophthalmic Nurses Associations (IONA) and Moorefield's Eye Hospital. Respondents will be sent a direct link to the online survey. The purpose of the Delphi process and participant information (e.g. voluntary participation, confidentiality/anonymity, right to withdraw) will be introduced at the front of the survey. Participants will provide consent by confirming the 'required field' button, which states "I have read the information provided, and agree to participate in this survey".

Sampling

The sample size for the Delphi methodology is anticipated to be approximately 120 participants comprising
40 patients with PSIU (20 with UMO, 20 without UMO), 20 carers, 40 health professionals and 20 policy-makers. Although there is no consensus on the sample size used in Delphi methodology, the chosen sample size is based upon previous Delphi studies [29, 32].

Delphi rounds

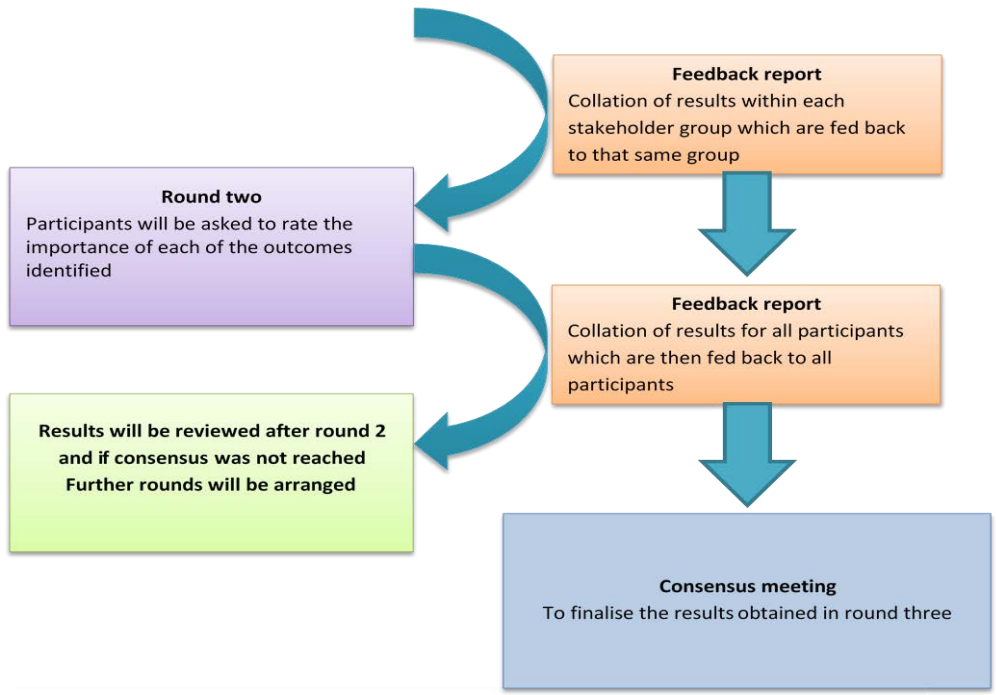
A minimum of two Delphi rounds, including all of the stakeholders' groups, will be conducted. If consensus is not reached, however, further rounds will be considered until consensus is reached [22].

Delphi round one

In the first round of the Delphi process, an online survey will be introduced for completion by the participants. Agreement will be confirmed with those who wish to participate and a unique ID number will be provided to gain access to the Delphi survey. If participants are not able to have access to the online survey, a paper copy of the survey will be provided. If the survey is not completed within 5 working days of the initial date, a reminder will be sent. Participants will be asked to identify the key stakeholder group they belong to; health professionals and health policy-makers will also be asked to provide their professional role and years of experience.
The list of outcomes generated in Phase 1 (systematic review and qualitative studies) will be presented to the participants, who will be asked to rate their importance on a 9-point Likert scale (1 = no importance; 9 = critical). Two additional free-text boxes will be provided to respond to the following questions: "Do you think there are any other outcomes that should be measured in patients with uveitis affecting the back of the eye (posterior-segment involving uveitis)?"and "Any other comments?".
At the end of round one, the response rate in each of the stakeholder groups will be assessed. If the response rate is below target, second reminders will be sent and if necessary further recruitment will be considered. If any additional outcomes have been identified by respondents these will be included in round two. The Delphi process is illustrated in Fig. 2.

Delphi round two

Participants from round one will be invited to participate in round two. Participants will be provided with the



results from the own stakeholder group. Participants will be asked to rate the outcomes again (including any new outcomes identified in round one) on the 9-point scale. Further Delphi rounds will be conducted if consensus is not reached.

Delphi analysis

At the end of the final round, responses will be analysed with a view to determining whether each outcome should be included in the final COS. 'Consensus In' will be based on an outcome being scored 7–9 by more than 70% participants, and being scored 1–3 by fewer than 25% participants. 'Consensus Out' will be based on an outcome being scored 7–9 by more than 70% and being scored 1–3 by less than 25%. Outcomes for which there is no consensus will be brought for discussion to the consensus meeting.

A pre-specified secondary analysis will also be under- taken looking at the effect of stakeholder group and the im- pact of the presence of UMO on the scoring of outcomes.

Phase 3: consensus meeting

The Delphi process will conclude with a face-to-face consensus meeting of key stakeholders, the aim of which is to achieve a consensus COS for PSIU. The results of the Delphi study will be fed back to participants, with greatest emphasis being placed on the results of the final round. Discussion will focus on the following three aims: approving all outcomes identified as 'Consensus In' at the end of the final Delphi round; considering whether further outcomes should be included when a clear ra- tionale is provided; and to check for redundancy be- tween outcomes. It is intended that all participants involved in Phases 1 and 2 will be invited to attend, al- though due to the practical constraints of a face-to-face meeting we anticipate that this will be around 20–30 people. A priority will be to ensure that there is appro- priate balance of representation of the different stake- holder groups.

Discussion

Currently there is no consensus on which outcome mea- sures should be collected in uveitis trials. This hetero- geneity of outcome renders comparison of trials and formal meta-analysis difficult or even impossible. All used outcomes currently have been largely determined by clinical experts, with minimal engagement from other stakeholders. Many of the outcomes used are not mean- ingful to patients, and most are not recognised as an ac- ceptable outcome by regulatory authorities such as the

Food and Drug Administration (FDA) or the European Medicines Agency (EMA). The development of a COS for PSIU would for the first time provide a standardised set of outcomes that has value to all stakeholders and can be used in all future effectiveness trials in uveitis.

The value of a COS is increasingly recognised. Benefits include maximising the value of each clinical trial since key outcomes are measured and reported in all relevant trials; ensuring that outcomes measured include those that are most important to each group of stakeholders, rather than just to one group; reducing outcome- selection bias and outcome-reporting bias since the whole COS is measured and reported; and improving the statistical power of any meta-analysis since more studies can be included [19, 20].

An important feature of most COS development is the involvement of patients and other key stakeholders from the outset, to ensure that the final COS does not simply reflect medical perceptions of the disease but includes those outcomes that matter to patients, and those which are required by regulators and policy-makers to make licensing and funding decisions. The current paradigm for outcome assessment and reporting in uveitis is based on the Standardisation of Uveitis Nomenclature (SUN) workshop in 2005. This was a major step forward in the process of standardising the methods for reporting clinical data in the field of uveitis [11, 33], but was based on the consensus of clinical experts only. Patients, carers and health professionals may differ as to which outcomes are most important, and there may be a tendency for clinicians to undervalue a number of outcomes that matter to patients [5, 34, 35]. Work in other diseases suggests that functional outcomes seem to be more meaningful to patients and may be under-represented compared to clinical and anatomic outcomes that are easier to measure [36].

Furthermore, since publication of the SUN criteria, a number of newer instrument-based measures have become available, notably optical coherence tomographic (OCT) measurement of macular thickness to detect and quantify macular oedema. Such measures provide ob- jectivity and sensitivity to change that is attractive to re- searchers and triallists but may be less meaningful to patients. Our proposed COS methodology will address these issues by compiling a contemporary long list of po- tential outcomes derived from systematic review of trials in PSIU and additional outcomes identified by patients and other key stakeholders, which will then be prioritised through a Delphi approach and a consensus meeting to produce the final COS [37–41].

A potential influence on the output from the Delphi is the cut-off values for determining consensus. We have sought to reduce bias by stipulating these a priori. These cut-off values are estimated empirically with the purpose of avoiding two pit-falls: first that an outcome that is critical to one group might wrongly be excluded due to it being scored low by one or more other groups; and second that the criteria for consensus were too stringent for a significant number of outcomes, leading to excessive weight being placed on the consensus meeting where personal dynamics and stakeholder power may have disproportionate influence.

These issues also hint at the fundamental question of whether the views of all stakeholders are equal in the COS process, and if not, then how should this be weighted. One of the advantages of the COS is that it is not limited to a predetermined small number of outcomes – there is room for the most important outcomes from any and all key stakeholder groups, provided that consensus can be reached.

Identification of the core outcomes for inclusion in the COS is an important step, which will improve data syn- thesis and allow cross-study comparison. The next phase is to go on to identify and agree measures for consistent assessment of these core outcomes. Candidate measures for these outcomes will have been identified during this project. Future work will include the assessment of the suitability of specific measurement tools aligned to the COS based on their measurement properties including their construct validity, reliability and responsiveness.

Whilst acknowledging some of the challenges to COS development, it is clear that COS has huge potential to improve the value of clinical trials to society and to re- duce research waste. The current approach to measuring outcomes in uveitis is acknowledged to be inadequate. The development of a COS for PSIU would be a major step forward for the uveitis community as we seek to improve the treatment of patients with the most sight- threatening uveitis.

Trial status

At the time of manuscript submission, the status of the trial is ongoing. Patient recruitment has not been completed.

Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials; COS: Core outcome set; IONA: International Ophthalmic Nurses Associations; OCT: Optical Coherence Tomography; PSIU: Posterior segment Involving uveitis; UMO: Uveitic macular oedema

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Authors' contributions
MOT is the clinical research fellow and is involved in all stages of the study design, data collection, focus groups and interviews. MOT drafted the manuscript. MOT, JM, AKD and MC led the development of the protocol. AKD and PIM provided clinical advice. JM and MC made substantial contributions to the protocol version. NB provided the patient's public perspective. DJM commented on protocol. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethical approval for the study has been granted by the National Research Ethics Service (NRES) West Midlands—South Birmingham Research Ethics Committee (reference number 17-WM-0111). A consent form will be obtained from all participants.

Consent for publication
We consent to publish this protocol.

Competing interests
The authors declare that they have no competing interests.

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Author details
[1]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. [2]Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK. [3]Patient Involvement Group in Uveitis (PInGU), Birmingham B15 2TT, UK. [4]Centre for Surgical Research, School of Social & Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Clifton, Bristol BS8 2PS, UK. [5]Centre for Patient Reported Outcome Research, Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. [6]Department of Ophthalmology, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2WB, UK. [7]NIHR Biomedical Research Centre at Moorefield's Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London EC1V 2PD, UK.

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Chapter 6: Outcomes Important To Adult Patients With Non-Infectious Posterior Segment-Involving Uveitis: A Qualitative Study

6.1 Background to chapter 6

A wide range of outcomes have been reported in clinical trials of uveitis. However, the majority of those outcomes have been selected by clinicians and members of the research team, without direct input from patients and carers (213). Outcomes that are meaningful to patients and their carers may be therefore under-represented in current clinical trials. For example, outcomes that focus on patients' ability to achieve specific tasks such as reading or distinguishing colours, that measure patient-reported difficulties with vision in particular environmental conditions (e.g. fogginess, or darkness), and that assess visual symptoms (e.g. flashing lights, floaters) have not been included in trials to date, in favour of other outcomes (e.g. best corrected visual acuity) (21). Patients' perspectives and patient reported outcomes are an integral part of healthcare and should inform outcome assessment in clinical trials (345). Thus, considering a broader range of outcomes may better reflect patients' and carers' views, highlight their main concerns and in turn lead to improvement in patient care (346, 347).

This chapter describes a qualitative research study informed by data collected from focus group discussions with adult patients who had a confirmed diagnosis of posterior segment involving uveitis, and their carers (348). The aim of this qualitative study in the context of the whole thesis was to: (a) Identify outcomes considered important by adult patients with PSIU and their carers; and (b) contribute to the long-list of outcomes that would feed into the Delphi

exercise; (c) help the development of a core outcome set (COS) in effectiveness trials in non-infectious PSIU. Outcomes defined via the research described in this chapter were used to supplement outcomes derived from the systematic review (Chapter 4). This chapter is presented in the format of a paper version published in the peer reviewed BMJ Open Ophthalmology. This chapter is comprised of this paper.

Publication

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6.2 The qualitative study (Outcomes importa nt to adult patients with PSIU)

Original research

BMJ Open Ophthalmology

Outcomes important to patients with non-infectious posterior segment-involving uveitis: a qualitative study

Mohammad O Tallouzi ,[1,2] David J Moore,[1] Nicholas Bucknall,[3] Philip I Murray,[2,4] Melanie J Calvert,[1,5] Alastair K Denniston,[6] Jonathan M Mathers[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Mohammad O Tallouzi; mohd.tallouzi@nhs.net

ABSTRACT

Objective Uveitis, a group of disorders characterised by intraocular inflammation, causes 10%–15% of total blindness in the developed world. The most sight-threatening forms of non-infectious uveitis are those affecting the posterior segment of the eye, collectively known as posterior segment-involving uveitis (PSIU). Numerous different clinical outcomes have been used in trials evaluating treatments for PSIU, but these may not represent patients' and carers' concerns. Therefore, the aims of this study were to understand the impact of PSIU on adult patients' and carers' lives and to explore what outcomes of treatment are important to them.

Methods and Analysis Four focus group discussions were undertaken to understand the perspectives of adult patients (=18) and carers (10) with PSIU. Participants were grouped according to whether or not their uveitis was complicated by the sight-threatening condition uveitic macular oedema. Discussions were audio-recorded, transcribed and analysed using the framework analytical approach. Outcomes were identified and grouped into outcome domains.

Results Eleven core domains were identified as important to patients and carers undergoing treatment for PSIU, comprising (1) visual function, (2) symptoms, (3) functional ability, (4) impact on relationships, (5) financial impact, (6) psychological morbidity and emotional well-being, (7) psychosocial adjustment to uveitis, (8) doctor/patient/interprofessional relationships and access to healthcare, (9) treatment burden, (10) treatment side effects, and (11) disease control.

Conclusion The domains identified represent patients' and carers' experience and perspectives and can be used to reflect on outcomes assessed in PSIU. They will directly inform the development of a core outcome set for PSIU clinical trials.

Key messages

What is already known about this subject?

- To date, patients' and carers' experiences of posterior segment-involving uveitis (PSIU) have not been explored in order to define patient-centred outcome domains that might be considered for use in clinical trials.

What are the new findings?

- This study publishes a qualitative piece of research informed by collected data from focus group discussions, proposing a novel outcome domain structure consisting of 11 core domains.

How might these results change the focus of research or clinical practice?

- These results provide the basis to reflect on the patient-centred nature of outcomes used in clinical research focused on patients with PSIU.
- The findings from this qualitative research study have been fed directly into the development process of a core outcome set for PSIU.

INTRODUCTION

Uveitis describes a group of disorders characterised by intraocular inflammation responsible for 10%–15% of total blindness in the developed world and up to 25% of blindness in the developing world.[1–5] Uveitis may be due to (1) an infectious agent or (2) non-infectious inflammation, either as part of an underlying systemic disease or as an isolated ocular phenomenon.[6] Although uveitis may affect any age group, it peaks in the working-age population and has a disproportionately high impact in terms of years of potential vision loss,[7] need for long-term therapy and socioeconomic impact.[8]

The most sight-threatening forms of uveitis are those that affect the posterior structures of the eye, classified anatomically as intermediate, posterior and panuveitis.[9 10] In clinical trials, these forms of uveitis are often grouped together as non-infectious posterior segment-involving uveitis (PSIU), sharing a number of features including a higher risk of sight-threatening complications and often requiring systemic or local injection-based therapy. Uveitic macular oedema (UMO) is one of the common major complications in PSIU affecting around one-third of patients with uveitis.[7 11–13] UMO is a leading cause of sight loss in patients since it affects the macula, which is responsible for detailed central vision. It, therefore, impacts a range of day-to-day activities such as reading, driving and working.

There is currently a major unmet need in the treatment of PSIU with a paucity of high-level evidence to allow evaluation and licensing of therapies by regulatory authorities[14] and to inform treatment decisions by clinical experts and patients.[15] The selection of outcome measures in trials is a critical issue, with evidence suggesting heterogeneity of outcomes used in recent clinical trials of uveitis,[14] meaning that the outcomes from different trials may not be comparable. Further, patients, carers and health professionals may differ as to which outcomes they deem most important, and there may be a tendency for clinicians to undervalue outcomes that matter to patients.[16 17] Consequently, these outcomes may not be included in uveitis research studies.

By understanding which outcomes matter to patients with uveitis and their carers, these perspectives can be included in the measured outcomes of uveitis trials to ensure that such trials are aligned to their priorities. These can be incorporated alongside the priorities of other stakeholders (clinicians, trialists, regulators and so on) into the construction of a core outcome set (COS) for uveitis, a recommended minimum set of outcomes to be assessed in all trials within the relevant health condition or group of conditions.[18 19]

COS methodology is well established and uses consensus methods with clinicians, patients, carers and other stakeholders to arrive at a recommended final set of outcomes.[20] Qualitative research approaches can be used in the early stages of COS development to provide indepth understanding of the range of outcomes that have significance to patients and carers.[18] As part of our study, 'Development of a Core Outcome Set for Clinical Trials in non-infectious Posterior Segment-Involving Uveitis (COSUMO)', qualitative research with adult patients and their carers was conducted to discover which outcomes matter to adult patients with PSIU, with and without UMO, and their carers.

METHODS

Study design

This is a qualitative research study.

Sampling

Eligibility criteria

Patient participants were eligible if they had a confirmed diagnosis of PSIU with or without UMO, for which they were receiving follow-up for uveitis. Participants were 18 or over with good spoken English and the capacity to give informed consent. For inclusion as a carer the participant had to be 18 or over and a friend, family member or spouse providing unpaid informal care to the patient during his/her illness and treatment journey.

Sampling characteristics

Sampling was undertaken with purposive criteria including patients of varying age, ethnicity and gender, with and without UMO.

Recruitment

Patients were recruited via the National Health Service (NHS, UK) uveitis clinics at the Birmingham and Midland Eye Centre (Sandwell and West Birmingham Hospitals NHS Trust) and University Hospitals Birmingham NHS Foundation Trust. Eligible participants were identified by consultant ophthalmologists and provided with an invitation letter and participant information sheet. A clinical research fellow (MOT) telephoned potential participants who had expressed their interests in the research, provided further information as required and answered any questions that arose. A suitable date, time and venue for a focus group discussion were arranged with those who agreed to participate. Written informed consent was taken from all participants on the day of the focus group prior to commencement.

Data collection

Focus groups are a qualitative data collection method that is able to provide in-depth understanding of participants' perspectives through group discussion and interaction.[21] Patient participants were allocated to either a PSIU with UMO group (n=2 groups) or a PSIU without UMO group (n=2 groups), based on whether they had UMO within 2 years preceding the data collection. Carers attended the same focus group as the patients they were carers for. Four focus groups ran between November 2017 and February 2018.

Prior to the start of the discussion, participants completed a short background questionnaire in order to gather participants' sociodemographic and clinical details. These data allowed monitoring and description of the sample characteristics. To supplement this, additional clinical data were collected from medical records by the clinical research fellow (MOT) with the consent of participants.

Private meeting rooms away from clinical areas were used to host discussions at the recruiting clinical sites. Audio-recorded discussions lasted between 87 and 106 min and were facilitated by the clinical research fellow (MOT) with the support of an experienced non-clinical qualitative researcher (JMM). A topic guide was designed to facilitate discussion. This was refined iteratively during the first two focus groups. Following an icebreaker discussion, where participants introduced themselves and gave a brief description of their uveitis background, three topics were used to provide data pertaining to participants' perspectives on core outcomes from PSIU. These three topic areas were (1) the impact of uveitis on patients' and carers' lives; (2) the meaning of stable versus unstable disease; and (3) participants' hopes and expectations related to treatment. The facilitators encouraged discussion and interaction, prompted to ensure that different group members were able to participate, and summarised discussion to probe for further insights around each topic area.

Data analysis

A thematic analysis of content was informed by the framework analytical approach.[22] Audio recordings were

transcribed for analysis that was supported by the qualitative data analysis software NVivo V.12 (QSR International). Following initial data familiarisation, using both audio recordings and transcripts, a coding framework was developed iteratively by two researchers (MOT and JMM) in consultation with the broader research team. The focus group data were coded for outcomes. During this process our definition of an outcome was broad, including any consequence of PSIU or its treatment that clearly had significance to patients and carers who participated in the focus groups. Once we had finalised our coding framework, it was then applied to the whole data set (indexing). Data were then summarised descriptively, retaining the original meaning of participants' discussions. Associative analysis was considered to assess similarities and differences between groups (eg, UMO vs non-UMO). Findings were discussed among the research team and at a COSUMO study meeting, where ophthalmologists, researchers and patient representatives were present. No significant changes to our analysis were necessary following these discussions. No novel issues emerged for discussion at the final focus group meeting.

Patient involvement

A patient representative (NB) was involved in the study from the outset, was a coapplicant on the funding application and was on the steering group of the whole project. Specific contributions included providing advice on key aspects of the study design, including helping define the research questions, informing the constitution of focus groups and specifying the project outcomes. In addition they cowrote the patient information sheet. Patient groups (such as Birdshot Uveitis Society, Olivia's Vision, Patient Involvement Group in Uveitis (West Midlands)) were also consulted to support the dissemination of this research.

RESULTS

A total of 47 participants were approached, and of these 30 agreed (64%) to take part and 17 declined (36%). Of the 30 who agreed, a total of 28 participants took part in the four focus groups: 18 patients and 10 carers, aged 31–72 years old. The sample included 4 male and 14 female patients, and 6 male and 4 female carers. Carers identified their relationships with the patients as spouse/partner (n=7), mother (n=2) and daughter (n=1). Uveitis was classified anatomically as intermediate (n=8), posterior (n=3) and panuveitis (n=7). Focus groups included UMO participants (n=7) and non-UMO participants (n=11). The main cause of uveitis was classified as idiopathic. A more detailed profile on the sociodemographic and clinical characteristics of the patients is shown in online supplementary tables 1 and 3, respectively. Carer characteristics are shown in online supplementary table 2.

Identification of outcome categories and core outcome domains

During analysis 11 overarching outcome domains that have relevance to patients and carers were defined: (1) visual function, (2) symptoms, (3) functional ability, (4) impact on relationships, (5) financial impact, (6) psychological morbidity and emotional well-being, (7) psychosocial adjustment to uveitis, (8) doctor/patient/interprofessional relationships and access to healthcare, (9) treatment burden, (10) treatment side effects, and (11) disease control.

Table 1 explains the outcome domains, their definitions and the items in each domain.

Outcome domain 1: visual function

Patients identified vision as one of the most important issues in PSIU and referred to the impact of different visual impairments on their everyday life (table 2). Participants discussed a wide range of challenges faced as a result of impairments to different aspects of visual function:

> Phone numbers are dreadful, I get dazzled in that one, I'm reliant on my left eye which is pretty rubbish, and so you almost have to freeze for a bit and then your vision will come back, which is not great. (FG2P7)
>
> Display stuff I really miss, especially at Christmas when they put all the bottles in the display stand. You just have to be really aware of that especially on the side of aisles and stuff that you don't skip the aisle round and clip whatever on there, because part of your vision is gone from you. (FG3P3)

As illustrated by these quotes visual function was linked to aspects of functional ability, including activities of daily living, work and the ability to drive. The perceived impact of PSIU on visual function varied in discussions, based on disease severity and presence of complications, for example, UMO and raised intraocular pressure. For example, this participant described the impact of an episode of UMO on vision and functional ability:

> When I had macular oedema, it was like seeing a dark hole in the middle of my vision so completely block the middle anything, missing spots in the central vision and I could not drive or work. (FG1P3)

During the focus groups progressive deterioration in visual function and related functional ability was a topic of discussion. This was sometimes linked to a perceived lack of effective medication:

> My expectation was that the medication would work, and I would recover sight lost. I've had uveitis now for about ten years, now to the point where I've virtually got very limited vision. I've got virtually no vision in my right eye, very blurred and distorted vision in my left eye. Up until about six months ago I could read. Now I'm actually struggling to read or go out, can't really watch TV. (FG4P4)

Table 1 Outcome domains

Number	Outcome domains	Definition of domain	Items in the domain
1	Visual function	The impact of PSIU on aspects of patients' vision.	Distance vision; near vision; colour vision; peripheral vision; contrast sensitivity; depth perception.
2	Symptoms	Patients' bodily experiences that result from PSIU.	An uncomfortable or painful eye; photosensitivity; redness; watery eyes; floaters; visual disturbance; distortion of vision; headache; fatigue.
3	Functional ability	The impact of PSIU on patients' ability to perform, maintain or continue their day-to-day functions.	Work/employment (maintaining/adjustments); educational participation; driving; activities of daily living and self-care; participation in social and leisure activities.
4	Impact on relationships	The impact of PSIU on relationships with others.	Intrafamily and spousal relationships; friendships.
5	Financial impact	The financial impact of having PSIU.	Financial cost to patients, for example, due to impact on work or treatment-related costs.
6	Psychological morbidity and emotional well-being	Psychological and emotional morbidity that may occur in patients with PSIU.	Depression; anxiety and stress; emotional well-being.
7	Psychosocial adjustment to uveitis	How well people with uveitis adjust to life with the disease and how it influences self-image. This partly results from day-to-day interactions with others, for example, family, friends and other people.	Threats to psychosocial well-being; coping strategies; indicators of psychosocial adjustment (reworked sense of self, identity, sense of normality).
8	Doctor/patient/interprofessional relationships and access to healthcare	An effectiveness of doctor–patient communication and between healthcare professionals; the ability to access uveitis clinics and uveitis care facilities.	Clinician–patient relationships; interprofessional communication; shared decision-making; access to health services and psychotherapy.
9	Treatment burden	The work that people with uveitis need to do to care for their health and its effect on their life.	Feeling of overall treatment burden; number of hospital visits; amount of medication; adherence.
10	Treatment side effects	Undesired effects of the treatment.	Treatment side effects (ocular and systemic).
11	Disease control	Control of PSIU and its complications.	Inflammation; complications (including raised intraocular pressure; UMO and cataract).

PSIU, posterior segment-involving uveitis; UMO, uveitic macular oedema.

Table 2 Components of visual function and impact on everyday life

Components of visual function	Definition of outcome	Examples of the impact on everyday life discussed in the focus groups
Distance vision	A patient's ability to see objects/people clearly from distance (beyond arm's length).	Difficulties in seeing faces, number plates, road signs, cars (only see the headlights), reading the guide on the television.
Near vision	A patient's ability to see near objects.	Difficulties in seeing the remote control, phone numbers, menus, coins, the writing on a bottle of the shampoo; missing certain parts of text when reading.
Colour vision	A patient's ability to distinguish colours accurately.	Difficulties in differentiating colours (eg, blues and yellows) or choosing items of clothing that match.
Peripheral vision	A patient's ability to see towards the edge of their vision.	Difficulties in seeing items in the periphery of their vision.
Contrast sensitivity	A patient's ability to distinguish objects from the background.	Difficulties in dealing with different contrasts between light and dark, for example, having to wear sunglasses on a foggy day.
Depth perception	A patient's ability to perceive the world in three dimensions.	Difficulties in judging distances (eg, estimating how far away or how high a step is).

Table 3 Components of patients' symptoms

Components of symptoms	Definition of outcome	Descriptive terms used by focus group participants
Uncomfortable or painful eye	A person complains of eye pain that may be severe and seem sharp, aching or throbbing, or a person may feel only mild irritation of the eye surface or the sensation of a foreign object in the eye (foreign body sensation).	Feeling irritation; scraping sensation or sandpaper when closing eyes, or experience of sharp pain; stabbing pain, terrible pain.
Watery eye	A person experiences a watery or a runny eye (excess tears).	Feeling your eyes streaming; like you have been crying.
Redness	A person experiences a visible bloodshot or redness to the white part of the eye.	Experience of having red eyes, a layer of blood go across the eye, and then as that goes down to my eyes it's almost like it's bloodshot.
Photosensitivity	A person experiences light intolerance or the eye is oversensitive to light (eg, in sunlight, fluorescent light, headlights, street lights).	Feeling light sensitive as just can't stand any light at all; sensitive eyes to sunlight, fluorescent light, headlights, yellow bright light in the street.
Floater	A person complains of seeing moving dark or grey spots, specks, strands or cobwebs.	Seeing floating things; blob; seeing like a fly in front of vision; and black circles or dots going round. I had floaters and the only way to explain it is like a cling film over my eye that's creased.
Visual disturbance	A person complains of seeing blurred, hazy, foggy, grainy vision, flashing/shimmering lights or double vision.	Seeing fog in front of vision; hazy vision; flashing lights; shimmering lights; a drifting across my eyes; grainy vision; loads of steam. Seeing things but not defined, but it's just like a milky haze.
Distortion of vision	A person complains that straight lines may appear bent, crooked or wavy.	Seeing things wavy rather than straight and lines appear bent.
Headache	A person experiences a severe or throbbing headache.	Feeling headache I can't spend more than an hour on the computer, because it just gives me bad headache; it is like throbbing.
Fatigue	A person experiences fatigue, exhaustion, feeling tired or lack of energy.	Feeling tired; very exhausted; I feel I am a sleepy person.

Outcome domain 2: symptoms

Participants reported a wide range of eye-related bodily symptoms as a result of PSIU. These are detailed further in table 3, including examples of the descriptive terms that participants used when talking about symptoms. Visual disturbance, distortion of vision and floaters were mentioned in all groups. For example, visual disturbances were described as a 'milky haze' or 'steam' and the resolution of which was associated with disease remission:

> You can sort of see things but it's nothing defined, but it's just like this. I always think of it like a milky haze, you can also say it's like opaque. Some days there's not a lot of steam, some days there's loads of steam. And you know when it's getting better that steam starts to disperse, the lines are wiggly and they're not straight, and I'm looking at that and a bit of that letter disappears. (FG2P5)

Another discussion in the first focus group highlighted patients' experience of eye discomfort and pain, which for some was significant:

> I think it's because I've had it so long you just know it's going to happen. You get a certain pain that it's like almost a bit like a stabbing pain, terrible pain I know I'm in trouble. (FG1P3)

> I actually do get quite a lot of irritation. I don't get pain with it actually, so I get really dry irritated eye, like how can you put it? Like you've got something stuck in it? Gritty? Yeah like that. Like sandpaper? Yeah, something like that yeah, when you close your eyelid it scrapes. (FG1P4)

Additionally, fatigue was discussed as a significant issue by patients:

> When I first started getting uveitis I was falling asleep at stupid times during the day. I would be talking to somebody one min, and that was when uveitis first started, and my ex-wife she says to me the one day, 'Your eye is ever so red.' I said, 'I'm just tired, I'm really exhausted'. (FG3P3)

Outcome domain 3: functional ability

Patients and carers discussed how uveitis and related loss of vision impact people's ability to function in a range of areas, including work, educational participation (eg, attending university), driving, activities of daily living and participating in social and leisure activities (table 1). For example, the impact on work, both the ability to maintain working life and adjustments required in work to do so, was mentioned frequently, as was the ability to drive.

These contributed to maintaining a sense of independence and autonomy:

> But also, it has impacted my life. I have to consider if I lost my sight how would I function. Because I live alone and when you live alone and to lose your independence it's a major thing for me, and driving independence again, if you lost that I would be lost. Working, when I'm at work and I have to ask somebody, or I'm going through my bad period and got to be. I'm a tutor and I do a lot of paperwork, a lot of computer work, and I just find it a struggle all the time, and then that has a physical impact, and I just feel stressed and thinking oh my God am I going to lose my sight? (FG2P2)

Impacts on activities of daily living and the ability to self-care were also key concerns for both patients and carers. Here one participant talked about uveitis impacting their ability to shave:

> I asked her, 'Can you shave me?' She goes, 'I can't shave you, I can't.' So, I go in the bathroom and because I can't see my face I can't see where I'm going so I've got too much off that and start bleeding everywhere on my face. (FG4P3)

Discussion also covered participation in social life and leisure activities:

> For him who would normally go out with his cousins and he can't go out with them because his vision is not good. He used to love going to the gym. He can't go to the gym. So, his activities are what he used to do for a social point of view have all changed. (FG2PC5)

Outcome domain 4: impact on relationships

Participants discussed the impact of PSIU and subsequent treatment on intrafamily and spousal relationships and future family unity. During one discussion a father with PSIU and his daughter reflected on the effect that the disease had on their family unit, relating this to a lack of understanding of the disease and its impacts on the part of the father's spouse:

> It's impact on the family unit as well. Yeah, the amount of arguments we've had because of it, and it isn't like arguments because we're upset with you that you have it, it's just I think again my mum she wants to understand it and she tries to understand it, but then I have to pull her back a bit and you've got to realize what you're saying because this is not his fault. (FG1PC1)

Other issues discussed included the impact of treatment on the ability to have children and on the relationship between parents and their children. The impact of PSIU was not limited to family relationships; it was also discussed in the context of friends, where participants had felt the need to distance themselves from friendships and colleagues because of a lack of understanding of PSIU on the part of others:

> People at work, friends, a lot of people I have had to distance myself from, because of the prejudice, because they don't understand what it's like to have something that is basically immune system eating your eyes which is essentially what this disease is. (FG2P7)

Outcome domain 5: financial impact

The financial impact of uveitis was discussed in detail and perceived as an important outcome among participants. The main source of this was related to early retirement or redundancy due to loss of vision and being unable to work. However, the additional financial burden associated with travel to specialist eye services and the cost of treatments was also highlighted.

Outcome domain 6: psychological morbidity and emotional well-being

The psychological and emotional impacts of PSIU were discussed in all of the focus groups and they were frequently raised by patients and family members, especially carers. Depression was a significant issue as illustrated by the following quote:

> I had three injections of steroids over the course of a week, and I was euphoric to start off with, and I wanted to die. I was so happy I wanted to die, seemed like a perfect time to die, and I was so mad I didn't know how to. I just thought all I have to do is say bye bye world and that's it I'm gone. And then the depression set in, and I am not one of these depressed people who goes to bed and pulls the duvet over me, but felt raging and aggressive and very unpleasant to be around. (FG2PC1)

Anxiety and stress were also raised. Influences on this were suggested to include the fear of sight loss, uncertainty and stress concerning the occurrence of flare-ups and the effectiveness of treatment, and anxiety about what the future holds. Emotional well-being, including feelings of frustration and anger, for example, when patients were in pain, was also a component of this domain.

Outcome domain 7: psychosocial adjustment to uveitis

While psychosocial adjustment will be influenced by psychological morbidity and emotional well-being, this domain is distinct and describes how well patients with PSIU are able to adjust to life with the disease and how it affects their self-image. This is influenced by day-to-day interactions with others. We have defined three components to this domain: (1) threats to psychosocial well-being—the things that indicate that patients are having difficulties with adjustment; (2) coping strategies—the strategies that people adopt in order to master, tolerate or reduce the impacts of PSIU on psychosocial

Table 4 Components of psychosocial adjustment to uveitis

Components of psychosocial adjustment to uveitis	Definition	Examples
Threats to psychosocial well-being	Things that indicate that individuals are having difficulty with psychosocial adjustment to uveitis or going through a process of adjustment, for example, social anxiety, acceptance of the disease, social reaction, changing personal items, autonomy and independence.	Grief for losses incurred, for example, vision/sight loss. Lack of acceptance of the disease and adjustments to life required. Lack of predictability of the disease and impacts-related uncertainty regarding the future. Anxiety related to perceived or actual social reactions to the person with the disease. Feeling of dependence on others and loss of autonomy. Sense of role disruption, for example, work, family. Need to change things that are components of self-image, for example, unable to wear make-up, unable to wear items of clothing that are tied to self-image.
Coping strategies	Things that individuals with uveitis do in order to cope with threats to their well-being and psychosocial adjustment. These can include a mix of psychological and behavioural strategies and can have an effect on how well people with uveitis are able to adjust.	Psychological, for example, acceptance of disease and impacts, adopting a positive attitude, good mindset, positive spiritual beliefs. Behavioural strategies and modifications, for example, changing driving behaviour, changing work or adjustments at work, change in day-to-day life patterns. Self-management, for example, pharmacological and non-pharmacological interventions that would help to prevent the disease from worsening, such as increasing eye-drops, lifestyle modifications such as diet, relaxation techniques.
Indicators of psychosocial adjustment	Indicators that people with uveitis have gone through processes of psychosocial adjustment.	Sense of self: how people with uveitis view themselves, that is, their self-image. Identity: how people with uveitis are viewed by and relate to others. Sense of normality: a person's ability to retain or regain some sense of normality within life.

issues; and (3) indicators of psychosocial adjustment (table 4).

Various threats to psychosocial well-being were discussed in the focus groups, for example, anxiety related to social reactions towards the person with uveitis, or a feeling of loss of autonomy and independence:

> I don't like crowds really, and I'm always conscious if anybody is next to me. Because you can't see out of your eye, and you don't know if you're walking into anybody, so normally I grab onto someone's arm or something, just so you don't make a fool of yourself and walk into things. I think it's made you quite…I'm conscious that it's made [referring to participant's husband] quite hyper-vigilant of me, I'm quite panicking in some ways; When we're coming up to a road I've been very conscious that you grab hold of my hand, because you're thinking oh am I going to bump into anyone. (FG1P4)

In response to these threats, participants talked about a range of coping mechanisms. These can include a mix of psychological (eg, acceptance of PSIU, positive attitudes, spiritual beliefs) and behavioural strategies (eg, changing driving, reading or working behaviours or change in day-to-day routines):

> There was a point where for days I couldn't get out of bed, what's the point? And then I'm thinking I'm lying in bed wasting these days, get up and do something. That's what I try to do, what you should do… (FG1P2)
>
> So, I suppose in some ways what I found the fact that I've got used to uveitis. I found ways of working round it, and I've got the flexibility that I can do. But obviously I was lucky that took place, so yeah. (FG3P1)

There may be certain indicators that individuals have gone through these processes of psychosocial impact and adjustment, successfully or not. Over time this may be a cyclical process dependent on disease progression and the impacts related to this. From the focus group discussions, we have defined three concepts that signify psychosocial adjustment or a lack of it: sense of self, sense of normality and identity.

Sense of self describes how patients with uveitis view themselves, for example, their self-image. It is influenced by interactions with others. This could be positive or negative or mixed, for example, feeling productive, useful, guilty, helpless or useless. Uveitis threatens sense of self:

> For me it's about self-image and self-body image to start with. But that's the one that feeds into the having to come to terms with your different abilities, and your different image and therefore the view that what others may think of us or think of me. (FG3P1)

In describing the impact of PSIU on sense of self, this participant also touches on impacts on identity, for example, how individuals with PSIU relate to others in their social and professional networks. Participants also described a desire to 'go back to normal' and to regain a sense of normality in life:

> The aim was to maintain his [the participant's son] normality. So, he wants to be independent despite all what's going on with him. (FG2C4).
> What's normal for me is when I can function and when can I start and complete a task, and when I'm not really on medication well it's being able to function normally and do your everyday stuff. (FG3P3)

Each of these concepts, a reworked sense of self with uveitis, identity or a new sense of normality, may be indicators of psychosocial adjustment.

Outcome domain 8: doctor/patient/interprofessional relationships and access to healthcare

This domain includes the quality of relationships between clinicians and patients; interprofessional relationships and communication between clinicians; and access to services (ie, eye, social and psychological). Often these were interrelated, with patients' perceived quality of relationships with clinicians being influenced by access:

> The clinic was so busy, and Mr. M was a superstar and squeezed me in literally, I rang the one day, I was in the next day, but the clinic was heaving, you don't like to bother them either. May be that's where I'm wrong. (FG1P2)
> One of the first things he said to me was that if anything changed with my sight I had to ring him, and my previous experience at the local eye clinic I lost all sight in one eye, I rang the eye clinic, emergency eye clinic to get an appointment; nobody answered the phone for an entire day. (FG1P1)

Participants identified a significant deficit in access to psychotherapy and counselling services, sometimes comparing this with other disease areas:

> It's really hard to get emotional support, because you do need emotional support, it's like you said there is no psychological counselling. I waited nine months to get NHS counselling from my GP, but it's only your eyes and you're getting all your medication so you must be fine living with it day to day, and you're getting all these injections. But it doesn't consider the psychological impact, the anxiety. You just don't know, I don't know if I'm going to be able to see my daughter's face the next day or watch her do her school plays or things like that, and causes an immense amount of anxiety for me. But there's no helpline, there's nothing. (FG2P3)

Outcome domain 9: treatment burden

Treatment burden is the workload of healthcare undertaken by patients and carers. Participants described feeling a significant burden of care, for example, associated with the number of follow-up appointments, waiting time, duration of treatment and the impact on family members who had to give up work to care for their partners. Further, the treatment burden in uveitis comprises the work of developing an understanding of the condition and treatments, interacting with others to get clinic appointments, taking medications and enhancing lifestyle factors. It was linked to participants' engagement in activities such as work, studying, leisure and being with friends and family, and influenced psychosocial adjustment:

> I was having triamcinolone injections and Ozurdex implants literally every six weeks, and that was because I've been in a constant flare for three and a half years. So, it never went away, and then that caused problems with glaucoma and had the treatment for that. So I couldn't work because I was constantly at hospital, and being treated constantly. So since February this year having the Iluvien allowed me to do more and go back to be normal, and go back to work, which I never thought I would ever say I would get excited about. (FG2P7)

Focus group participants also discussed the routines they had to establish around treatment and how burden and routine could influence treatment adherence:

> You have to set your phone to put an alarm on it every few hours to do it. You have to put in practices and procedures to enable the treatment. Because treatment is fine if you comply with it, but if you don't comply it's no good. At the moment my eye drops are in the morning and of an evening so that's not too bad, it's just remembering, especially now that I'm working, remembering to take my tablets to work to take them at the right time. (FG1P4)

Outcome domain 10: treatment side effects

Most of the patients reported experiencing significant side effects from medication, particularly corticosteroids. These included ocular side effects, such as irritation and discomfort, and systemic effects, such as feeling generally unwell or weight gain. Participants linked side effects to negative psychological and psychosocial impact, identifying additional treatment burden imposed by medications prescribed to address side effects.

> I had that emotional mood swings, I don't know what the doctor said, but I basically got really bad

oral thrush, and I couldn't eat or drink for a week. (FG2P3)

Outcome domain 11: disease control

Uveitis by definition is an intraocular inflammation; therefore, control of inflammation and flares was perceived as an important outcome for patients with PSIU:

> I had one treatment which I knew that you couldn't have long term. Then my expectation from that treatment was that it would stop the inflammation and the high pressure at the same time. (FG2P3)

Patients experienced a number of ocular complications including raised intraocular pressure, macular oedema or cataract, and controlling those complications was perceived as being an important outcome. Further, when participants perceived their disease was under control, they were able to regain their functional ability and sustain their sense of normality:

> I ended up with cataracts in both eyes, raised ocular pressure, glaucoma drops, and not able to even see my feet. Then I had surgery, vitrectomy and cataract surgery, sight came back, but medication I have been on before haven't controlled the inflammation, didn't control inflammation afterwards, and I ended up having Avastin and Lucentis injections, and they gave me the sight to be able to work again. (FG1P4)

DISCUSSION

The aim of this research was to identify outcomes and outcome domains that are important to adult patients with PSIU and their carers. To our knowledge, this is the first qualitative research study to do this. From our analysis of the qualitative data collected, we have proposed 11 domains that cover the issues that were clearly significant to participants in this research study.

The current paradigm for PSIU assessment is based on outcomes reported by the Standardization of Uveitis Nomenclature (SUN) workshop in 2005.[10] Although this was a major step forward in the process of standardising methods for reporting outcomes and clinical data in the field of uveitis,[11 23] it was based on the opinion of clinical experts, without patients' or carers' input. It focused on items that would all be categorised within the disease control and visual function domain described in this paper and does not reflect the broader set of issues discussed by patients and carers who attended the focus groups. Systematic reviews of trials in PSIU similarly demonstrate that clinical studies have predominantly focused on disease control and visual function outcomes,[14 24] with a smaller number of trials looking at treatment side effects or quality of life.[23 25–27]

Disease control outcomes reported in clinical trials include inflammatory activity (eg, anterior chamber cells and vitreous haze), disease complications (eg, macular oedema, raised intraocular pressure and cataract) and visual function.[14 24] Interestingly distance vision is the only measure of visual function used in clinical trials and has been a standard test in the clinical practice of ophthalmology.[14 24] However, this qualitative work highlights that from a patient's perspective the impact of PSIU on visual function is multifaceted and goes beyond what is being measured currently to include near vision, peripheral vision, colour vision, contrast sensitivity and depth perception. Additionally, focus group participants discussed ocular symptoms, such as visual disturbances and distorted vision, all things that were seen to impact on functional ability and other broader outcome domains identified here. Some participants reported good distance vision while experiencing ocular symptoms that impinged on the clarity of their vision. Other systemic symptoms were also discussed by patients and carers, with fatigue being mentioned most frequently.

Domains commonly discussed in the focus groups but not covered in SUN or clinical trials in uveitis were functional ability; the impact on relationships and finances; psychological morbidity and emotional well-being; psychosocial adjustment to uveitis; doctor/patient/interprofessional relationships and access to healthcare; and treatment burden. The impact on diverse functional abilities (including employment, activities of daily living and self-care, driving and participation in social and leisure activities) was a key consequence of disease activity, impairments to visual function, symptoms and the treatment burden experienced. In turn, this could impact on finances and relationships. Focus group participants discussed resultant psychological morbidity including depression and anxiety, and also talked about influences on day-to-day emotional well-being.[28 29]

While potentially influenced by psychological morbidity and emotional well-being, we have also identified a separate domain describing patients' psychosocial adjustment to life with uveitis. We believe that this is an important domain to consider separately to the others presented here. It describes people's adaptation to life with uveitis and how the disease and its consequences impact on self-image (people's sense of self), something that has been identified as a fundamental concern for those living with debilitating chronic conditions.[30] The importance and nature of adjustment to chronic disease have been studied in other conditions and theorised in both the sociology and psychology of medicine.[31–33] From the focus group data, we were able to identify how participants talked about the things that indicate difficulties with psychosocial well-being, psychological and behavioural coping strategies that they adopted, and potential indicators of adjustment.

As demonstrated here there is obvious discordance between the diversity of outcomes currently assessed in uveitis research and practice, highlighting the range of concerns that patients and their carers report in this qualitative research study. The question remains as to the implications of this for future outcome assessment in research and clinical practice. One could argue that the

broader impacts of PSIU described by patients and carers, for example, functional impairment and psychological and psychosocial impacts, are all sequelae to disease activity and visual function, and hence assessment of those outcomes, that is, the status quo, will implicitly reflect the broader impacts that patients and carers give weight to. However, in the absence of cure, or treatments that allow patients to live their lives as if there was an absence of disease (total and permanent remission), there remains a question regarding the association in response between measures of disease activity and visual function and the broader issues within patients' lives that they discussed in the focus groups. In other words, do incremental improvements in treatment outcomes measured by disease activity and visual function translate to significant improvements in patients' lives overall? Establishing this would seem crucial considering the impact of significant treatment burden that patients and carers described.

Traditionally this has been an argument for measures of health-related quality of life (HRQoL) to be incorporated in clinical research and practice. Within the domain framework we present here, we have not identified components of HRQoL or referred to this concept specifically. Patients and carers did not actually refer to quality of life as an umbrella term within the focus group discussions. There are often varied definitions and conceptualisations of HRQoL. Without detailed reflection on the components of measures, there is a danger that by including any measure of HRQoL we assume that patients' and carers' views are being incorporated in patient-centred manner. However, this may not necessarily be the case, for example, where psychosocial adjustment is not a component of HRQoL measures. This is becoming recognised, for example, with a recent call to incorporate adjustment into the International Classification of Functioning, Disability, and Health,[34] and with work examining specific tools available to assess living with chronic conditions.[35]

It is worth noting that the National Eye Institute Visual Functioning Questionnaire-25 has been validated for many eye conditions, including macular degeneration, cataracts, diabetic disease and glaucoma.[29 36] However, its validation among patients with uveitis is limited.[29 37] Interestingly, this tool covers items related to several of the domains identified here, including aspects of functional ability, visual function, emotional well-being and certain threats to psychosocial adjustment.

Strengths and limitations

This is the first qualitative research study to investigate patients' and carers' views regarding the outcome domains relevant to outcome assessment in PSIU. The focus groups were successfully conducted with a relatively diverse range of adult patients and their carers by researchers with a clinical background in PSIU and an experienced qualitative researcher. All four groups generated in-depth discussion of issues in a participant-led manner. Participants were keen to share their views with other attendees and researchers. No new issues were emerging for discussion by the fourth focus group, suggesting that our domain structure provides a comprehensive picture of the issues of importance to patients and their carers, and that saturation had been achieved.[38]

There are some limitations to our study. First, we did not include children and do not therefore claim that the outcome domains presented here will represent the experience of children or their guardians. Second, while grouping dyads of patients and carers together within the same focus groups was more practicable and allowed joint discussion of issues from a carer and patient perspective, we cannot be certain whether individual participants may have been inhibited in discussing certain issues in front of significant others. Finally, while purposive sampling was successful across a range of characteristics, we were unsuccessful in recruiting from certain ethnic groups despite recruiting from a strongly multiethnic clinical service; it is recognised that certain communities and ethnic groups are more hesitant to engage with research, and this is a recurrent challenge in such studies.[39 40] Similarly, many studies including ours have noted the difficulties in recruiting the younger adult age group (18–30 years), usually attributed to work or family commitments at this stage in people's lives.[41]

CONCLUSION

We suggest that this outcome domain framework can be used as a basis for reflection on the outcomes assessed in research focused on adult patients with PSIU and their carers. Domains detailed here are not currently encompassed in trial research within PSIU. This work forms part of the basis for the COSUMO study (manuscript in preparation). The development of a COS for PSIU would provide for the first time a standardised set of outcomes that has value to all stakeholders and can be used in future effectiveness trials in uveitis. The value of COS is increasingly recognised. Benefits include maximising the value of each clinical trial since key outcomes are measured and reported in all relevant trials; ensuring that outcomes measured include those that are most important to each group of stakeholders, rather than just to one group; reducing outcome selection bias and outcome reporting bias since the whole COS is measured and reported; and improving the statistical power of any meta-analysis since more studies can be included.[18 42] The outcome domains detailed in this research are highly relevant to a COS in uveitis, and this is a key step in the development process to ensure that such a COS includes the outcomes that matter most to patients with PSIU and their carers.

Author affiliations
[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[2]Birmingham and Midland Eye Centre, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
[3]Patient Involvement Group in Uveitis (PInGU), Birmingham, West Midlands, UK

[4]Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham College of Medical and Dental Sciences, Birmingham, West Midlands, UK
[5]NIHR Birmingham Biomedical Research Centre, NIHR Surgical Reconstruction and Microbiology Research Centre and NIHR Applied Research Collaboration (ARC) West Midlands at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham, Birmingham, West Midlands, UK
[6]Ophthalmology Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, West Midlands, UK

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ORCID iD
Mohammad O Tallouzi http://orcid.org/0000-0002-1356-9381

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Chapter 7: Health Care Professionals' Views on the Most Important Outcomes for Non-Infectious Posterior Segment-Involving Uveitis: A Qualitative Study

7.1 Introduction

Uveitis is a sight threatening group of inflammatory disorders that is responsible for 10–15% of total blindness in the developed world (23, 24, 313). Intermediate, posterior and panuveitis are the most critical forms of uveitis named as posterior segment-involving uveitis (PSIU). They often share common clinical features and potential complications (e.g. macular oedema) requiring additional treatment, either systemic or local injection-based therapy (29).

Trialists and clinicians aim to report certain measurements known as outcomes to assess the clinical effectiveness and efficacy of new or existing medical treatment or device. However, inconsistency and heterogeneity around those reported outcomes negatively impact evidence synthesis and means that the results from such trials are not comparable (27). Development of a core outcome set could address this.

Chapter 4 (systematic review) reported the outcomes that have previously been used to measure the efficacy and the effectiveness of therapeutic pharmacological agents in PSIU, but this does not necessarily align with patients' and carers' concerns (addressed in Chapter 6), nor may it include potential useful outcomes that professionals have identified as important but which have not yet been adopted into trial practice (addressed in this chapter).

There is evidence from other diseases that patients may differ on what they think is important compared to healthcare professionals (206). Clinicians tend to evaluate and quantify diseases

by assessing structural changes or direct measures of physiology, but these may not be meaningful to patients and carers, nor directly related to the things that do matter to them (e.g. aspects of function in daily life) (349, 350). There is a need to combine the voices of patients and carers with those of healthcare professionals (e.g. researchers, clinicians, and decision-makers) to develop a comprehensive list of outcomes that matters to all stakeholders and feed into the development of a core outcome set (Chapters 4, 6, 8) (199).

My aim in this part of my project was, therefore, to (a) understand the perspectives of healthcare professionals on what sort of outcomes they thought to be important for adult patients with non-infectious PSIU and their carers; and (b) contribute to the long-list of outcomes to feed into the Delphi exercise; (c) help the development of a core outcome set (COS) providing, for the first time, a standardised set of outcomes that have value to all stakeholders and can be used in all comparative efficacy or effectiveness trials in PSIU (217).

7.2 Methods

7.2.1 Study design

This was a qualitative piece of research informed by data collected from interviews. Semi-structured telephone interviews were conducted with healthcare professionals exploring outcomes that are important to patients with non-infectious PSIU and their carers.

7.2.2 Sampling

7.2.2.1 Eligibility criteria

Participants were deemed eligible for telephone interviews if they are healthcare professionals (e.g. ophthalmologists, nurse practitioners) involved in caring for patients with PSIU, or health policy-makers/commissioners who are involved in the area of ophthalmology or had influence on PSIU care.

7.2.2.2 Sampling Characteristics

Participants were purposively sampled, using various characteristics including level of experience in ophthalmology and uveitis, level of experience in clinical trials and level of involvement as professional members of disease-specific patient groups, and various NHS trust sites across the UK. A pragmatic number of interviews (approximately 15) were considered given the time frame of the study, the availability of healthcare professionals and our assessment that this would be sufficient to achieve saturation.

7.2.2.3 Recruitment

Ophthalmologists, health policy-makers and health commissioners were recruited via UK and international clinical, research and health service networks; nurse practitioners were invited via an International Ophthalmic Nurses Group. Eligible participants were identified by consultant ophthalmologists (PIM, AD) and contacted via email, including a recruitment pack with an invitation letter and a participant information sheet. The clinical doctoral research fellow (MT) contacted all potential participants who had agreed to participate in the study, provided further information about the research and answered their enquiries prior to arranging an interview date. Participants were asked to provide their preferred method of contact and their telephone number for the interview. A convenient time and date were agreed and a reminder was sent two days prior. Verbal consent was obtained from each participant prior to commencing the interview.

7.2.3 Ethics

Ethical approval for the study was granted by the National Research Ethics Service (NRES) West Midlands – South Birmingham Research Ethics Committee (Reference number 17-WM-0111).

7.2.4 Data collection

Interviews are a qualitative research data collection method that is widely used to gain in-depth knowledge and understanding of people's perceptions, attitudes, opinions, and experiences about uveitis and treatment (286). Interviews are often used in the initial stages of COS development to identify outcomes and outcomes domains that are important to patients for any particular health condition (221).

Telephone interviews were conducted by the clinical doctoral research fellow (MT) between March and September 2018 and lasted from 34-52 minutes. Telephone interviews were audio-recorded and professionally transcribed. A topic guide was used. The guide was refined iteratively during the first few interviews. Three topics were discussed in the interviews to understand healthcare professionals' perspectives regarding the most important outcomes that should be assessed in clinical trials focusing on PSIU. These three topic areas were (1) the impact of uveitis on patients' and carers' lives; (2) healthcare professionals' thoughts about patients' expectations from treatment and whether there are differences between patients' and clinicians' expectations, and (3) the impact of the PSIU on carers and other family members. Prior to the start of interviews, all participants were asked to complete a short background questionnaire that gathered data on sample characteristics and helped to ensure diversity amongst the interview sample.

7.2.5 Data Analysis

Qualitative data were analysed using thematic analysis informed by the Framework analytical approach (271, 351). A professional external specialist transcription service transcribed interviews clean verbatim. The clinical doctoral research fellow (MT) checked the quality of the transcription against the recordings by listening to each audio recording and reading the

transcript repeatedly to become familiar with the data. Initial codes were generated and then established into a coding framework supported by the use of qualitative analysis software Vivo version 12 (QSR International, Ltd, Australia).

The coding framework was developed by two researchers (MT and JM) who coded a percentage of the transcripts independently to cross-check the coding strategy. MT and JM met frequently, discussed and refined the coding framework. Several iterations of this were undertaken. Thus some codes were renamed and others were aggregated where better understanding and interpretation of the data were constructed. Similar codes were merged before finalising the coding framework. Findings were discussed among the research team and agreement was obtained for the final coding framework.

The final coding framework was then applied to the whole dataset (indexing) and data were summarised retaining the original meaning of the participants' discussions. The same codes developed during the coding of focus groups with patients and carers were applied to the healthcare professional data where relevant (Chapter 6). Additional codes were created where healthcare professionals introduced new outcomes/concepts not covered in the focus groups. Following final coding, outcome domains were proposed to group outcomes together where appropriate. No new insights emerged for discussion at the final telephone interview and no new outcomes or relevant concepts were being identified with further data collection i.e. a point of code saturation had been reached despite the pragmatic nature of the interview sample (266, 352).

7.3 Results

7.3.1 Sample characteristics

A total of 15 participants were approached, and of those 12 (80%) agreed to take part.

Telephone interviews included 5 ophthalmologists, 3 nurse practitioners and 4 policy-makers/commissioners. The sample included 5 females and 7 males. The mean ophthalmology experience was 14 years. The majority (9 interviewees) reported their involvement in clinical trials of uveitis, and 6 interviewees expressed their involvement in disease specific patients groups such as National Rheumatoid Arthritis Society (NRAS), Patients Involvement Group in Uveitis (PInGU), Birdshot chorioretinopathy group, Behcet's disease. Further details on participants' characteristics are reported in Table 7.

Table 7: Interviewee details

No	Job Role	Years of experience in ophthalmology	Contributed to clinical trials (y/n)	Experience in ophthalmology commissioning (y/n)	Involvement in patient groups (y/n)
1.	Ophthalmologist	20	Yes	Yes	Yes
2.	Ophthalmologist	12	Yes	No	No
3.	Ophthalmologist	4	Yes	No	Yes
4.	Ophthalmologist	5	Yes	No	No
5.	Ophthalmologist	33	Yes	Yes	Yes
6.	Nurse practitioner	24	Yes	No	Yes
7.	Nurse practitioner	5	No	No	Yes
8.	Nurse practitioner	5	No	No	Yes
9.	Health policy-makers/ commissioners	25	Yes	No	Yes
10.	Health policy-makers/ commissioners	10	No	Yes	No
11.	Health policy-makers/ commissioners	20	Yes	No	No
12.	Health policy-makers/ commissioners	5	Yes	Yes	Yes

7.3.2 Identification of outcome categories and core outcome domains

A total of 38 separate outcomes were identified and synthesised into 11 outcome domains: (1) visual function, (2) symptoms, (3) functional ability, (4) impact on relationships, (5) financial impact, (6) psychological morbidity and emotional well-being, (7) psychosocial adjustment to uveitis, (8) Doctor/patient/inter-professional relationships and access to health care (Service outcomes), (9) treatment burden, (10) treatment side effects, (11) disease control. Table 8 reports the list of outcomes in each of the core domains.

Table 8: Items in the outcome domains

No	Outcome domains	Definition of domain	Items in the domain
1.	**Visual function**	Describes the impact of NIU-PS on aspects of patients' vision	Distance vision, near vision, contrast sensitivity, colour vision, peripheral vision
2.	**Symptoms**	Describes patients' bodily experiences that result from NIU-PS	Painful eye, photosensitivity, redness, floaters, visual disturbance, distortion of vision
3.	**Functional ability**	Describes the impact of NIU-PS on patients' ability to perform, maintain or continue their day-to-day functions	Work/employment (maintaining / adjustments), driving/commuting related impact, activities of daily living and self-care; participation in social and leisure activities
4.	**Impact on relationships**	The impact of NIU-PS on relationships with others	Intra-family and spousal relationships; friendships
5.	**Financial impacts 2**	Describes the financial impacts of having NIU-PS	Financial cost to patients due to work loss, early retirement and other treatment related cost (e.g. travelling cost)
6.	**Psychological morbidity and emotional well-being**	Describes the psychological and emotional morbidity that may occur in patients with NIU-PS	Depression and mental illness; anxiety, stress; emotional well-being
7.	**Psychosocial adjustment to uveitis**	Describes how well people with uveitis adjust to life with the disease and how it influences self-image. This partly results from day-to-day interactions with others e.g. family, friends, and other people.	Threats to psychosocial well-being; coping strategies; Indicators of psychosocial adjustment (sense of normality)

No	Outcome domains	Definition of domain	Items in the domain
8.	**Doctor/patient/inter-professional relationships and access to health care (Service outcomes)**	Describes the communication between doctor and patients; the ability to access uveitis clinics and uveitis care facilities	Clinician-patient relationship, shared decision-making, access to physical aids and other resources, access to counselling and psychotherapy services
9.	**Treatment burden**	Describes the work that people with uveitis need to do to care for their health and its effect on their life.	Number of hospital visits, amount of medication, adherence and tolerability
10.	**Treatment side effects**	Describes undesired effects of the treatment	Treatment side effects (ocular and systemic)
11.	**Disease control**	Describes how to control NIU-PS	Anterior segment activity (cells, flares); vitreous activity (cells, haze); retinal vasculitis; retinitis; raised intraocular pressure; macular oedema; cataract; other ocular comorbidities; prevent disease progression and long-term damage including retinal scar/atrophy/ischaemic, optic atrophy and prevent Flare/relapse/recurrence

7.3.3 Outcome domains

Outcome domain 1: Visual function

Healthcare professionals used vision as a broad term comprising distance vision, colour vision, peripheral vision and contrast sensitivity. Thus the term vision and visual function were used interchangeably. Although healthcare professionals identified distance vision as a basic test in ophthalmology practice and widely used in clinical trials, they emphasised other important elements of vision/visual function to be addressed prior to making decisions for uveitis treatment. Whilst there are limited measures of vision in clinical practice there is recognition amongst at least some interviewees that visual function is broad and multi-faceted:

> *"So when I say vision usually this means Snellen vision in clinical practice, but vision means more than just Snellen vision, it means visual acuity, it means field of vision, it*

means contrast sensitivity, it means colour vision, it means all these other things, lack of distortion and so on, reading speed, all these things. So vision is a broad term that can mean different things for different patients, so acuity is the bread and butter visual outcome, but there are other things that are important when measuring visual outcome." HCP 2

Healthcare professionals stressed the point of treating distance vision and changes in the retinal structures (e.g. UMO) which is a common clinical practice; however, this might not be as meaningful to patients as other-related elements of visual function:

"I think clinicians we go very much on the visual acuity and the presence or absence of macular oedema or signs of inflammation in the eye. So there is a temptation to treat what we see on imaging and what we see on a visual acuity measurement, whereas for the patient they might not really see that in the same way, they might be more concerned about how they feel, the side effects of the steroids and what their visual acuity is." HCP 3

Visual function was identified as an important outcome by the majority of interviewees and was associated with patients' functional ability (e.g. working, driving, and daily activities), independence and financial status. Consequently, changes in patients' emotional and psychological wellbeing are thought by healthcare professionals to be associated with changes in patients' visual function (poor vision). In summary, changes in patients' visual function could impact other outcome domains that are discussed below including functional ability, relationships, financial impact, psychological and emotional wellbeing and psychosocial adjustment to uveitis:

"I mentioned to you right at the beginning when we were talking before there is a huge impact on the dynamics of day-to-day, so those people will first be worried about their

visual loss, they may change their mood, they may change the way they interact with the rest of the family, with people around them in general, they will have to be brought sometimes to hospital by someone else so someone has to take time off work and come with them, there will be an impact if they can't work properly, so they are not going to make money, so there is a financial consequence to the family. So there are many angles of the care of these patients and the disease itself that can impact on the people around the patient." HCP 5

Outcome Domain 2: Symptoms

A wide range of sensory-related bodily experience was discussed in the interviews (e.g. pain, red eye, visual disturbance) that may have a great impact on patients' functionality:

"I think obviously patient symptoms are important, if they have pain, inflammation, red eye, floaters, blurred vision, poor vision. The aim is to be symptom free." HCP 7

Clinicians thought the impact of floaters varied between patients depending on the type of work patients have to carry out. For patients whose quality of vision was affected by floaters impacting on their day-to-day activities and professional work, interventions were needed to resolve this issue and enable them to function properly. Thus floaters were correlated to patients' functional ability (e.g. ability to maintain and continue working):

"So take for instance the issue of floaters, now most of the time we as clinicians ignore floaters, but for some patients they're really important, so what I'm thinking here is may be a professional squash player, suddenly he sees ten balls coming at him at once rather than one, or the worst one I had was actually an ornithologist, his job was to stand in fields and count the number of birds in a flock, and you can imagine with a whole load of floaters what a problem that was, and because he brought this up that was the one time or one of the few times that I've actually recommended that these

patients actually have a vitrectomy. So there are instances where the patients will bring up something that's seriously important to them or really important to their working lives and of course they will pay attention to that." HCP 1

Outcome Domain 3: Functional ability

Healthcare professionals discussed the impact of uveitis on patients' functional ability in a wide range of aspects (e.g. working, driving, carrying out normal daily activities and participating in social and leisure activities). Healthcare professionals linked patients' functional ability to quality of life:

"Uveitis can have a profound effect on quality of life (QoL) if it's somebody of working age , if they can no longer competently do their job, if they can't… if they have to drive to work and they can't drive any longer. I think it can affect all aspects of their lives really. Yeah, even as a daily chore to going to work or looking after the kids, or if they have got carers it does impact a lot. If they can't work they will not bring salary home and that will make their life even worse than when they're working." HCP 3

Healthcare professionals described uveitis as a debilitating disease that leaves a huge impact on people's ability to engage in usual daily activities including cooking, cleaning and shopping. Thus, being unable to carry on such day-to-day activities could physically burden their carers. It may also be unsafe for patients to perform such activities:

"So for example the need for a carer to take a day off and come to the clinic with the patient, the need to do all the cooking and the cleaning and the shopping at home because it may not be safe for their partner to do it, so an increased level of domestic responsibility." HCP 5

Healthcare professionals linked uveitic macular oedema to patients' visual function leading to

a negative impact on patients' functional ability (working, driving). In consequence patients suffer financial difficulties due to loss of work or redundancy:

> "*Then those patients with macular oedema who perceive things as looking through a mist and are unable to read, that's a huge limitation for them in-terms of their work, so they are not able to work effectively. We have a disproportionate number of people who have to miss work because of their inability to see properly for periods of time while they are being treated for ocular inflammation."* HCP 7

Healthcare professionals made a point that functional ability is influenced by visual function and may need further intervention including psychological, social and physical action to be in place:

> *"It's the visual function that affects the function of your life when we're talking about uveitis, particularly if the vision has fallen to such an extent as the person can't do their job, can't drive or can't enjoy life, or needs additional caring. You can't see, so yes at the end of the day it all comes back to vision."* HCP 1

Outcome Domain 4: Impact on relationships

The impact of PSIU and subsequent treatment on family relationships and future family unity was discussed in the interviews. This was linked to the degree of visual loss and the level of dependence that patients may end up with. Thus the impact of PSIU was a major reason to create tension between family members:

> *"Yes, I would think extremely important, particularly if the vision has fallen to such an extent as the person can't do their job or can't enjoy life, or needs additional caring and what have you, that's going to have a major impact of the if you like the family unit or whoever is closest to the patient themselves. They may lose their job or be unable to work or then their partner will have to support them or their families will*

have to support them which can lead to lots of tension." HCP 1

Furthermore, healthcare professionals discussed the impact of uveitis on patients' ability to look after children and the role of parenthood and the relationship between a mother/father and children:

> *"I think it goes broader than just the direct family, I think there are ripples beyond, if you're a mother then you have children and those children can be impacted, so it's not necessarily just the person that turns up to the clinic, it can be on other people who don't get what's going on."* HCP 11

Interviewees linked spousal relationships to patients' financial and functional ability. Therefore being unable to work and earn income impacts upon the family relationships and unity:

> *"Even relationship, relationship is a big role where your eyes are concerned, and there are a lot of things you can't do that you could do before, so you would be depending on a carer or your partner. Basic things, relationship-wise things they could do before, their partner might feel they are a burden on them, so they have to work things around the patient themselves. So the partner might feel frustrated themselves that they are doing so much, or they might get stressed out themselves and doing too much and get burnt out."* HCP 7

Outcome Domain 5: Financial Impact

The financial impact of PSIU was highlighted by healthcare professionals and perceived as an important multi-faceted outcome. For example, loss of work was one of the major issues that negatively impacted the financial status of patients and their families. Consequently, interviewees felt that financial struggles could negatively impact patients and family relationships:

"It can have an effect on if the person is not able to work, it can affect the income coming into the family, so they could have financial concerns about their mortgage, even as a daily chore to going to work or after looking after the kids, or if they have got carers it does impact a lot. If they can't work they will not bring salary home and that will make their life even worse than when they're working." HCP 6

Interviewees noted other financial impacts in patients from particular socio-economic backgrounds (working class) who are having time off of work to attend uveitis speciality clinics. Further financial costs included treatment costs, travel costs and frequent hospital visits:

"Pretty much [for] any working class [person] having to visit the hospital and having to take medication, will have an economic impact. Obviously whatever the environment they have worked in, often they may not get time off to come where they need to come and they may have to lose their pay, or they may have to go off sick for a while which all will have an impact on their work life balance and their economy." HCP 4

Furthermore, the financial burden was also discussed in relation to psychological and emotional illness (e.g. depression, anxiety), thus the psychological well-being and family relationships (family unity) are influenced by the financial impact:

"It's all interconnected really. It's all part of the same problem; I think it has lots of connotations in terms of how a partnership or a family unit, the dynamics of a relationship or a family unit would work. If there's things like loss of income, or there's one of the parents is actually very depressed, of course that's going to have a big impact upon the way that unit works together, and lives together." HCP 6

Outcome Domain 6: Psychological morbidity and emotional well-being

The impact of PSIU on patients/carers psychological and emotional well-being was frequently

highlighted among interviewees, especially ophthalmologists. Psychological impacts occur due to loss of vision or fear of loss of vision. Psychological morbidity and emotional well-being are broad and multi-faceted including depression, stress, frustration and anxiety. Thus mental illness and depression were demonstrated in the following quote:

> *"Uveitis can cause a mental problem as well, depression from being unable to see and vision being blurred and poor vision, it causes patients to be depressed. They are very anxious and depressed very often because they're scared that they will never be able to see again or they might go blind; their partner often is involved with that."* HCP 7

Psychological and mental health are now well-recognised in patients with PSIU; some ophthalmologists now include psychology support services within specialist uveitis clinics. In these cases patients may have an initial psychological assessment in the uveitis clinic and then referred to the psychology support service if ophthalmologists feel further care is needed:

> *"I think I have seen that many patients, once they have a diagnosis of uveitis their lives change, they become focused on that, it takes over, and that's the reason why we developed these psychological or a psychology support service, because I felt that many patients were trapped into this, and they would continue their normal life, they were taken over."* HCP 5

Outcome Domain 7: Psychosocial adjustment to uveitis

Whilst psychosocial adjustment is influenced by psychological morbidity and emotional well-being, this domain describes patients' ability to adjust their life with the disease and how it affects their self-image. This is influenced by day-to-day interactions with others. Three components were identified in this domain (1) threats to psychosocial well-being – the things that indicate that patients are having difficulties with adjustment; (2) coping strategies – the strategies that people use in order to master, tolerate, or reduce the impacts of PSIU on

psychosocial issues; and (3) indicators of psychosocial adjustment. Related to this, interviewees discussed various threats to psychosocial well-being, for example, a feeling of loss of autonomy and independence:

> ***"I****t all relates back to I think the patient's ability to lead an independent life so that they can lead the life that they want to lead as best as they can do, and live with the disease rather than have their life dictated to them by the disease. Thus to cope with it, so they can manage their lives in such a way that their eye disease is a secondary thing, it's not impacting on their ability to move forward, new careers or their present career that they can… I think for a lot of them it reverts back to a facsimile of a life that they used to have prior to their diagnosis."* HCP 5

Another threat to psychosocial well-being discussed in the interviews was lack of predictability of the disease and impacts – related uncertainty regarding the future of the disease:

> *"We know that we cannot always give them a name, [or] that we can give a name that doesn't mean much as a descriptive thing and we don't really understand many times why they are having it. So we can say 'I can see the signs of the disease, I know where it's affecting your eyes but I don't know exactly why it's happening', and the second aspect is that we are realistic about knowing that what I want to do is prevent visual loss, but knowing that there is many times a limitation to that, and I can't just switch it off, I can't just cure them completely."* HCP 10

In response to those threats, interviewees pointed to the importance of the coping strategies that patients with PSIU use to enable them to master, tolerate, or reduce the impacts of PSIU on psychosocial issues. These may include a mix of psychological (e.g. acceptance of PSIU, positive attitudes, psychological support) and behavioural strategies (e.g. changing diet, stopping smoking or modifying day-to-day routines):

"I suspect things that might help is modifying their lifestyle … a very common question from patients is 'Is there anything I can do? Is there any diet I can follow? Anything like that will help improve this disease?', … I normally tell patients to go away and try [it], because who knows? Maybe they do.

Additionally… it's well known that if people smoke it makes macular oedema worse, so we always advise against that sort of thing. And then there are a small, I have to say a very small group of patients, where there are lifestyle events which seem to trigger off relapses of uveitis." HCP 1

Interviewees felt that psychosocial adjustment is crucial in patients with PSIU and is highly linked to patients' psychological and emotional support which helps to promote positive coping mechanism and helps to strengthen patients' ability to accommodate the disease:

"I think it's about facilitating support for that patient and not just expecting them to go out and find it themselves. For instance if they needed any support with employment, if they needed some advice or they their employers needed advice about what they could do to help, say the person has got problems using a computer and they need some support with that, some new equipment, and it's about putting them in touch with the right people and helped them to gain support, and that's what we would do in the hospital. So it's just making sure that when patients leave us they have contact numbers, they know that if they run into any problems that they have got someone they can call, they've got rapid access to hospital services, those sorts of things. I think there are some patients who really find it very difficult to cope with, and I think psychology support is essential." HCP 6

Interviewees also talked about indicators that people with uveitis have gone through processes of psychosocial adjustment. Related to this, this interviewee discussed patients' perceptions

of regaining vision and a sense of normality. Thus, there is a need for psychosocial adjustment to facilitate acceptance of the disease and required treatment that helps patients to function and carry on their normal activities:

> *"The expectation is to return back to normal. I mean your ability to see clearly enough to enable you to conduct your activities of daily living, the standard which you would deem normal for you. [This] could encompass field of vision (a proportion of patients have reduced field of vision); it could involve central vision acuity; it could involve near vision acuity, [or] distance visual acuity. These are all parameters of visual function.*"
>
> HCP 4

Outcome Domain 8: Doctor/patient/inter-professional relationships and access to health care

This domain describes the quality of the relationship between healthcare professionals, especially ophthalmologists, and patients. One ophthalmologist described how important it is to build a trusting relationship with patients and keep them in the loop during disease progression to create a better understanding of their situation. This participant touched on this by showing patients their eye scans and taking them through the changes comparing before and after treatment. The aim of this approach is to help patients have a better understanding of their eye condition, create positive engagement, enhance the patient and clinician relationship and encourage clinicians to listen to patients' concerns and try to help them:

> "*I always like to share what I see with the patient, so if I'm getting the results back and I can see what's happening, I try to explain to them what we are achieving with those steps that we are doing. So they have a feeling for 'yes my disease is changing'. So if you do a visual field …and the patient's fields are getting better you share that with*

them. You explain to them. It's easier for them to be reassured that something positive is happening even though they are not totally aware of it; that things are not getting worse or that they are getting some improvement. So it's important that this information, these things are shared with the patient and explained to them." HCP 5

In describing the doctor/patient relationship patients' engagement in treatment, decision-making was discussed. This participant expressed some degree of uncertainty around how much engagement in shared decision-making some patients desired and expressed a need for both parties to understand the other's perspective:

"We don't communicate with patients particularly well, and I don't know how engaged or how much they want to be engaged with understanding what our outcomes are… shared decision-making is a great expression, but it's tough to make shared decision-making when neither understand the other's perspective. So that involves a certain amount of understanding and also an understanding of the willingness of the patient to understand the medical perspective, but also willingness of physicians to take heed of the patient perspective." HCP 3

Healthcare professionals expressed the importance of access to healthcare facilities including psychological, social and practical facilities (e.g. visual aids). This was described by counselling advice received from ophthalmologists and referral to specialist support services where appropriate. Ophthalmologists emphasised the need to inform patients about available support services and advise on the referral process. For example, ophthalmologists advised on available psychotherapy and counselling services and the process of including them in this service which has become a part of the uveitis care service in a few NHS Trusts. The emphasis given to this topic by the participants indicates the importance and the role of psychological support:

"We created a group of psychologists; we have two psychologists working with us who we would flag to them anyone in clinic who we felt needed to talk to them and we offer that to patients and the patients would have a chance to speak to them. They would assess the patients, they would decide if anything beyond that needs to be done so they could escalate the care towards something higher like a senior psychiatrist or any help, mental health groups in the location when they leave. [We] involved them with that intention because we knew that these patients were struggling. Many of them were struggling very badly with the disease, with the management, with everything, and they had no one to talk to. In clinics we are not equipped to talk, we don't have the time, and most of the patients leave frustrated because they get the prescriptions, the instructions and all that but they haven't had a chance to talk to anyone about their problems. That's why I fought very hard to introduce this." HCP 5

Further discussion focused on accessing visual support services that aim to provide visual aids and support patients with PSIU to live their lives:

"I meant referring them to visual support services, whether that's the RNIB, whether it's Action for Blind People, that kind of thing. So it's about facilitating that and just enabling that process. There's Russell's, they have got loads of aids, walking stick, and they gave gadgets that when you are pouring a drink it tells you when to stop. There's the scanner they use where you can scan a newspaper and it projects on the TV, things like this. There's loads of gadgets that you use now, people have been using in trial, those glasses that can detect some motion." HCP 6

Outcome Domain 9: Treatment burden

Treatment burden is the workload of healthcare undertaken by patients and carers. Healthcare professionals described the amount of effort that patients are required to make in order to

manage their health condition. Interviewees highlighted a significant treatment burden as a result of frequent hospital visits, amount of medication and adherence to the treatment. Thus treatment burden could hamper patients' general well-being and day-to-day life:

> *"Well I suppose another thing might be they might start to feel a bit institutionalised because they're having to come to hospital a lot, and being checked… frequent hospital visits, I think that can be difficult."* HCP 6

Additionally healthcare professionals expressed a proportional relationship between frequency/intensity of symptoms and the amount of effort needed to manage those symptoms including frequent hospital visits and additional treatment:

> *"I think obviously patient symptoms are important, if they have pain, if they have visual quality of life issues, it will impact their life in-terms of how many times they have to go to the hospital, how many times they have to inject the medicines, how many times they have to see the doctor."* HCP 10

Additionally, healthcare professionals discussed the impacts of treatment on patients' psychosocial status and the routine they have to establish around the treatment in order to run a normal life:

> *"So taking the drugs it's not easy. People who don't need to take medication don't realise the burden of having to take medications. There is a burden to the body and to the mind of having to do that, every day remembering you have to take tablets in the morning, in the middle of the day, at night, two drops, so their lives change, they cannot run a normal life anymore. If you are going to travel they have to remember to bring all the medication with them, they are afraid of relapses when they are going away, all this is stuff that we don't think about but they think about."* HCP 5

Outcome Domain 10: Treatment side effects

Discussion with healthcare professionals also focused on the safety aspects of medication and their potential side effects. Healthcare professionals referred to reducing or having no side effects as a desired outcome. Healthcare professionals indicated that general health matters the decision of the healthcare professional as to what medication should be given to the individual. Consequently, clinicians are working with their patients to achieve symptom-free and minimal or no side effects:

> *"Everything needs to be done within the safety of the patient's general health, so you have patients who because of other problems to their health will not tolerate some treatments well or have more side effects or will really have problems that will stop some drugs being used, and so the outcome is apart from all this making sure safety of the patient, safety on the way you manage the patient, you don't induce any more complication."* HCP 5

Healthcare professionals reported two main side effects comprising ocular and systemic aspects as described in the following quote:

> *"Aspects like cataracts or intraocular pressure rises that could be an adverse effect, corneal health, retinal detachment, any of these that could be safety issues-related to the treatment should be captured. From my experience the most common morbidity and side effects are due to long term steroids, so the side effects and adverse effects of long-term steroids are significant. So I think osteoporosis, diabetes, weight gain, stomach problems, infections, hypertension, skin, all these side effects of steroids are probably cumulative and much greater than the side effects from people on immunosuppression."* HCP 2

Further discussion highlighted the treatment adverse effects on the psychological and

emotional status of patients, especially of corticosteroids:

> *"The treatment itself, especially steroids can make them have psychological side effects which we completely under acknowledge, so they will be stressed, they will be sleepless, they will be either very happy or very sad, and then their partner is the one who has to tolerate it.*" HCP 7

Side effects were associated with treatment burden by which additional hospital visits, admissions and further treatment are required. Interviewees felt this is very costly to the patient in ways other than money e.g. health issues:

> *"The cost I mean the side effects, all the damage that they can suffer from the treatments we are giving. So patients who develop renal problems because of the drugs we use, or become diabetic, or the diabetes develops further, anything that is related to the treatment, exposure to the treatment which can cause health issues is a price you are paying, so they are paying a price for that, it's a question of how high is that price will be. So if you think they are okay with a low level of medication, controlling the eye problem and not suffering anything wonderful."* HCP 5

Furthermore, side effects negatively impact patients' functional ability and psychological and emotional well-being. This encompasses time lost from work and other day-to-day activities; as a result quality of life can be affected:

> *"There is an aspect of quality of life that I didn't mention and that's side effects. Some patients simply cannot get along with the medication that we offer them, and are debilitated by side effects. [It is] either their visual function or to be distraught by side effects. [This] also constitutes a problem for their quality of life. Quality of life means the ability to conduct their daily activities that exist without a feeling of lack of wellness. So that lack of wellness could be manifested by systemic symptoms, so for*

example: headache as a result of side effects, anxiety due to steroids, or depression induced by steroids. These are all physical symptoms which impact in terms of wellbeing. So I'm talking about a feeling of wellbeing." HCP 3

Outcome Domain 11: Disease control

Uveitis is essentially an inflammatory process within the eye, thus clinicians' main concern was to stop or control inflammation. This was explored in detail by healthcare professionals, especially ophthalmologists:

"*Chronic recurrent inflammation is damaging to the eye, so your objective is to control inflammation the best you can and prevent the recurrences of the disease in the future. So it prevents progression to a chronic disease or prevents recurrences that could be damaging. It's very intense. So I think objective is to try to improve inflammation, prevention of recurrences and hopefully prevention of visual loss."* HCP 5

Ophthalmologists highlighted how important it is to stop the disease process and prevent disease progression to preserve patients' vision where possible, with no or minimal side effects. It is therefore important for patients not to suffer major adverse effects and to try to maintain a lifestyle where possible:

"The aim is to stop the disease process itself; often it's not possible in uveitis, and particularly in conditions like idiopathic uveitis. Often you have to deal with patients balancing the treatment and lifestyle issues. [The aim is to] balance between good control of the disease, less side effects in the medication patients have to take, less visits a patient has to make to the hospital, and create a good work life balance." HCP 4

Disease complications were also perceived as an important outcome in the process of

controlling the disease and its progression. Ophthalmologists described a positive relationship between visual function and retinal complications. For example, uveitic macular oedema (UMO) is associated with poor distance vision and reading vision which can consequently impact patients' functional ability (e.g. driving, working, reading, computer work and day-to-day activities). Furthermore, retinal vasculitis/retinitis describes inflammation either to the retinal blood vessels or to the retina (the light sensitive layer at the back of the eye) is also linked to patients' peripheral vision. Therefore assessing patients' visual field is essential in those patients:

> "*Visual function was correlated to the retinal findings. For example drop in visual acuity is linked to macular oedema. So for example if you've got [some forms of] posterior segment involving uveitis there may be no retinal vasculitis but there is macular oedema, in which case you should select pure visual acuity and macular thickness [as your outcome measures]. If you have retinal vasculitis you would select visual field for example as one of your [outcome] measures, and that's what your index consists of. You have a minimum of two or three features within the index that you target for use, or for your patients, because clearly not everyone will have all aspects of disease who have expected to have inflammation."* HCP 3

Furthermore, ophthalmologists described several inflammatory markers used to assess the disease activity (e.g. anterior chamber activity, vitreous activity or vitreous haze) which are useful measures to support structural changes (e.g. macular oedema). However, it is most important to link those findings to patients' functional ability and visual function:

> "*Certainly any marker of inflammation that can be linked to patient benefit would certainly be considered: change of anterior chamber inflammation grade, change in vitreous inflammation or vitreous haze, change in visual acuity. So I think anatomical*

measures are potentially relevant if they are supportive of its physiological parameters and if they can be linked to patient benefits and quality of life." HCP12

Further discussion was constructed in regards to flare up and relapses. Relapse was also associated with visual function and therefore was considered as an important outcome in controlling uveitis:

"So one definition might be a relapse that requires an increase in systemic steroid dose for example. So for that patient each time they have a relapse they need the steroid dose to go up, so the cumulative steroid dose over one year if they have two or three relapses is high. So the outcome in that patient would be the aim would be to reduce the number of relapses to zero so you don't need to have recurrent flare ups… recurrent doses of steroids. Then there's each relapse is associated with a reduction in vision, then the aim would be to prevent any relapses that's reducing their vision, so they have good vision throughout the year instead of every three months they can't see properly." HCP 2

7.3.4 Comparison of healthcare professionals views on outcomes with (a) patients and carers views and (b) findings of a systematic review of the effectiveness of pharmacological agents for macular oedema associated with non-infectious uveitis of the posterior segment

Healthcare professionals discussed all outcomes and outcome domains identified in our systematic review. A comparison of outcome domains and items between professional interviews, focus groups with patients and carers and outcomes assessed in clinical research identified via systematic review is reported in Table 9. This illustrates the limited range of outcomes assessed in trials to date. In these interviews healthcare professionals focused on

outcomes in the disease control domain, identifying various outcomes that were not expressed by patients/carers in the focus group discussions such as inflammatory grading (e.g. anterior segment inflammation, vitreous inflammation, and vitreous haze) and structural changes (e.g. retinal vasculitis, retinal scar/atrophy/ischaemic, optic atrophy). They also highlighted outcomes that help to prevent the progression of the disease and stop or limit the disease process, and which help to reduce medication load and hospital visits.

Table 9: Comparison of outcome domains and items between professional interviews, focus groups with patients and carers and outcomes assessed in clinical research identified via systematic review

Outcome domains and items	Healthcare Professionals	Patients/carers	Systematic review
Visual function			
Distance vision	✓	✓	✓
Near vision	✓	✓	
Contrast sensitivity	✓	✓	
Colour vision	✓	✓	
Peripheral vision	✓	✓	
Depth perception		✓	
Symptoms			
An uncomfortable or painful eye/s	✓	✓	
Photosensitivity	✓	✓	
Redness	✓	✓	
Floater	✓	✓	
Visual disturbance	✓	✓	
Distortion of vision	✓	✓	
Fatigue		✓	**
Watery eye		✓	

Headache		✓	
Functional ability			
Work/employment (maintaining / adjustments)	✓	✓	
Driving/commuting related impact	✓	✓	
Education related impact		✓	
Activities of daily living and self-care	✓	✓	
Participation in social and leisure activities	✓	✓	
Impact on relationships			
Intra-family and spousal relationships; friendships	✓	✓	**
Financial impacts			
Financial cost to patients due to early retirement, the need to take a part-time job or redundancy	✓	✓	
Financial cost to patients due treatment-related cost (e.g. travelling cost)	✓	✓	
Psychological morbidity and emotional well-being			
Depression and mental illness	✓	✓	**
Anxiety	✓	✓	
Stress	✓	✓	
Frustration and Anger		✓	
Emotional wellbeing	✓	✓	
Psychosocial adjustment to uveitis			
Threats to psychosocial well-being	✓	✓	
Coping strategies	✓	✓	
Indicators of psychosocial adjustment (sense of normality, sense of self and identity)	✓	✓	
Doctor/patient/inter-professional relationships and access to health care			
Clinician-patient relationship/communication	✓	✓	

Inter-professional relationships		✓	
Shared decision-making	✓	✓	
Access to uveitis clinics and/facilities		✓	
Access to physical aids and other resources	✓	✓	
Access to counselling and psychotherapy services	✓	✓	
Treatment burden			
Number of hospital visits	✓	✓	
Amount of medications	✓	✓	
Adherence	✓	✓	
Treatment side effects			
Treatment side effects (ocular and systemic)	✓	✓	✓
Disease control			
Anterior segment activity (cells, flares)	✓	*	✓
Vitreous activity (cells, haze)	✓	*	✓
Retinal vasculitis	✓	*	✓
Retinitis	✓	*	✓
Raised intraocular pressure	✓	✓	✓
Macular oedema	✓	✓	✓
Cataract	✓	✓	✓
Other ocular comorbidities	✓	✓	
Prevent disease progression and long-term damage including retinal scar/atrophy/ischaemic, optic atrophy	✓	✓	
Prevent Flare/relapse/recurrence	✓	✓	✓

* Patients discussed inflammation but didn't use these specific terms to reflect inflammatory markers and retinal inflammation highlighted by the healthcare professionals

** A single study stated that these components of HRQoL were assessed using the SF-36, but no further information was provided.

7.4 Discussion

This chapter reports important outcomes and outcome domains for a non-infectious PSIU COS identified through telephone interviews with healthcare professionals. The study identified 38 outcomes and grouped these into 11 outcome domains; 1) visual function, 2) symptoms, 3) functional ability, 4) impact on relationships, 5) financial impact, 6) psychological morbidity and emotional well-being, 7) psychosocial adjustment to uveitis, 8) doctor/patient relationships and access to healthcare, 9) treatment burden; 10) treatment side effects, 11) disease control.

Healthcare professionals' views were actually quite similar to patients and carers during the focus group study (Chapter 6). The domains developed via the analysis of the focus group data were directly applicable to the data elicited during the interviews with professionals. Healthcare professionals recognised most of the issues discussed by patients and carers in the focus groups. There were some subtle differences in the contents and emphasis of discussion between patients and carers and healthcare professionals. For example, whilst both patients/carers and healthcare professionals identified a wide range of symptoms (e.g. pain, red eye, visual disturbance), patients and carers focused a lot on fatigue, whereas healthcare professionals focused more on visual symptoms such as floaters and their impact on patients' functional ability.

Healthcare professionals tended to discuss the disease control and side effects/complications to a greater degree. Despite this, there is a notable concordance when considering the recognition of relevant issues and concepts between patients, carers and healthcare professionals. Despite this shared recognition of the wide range of impacts of PSIU, the discordance with outcomes identified in the systematic review highlights the extent to which these issues are not adequately addressed in either clinical practice or clinical trials. A good

example is the fact that patients, carers and healthcare professionals all conceived visual function in a multi-faceted (e.g. distance vision, near vision, peripheral vision, colour vision, and contrast sensitivity) and holistic manner compared to the relatively limited measures and assessments available and used in clinical practice and research (328, 329, 336).

Although healthcare professionals focused on floaters, evidence suggests that in clinical practice the impact of floaters on patients' functionality might be under-estimated by clinicians. Interventions e.g. medical and/or surgical may be indicated in some patients to improve their quality of life and functional ability. Younger patients who belong to a working class population are more likely to be affected by those visual symptoms and they may need therapeutic interventions to improve their lifestyle and functionality (353). Interestingly, the effect of floaters on functional ability and quality of life was assessed using time trade-off (TTO) utility value and was found to have a significant negative impact on patients' quality of life. The utility values for patients with floaters are comparable to those patients with age-related macular degeneration and diabetic retinopathy who are having similar visual acuity (353, 354). Furthermore, recent studies found a positive correlation between floaters and reduction in contrast sensitivity function (355, 356), therefore patients with symptomatic floaters are likely to suffer more psychological problems such as anxiety, depression and stress (357).

To our knowledge, this is the first piece of qualitative research to explore the views of healthcare professionals on outcomes of importance in the management of patients with non-infectious PSIU. Although clinical experts' opinions were sought at the Standardisation of Uveitis Nomenclature (SUN) workshop in 2005, the SUN workshop aimed to help clinicians assessing uveitis ocular inflammation and agree standardised grading tools rather than providing a comprehensive list of outcomes in the field. Our qualitative findings present a broader picture of the impact of PSIU and related treatment on patients' lives that was not

addressed in the SUN workshop.

The disease control domain and its associated outcomes were discussed in all interviews. From clinicians' point of view, it is important to assess the disease activity and severity of the disease. Some but not all components of disease control are linked to visual function. For example, uveitic macular oedema (UMO) is linked to central vision (e.g. reading vision) and retinitis/retinal vasculitis is linked to peripheral vision. Healthcare professionals noted that treatment decisions were multi-factorial and included a consideration of the clinical findings including inflammatory markers, structural changes (e.g. UMO) and visual function and the patient's associated functional ability. Considering all those components would allow a comprehensive assessment of patients' health condition and provide a meaningful dialogue with patients, carers, and other stakeholders involved in the management of PSIU. It is crucial to understand whether an improvement in disease control outcomes would result in an associated positive impact on patients' lives through improved functionality. For example, a patient is likely to notice a benefit after improved disease control if they have reversible macular oedema but not if that inflammation has become associated with a macular scar.

Strengths and limitations

This is the first qualitative research study to investigate healthcare professionals' views regarding outcome domains relevant to outcome assessment in non-infectious PSIU. It explicitly asked healthcare professionals to identify outcomes that can impact adult patients with non-infectious PSIU. Interviews created an in-depth discussion that was compatible with the research objectives. Interview discussions provided a comprehensive data set. No new insights were emerging during the last interview suggesting that data saturation was achieved within this sample (266, 352).

Secondly, a purposive sample was utilised covering a wide range of sampling characteristics including the level of experience in ophthalmology and uveitis, level of involvement in uveitis clinical trials and patients groups. Furthermore, various NHS sites across the UK were used.

There are two limitations to the study sample: Firstly the study did not include healthcare professionals outside the UK. Therefore data in this chapter was gathered from UK participants only. However, most of the healthcare professionals interviewed have some international experience and are part of international expert groups. It is likely that the issues relevant to clinicians practising in uveitis in the UK will have international relevance. Secondly, the number of health policy-makers and commissioners was relatively low. We cannot, therefore, be sure that further interviews with this group would not identify other domains and outcomes relevant to policy-makers and commissioners.

7.5 Conclusion

This project explored healthcare professionals' perceptions on outcomes important to non-infectious PSIU patients with and without UMO. These telephone interviews provided rich data on the perceived impact of PSIU covering eleven outcome domains. The data collected from the healthcare professionals were combined with those identified through a systematic review (Chapter 4), with those collected from patients and carers (Chapter 6) to provide the long-list of outcomes used to inform our Delphi methodology, the next stage in the development of a COS for uveitis (see chapter 8). This combined qualitative study for the project (focus group discussion and interviews) provides a platform for the development of COS that has value to all included stakeholders.

Chapter 8: Development of a Core Outcome Set for Clinical Trials in Non-Infectious Posterior Segment-Involving Uveitis

8.1 Background to chapter 8

A wide range of outcomes have been reported in clinical trials of uveitis with marked heterogeneity and inconsistency around those measured and reported outcomes, hindering evidence synthesis. A core outcome set (COS) offers a solution to overcome this issue and provides an agreed set of outcomes for use in all effectiveness PSIU trials (Chapter 5).

This chapter addresses the central aim of the thesis and presents a robust methodology recommended by the Core Outcome Set Measures in Effectiveness Trials (COMET) initiative in the development of a Core Outcome Set for clinical trials in non-infectious PSIU. The study was registered and published in COMET initiative database, and the full protocol was published prior to study commencement and presented in chapter 5.

The findings of this chapter describe in-detail the phases used to arrive at a standardised set of outcomes for use in PSIU trials. *Phase 1*: A comprehensive list of outcomes was identified through both a systematic review of effectiveness trials of PSIU and qualitative research with stakeholders. *Phase 2*: A consensus process was used to ascertain what outcomes participants think are important for adult PSIU to be included in the core set through both a two round Delphi exercise and a consensus meeting with key stakeholders. Pre-defined consensus criteria were used to establish which outcomes were included in the COS. The COS includes 16 outcomes grouped into 4 outcome domains comprising visual function, Health-Related Quality of Life (HRQoL), treatment side effects and disease control. This chapter is presented in the format of a paper version, submitted to the peer reviewed Journal, *Ophthalmology*. At the

time of writing the paper is currently under review.

Publications

1. Tallouzi, M.O., Mathers, J.M., Moore, D.J., Murray, P.I., Bucknall, N., Blazeby, J.M., Calvert, M. and Denniston, A.K. Development of a core outcome set for efficacy and effectiveness trials in adult patients with posterior segment-involving uveitis. COMET database 2015. Available from http://www.comet-initiative.org/Studies/Details/640

2. Tallouzi, M.O., Mathers, J.M., Moore, D.J., Murray, P.I., Bucknall, N., Blazeby, J.M., Calvert, M. and Denniston, A.K., 2017. COSUMO: study protocol for the development of a core outcome set for efficacy and effectiveness trials in posterior segment-involving uveitis. *Trials, 18*(1), p.576.
   Available from: https://doi.org/10.1186/s13063-017-2294-8

3. Tallouzi MO, Mathers JM, Moore DJ, Bucknall N, Calvert MJ, Murray PI, Denniston AK; COSUMO Working Group. Development of a Core Outcome Set for Clinical Trials in Non-infectious Uveitis of the Posterior Segment. Ophthalmology:S0161-6420(21)00070-1.
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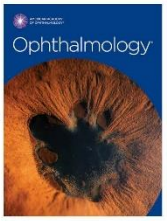
8.2 Accepted COS paper

Journal Pre-proof



Development of a Core Outcome Set for Clinical Trials in Non-infectious Uveitis of the Posterior Segment

Mohammad O. Tallouzi, Jonathan M. Mathers, David J. Moore, Nicholas Bucknall, Melanie J. Calvert, Philip I. Murray, Alastair K. Denniston, COSUMO Working Group

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Development of a Core Outcome Set for Clinical Trials in Non-infectious Uveitis of the Posterior Segment

Mohammad O. Tallouzi[1, 2, 5], Jonathan M. Mathers[1], David J. Moore[1], Nicholas Bucknall[3], Melanie J. Calvert[1, 5, 6*], Philip I. Murray[2, 4 *], Alastair K. Denniston[4, 5, 7*], COSUMO Working Group

[1]Institute of Applied Health Research, College of Medical and Dental Sciences. University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

[2]Birmingham and Midland Eye Centre, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham B18 7QH, UK

[3] Patient Involvement Group in Uveitis (PInGU), Birmingham, B15 2TT, United Kingdom.

[4]Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK.

[5]Centre for Patient Reported Outcome Research, Institute of Applied Health Research, College of Medical and Dental Sciences. University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

[6]NIHR Birmingham Biomedical Research Centre, NIHR Surgical Reconstruction and Microbiology Research Centre and NIHR Applied Research Collaboration (ARC) West Midlands at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham

[7]Department of Ophthalmology, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2WB, UK

* These authors contributed equally to this work and share the role of senior author.

Corresponding author: **Mr Mohammad Tallouzi**, Institute of Applied Health Research, College of Medical and Dental Sciences. University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Academic Unit of Ophthalmology. Birmingham and Midland Eye Centre, Sandwell and west Birmingham Hospitals NHS Trust, City Hospital, Dudley road B18 7QH. Email: mohd.tallouzi@nhs.net

Abstract

Purpose

To develop an agreed set of outcomes known as a core outcome set (COS) for Non-Infectious Uveitis of the Posterior Segment (NIU-PS) clinical trials.

Design

Mixed-methods study design comprising a systematic review and qualitative study followed by a two round Delphi exercise and face-to-face consensus meeting.

Participants

Key stakeholders including: patients diagnosed with NIU-PS; their caregivers; healthcare professionals involved in decision-making for patients with NIU-PS including ophthalmologists, nurse practitioners and policymakers/commissioners.

Methods

A long list of outcomes was developed based on the results of (1) a systematic review of clinical trials of NIU-PS and (2) a qualitative study of key stakeholders including focus groups and interviews. The long list was used to generate a two-round Delphi exercise of stakeholders rating the importance of outcomes on a nine-point Likert scale. The proportion of respondents rating each item was calculated, leading to recommendations of 'include', 'exclude' or 'for discussion' that were taken forward to a face-to-face consensus meeting of key stakeholders at which the final COS was agreed.

Main outcome measure

Items recommended for inclusion in the COS for NIU-PS

Results

A total of 57 outcomes grouped in 11 outcome domains were presented for evaluation in the Delphi exercise, resulting in 9 outcomes directly qualifying for inclusion and 15 outcomes being carried forward to the consensus meeting of which 7/15 were agreed for inclusion. The final COS contained

16 outcomes organized into 4 outcome domains comprising visual function, Health Related Quality of Life (HRQoL), treatment side effects and disease control.

Conclusion

This study builds on international work across the clinical trials community and our qualitative research to construct the world's first COS for NIU-PS. The COS provide a list of outcomes that represent the priorities of key stakeholders and provides a minimum set of outcomes for use in all future NIU-PS clinical trials. Adoption of this COS can improve the value of future uveitis clinical trials and reduce non-informative research. Some of the outcomes identified do not yet have internationally agreed methods for measurement and should be the subject of future international consensus development.

Trial Registration

The study was registered with COMET (http://comet-initiative.org/studies/details/640)

Key words

Uveitis, outcomes, core outcome set, macular oedema/edema, domain, Delphi technique/exercise, consensus method, clinical trials, key stakeholders.

Precis

This study presents the development of a core outcome set (COS) for non-infectious uveitis of the posterior segment (comprising intermediate, posterior and panuveitis) to ensure outcomes represent the priorities of all stakeholders, to enhance evidence synthesis and reduce research waste.

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1. Background

Uveitis describes a group of diseases characterized by intraocular inflammation (1-6), responsible for 10–15% of total blindness in Europe and North America (7) and up to 25% of blindness in the developing world (1-5, 7). Intermediate, posterior and panuveitis are the most sight-threatening forms of uveitis that often share a number of common features including their higher risk of sight-threatening complications (e.g. uveitic macular edema, UME) and their requirement for systemic or local injection-based therapy. Those forms affect the more posterior structures of the eye and are often grouped together as non-infectious uveitis of the posterior segment (NIU-PS) (8, 9). Uveitis may be due to (a) an infectious agent or (b) non-infectious inflammation, either as a part of an underlying systemic disease or purely confined to the eye (10). Non-infectious uveitis is the most common type observed (11) and is the focus of this study.

A clinical trial is conducted to evaluate the safety and efficacy of a new or existing medical treatment, drug, or device (12) with a view to providing the evidence that will enhance decision making across individual patient care, clinical guidelines and health policy (13). The information gained from such trials may however be limited if key stakeholders do not regard the outcomes measured as being relevant, or if trials all measure different outcomes or the same outcomes are being reported/measured in different ways such that findings cannot be compared or evaluated across studies such as through a meta-analysis (14). Within NIU-PS, there is marked inconsistency and heterogeneity in reporting and measuring outcomes (15), with a systematic review noting that across 104 clinical trials identified, 14 different outcomes were used as a primary outcome, most

commonly 'visual acuity', 'vitreous haze' or 'macular edema'. Even where the same outcome was used there was often variation in the way it was measured, analyzed and reported (16). Additionally some trials failed to report the outcome and its measurement sufficiently well for comparison or replicability further limiting the contribution of such trials to evidence synthesis (17, 18).

The standardization of a core outcome set (COS) for use in effectiveness trials is one way to address inconsistent use and inappropriate reporting of outcomes (19). A COS is an agreed minimum set of outcomes for use in clinical trials for a specific health condition using a systematic, standardized approach for outcomes selection and reporting. COS are not restrictive since other outcomes can be collected in addition to the COS, but rather this approach ensures that certain key outcomes are always collected in a standardized way, reducing reporting bias and facilitating study comparison and meta-analysis (19, 20). COS methodology is designed to ensure that the views of all key stakeholders are elicited for consideration during COS development to ensure that the final COS includes outcomes that matter to patients, clinicians and policy-makers/commissioners (20).

To date COSs have been developed for a number of areas in ophthalmology including dry eyes (21), cataract (22), macular degeneration (23), glaucoma (24), thyroid eye disease (25), strabismus and ocular motility disorders (26), with ongoing work in cerebral visual impairment (27) and Behcet's syndrome (28).

The development of a COS for NIU-PS has the potential to profoundly enhance the value of trials in this condition, through avoiding inappropriate outcome measures and providing the standardization needed to enable comparison and meta-analysis of outcomes across trials (even where they may have selected different primary outcomes) (20, 29). In this study we aimed to develop a COS for NIU-PS according to robust methodology that represents the priorities of all groups of stakeholders and supported by international consensus, with a view to supporting the uveitis community to enhance research pertinence and provide long-term value for every future clinical trial into this sight-threatening condition (30).

2. Methods

2.1 Study design

The study was registered with the Core Outcome Measures in Effectiveness Trials (COMET) initiative (published online at http://www.comet-initiative.org/Studies/Details/640) (19), and the full protocol was published prior to study commencement.(31) In brief, a three-phase approach was used to develop the COS (**Error! Reference source not found.**). First, a comprehensive list of outcomes was identified through a review of outcomes reported in existing trials (systematic review) and focus groups and semi-structured interviews with stakeholders (qualitative study). Second, a Delphi exercise was conducted with key stakeholder groups to prioritize outcomes for inclusion through sequential online surveys. Third, a consensus meeting was held with key stakeholders (patients, caregivers, health care professionals) to discuss the Delphi results and agree on the final outcomes in the COS (31).

Methods from Phase 1: Identifying a comprehensive list of potential outcomes for consideration

A) Outcomes identified through systematic review of trials in NIU-PS

A systematic review was conducted on the effectiveness of pharmacological agents for NIU-PS (including NIU-PS with UME) to identify candidate outcomes for inclusion in the core outcome set (32, 33).

Standard systematic review methodology (34, 35) was employed to identify, select and extract data from comparative studies of pharmacological interventions in patients with NIU-PS and associated macular edema. Searches were conducted (February 2017) through bibliographic databases (Cochrane Library, MEDLINE, EMBASE and CINAHL) and clinical trials registers e.g. clinicaltrials.gov, International Standard Randomized Controlled Trials, WHO International Clinical Trials Registry Platform and UK Clinical Research Network. No restriction was placed on either language or year of publication. Translation of non-English language articles was undertaken to minimize selection bias. Data extraction included the following: basic trial information and name; investigator names; year of study; primary outcome and secondary outcomes; method of measurement and analysis for all outcomes (33).

B) Outcomes identified through qualitative research with key stakeholders

- **Focus groups**

Four focus group discussions were conducted with patients who had NIU-PS. Participants were grouped according to whether or not their uveitis was complicated by the sight-threatening condition uveitic macular edema (UME). Macular edema is the most common cause of vision loss in uveitis and is a frequent outcome measure in major clinical trials in the field (6, 16, 36) . This part of the study is described in full in our previous report (37).

- **Telephone interviews**

Twelve one-to-one telephone interviews were conducted with UK healthcare professionals (ophthalmologists, nurse practitioners and policy-makers/commissioners) who are involved in decision-making for patients with NIU-PS either directly or through policy.

Focus group discussions and interviews were audio recorded, professionally transcribed and analyzed using a framework analytical approach (38). Initially, the transcripts were read repeatedly to allow familiarization with the data and help the generation of the preliminary codes supported by the qualitative data analysis software NVivo version 12 (QSR International- Pty Ltd, Australia). A coding framework was developed iteratively (4-6 times) by two researchers in consultation with the broader research team. During this process our definition of an outcome was broad, including any consequence of NIU-PS or its treatment that clearly had significance to NIU-PS patients. Once we had finalized our coding framework it was then applied to the whole dataset from interviews and focus groups (indexing).

Compiling the 'long list' for evaluation

The outcomes identified through the systematic review and qualitative research were aggregated and evaluated by two researchers (MT and JM) for removal of any duplicates, and refinement to ensure their meanings were clear, with any disagreement being adjudicated by (PIM and AD). Outcomes were then grouped into broader *outcome domains*. For example, the domain '*Functional*

185 *ability'* was created to group the following items: work/employment, educational participation;
186 driving; activities of daily living and self-care; participation in social and leisure activities (37).

187 All outcome domains were then converted into questionnaire items which asked participants to rate
188 the importance of including each outcome in future research trials. To ensure the questionnaire was
189 easy to read and understood by all stakeholder groups, definitions of outcomes including the type of
190 language used was informed by the qualitative research findings, NHS choices and patient facing
191 medical information. The questionnaire was piloted with patients and caregivers to examine
192 understanding, usability and highlight any potential practical issues prior to the next phase.

193 **Methods from Phase 2: Delphi Methodology**

194 **2.2 Delphi participants' eligibility criteria**

195 Participants were recruited from all key stakeholder groups. Inclusion criteria were as follows:
196 *Patient participants*: confirmed diagnosis of NIU-PS (intermediate uveitis, posterior uveitis or
197 panuveitis) with or without macular edema; were under active follow-up for the disease; were at
198 least 18 years of age; had a capacity to read and write in English.
199 *Caregiver participants:* adult caregiver for someone with NIU-PS. A caregiver was defined as a person
200 who was at least 18 years of age (e.g. friend, family member or spouse) and providing unpaid care to
201 the patient during his/her illness.
202 *Healthcare professional participants:* ophthalmologists or nurse practitioners directly involved in
203 caring for patients with NIU-PS.
204 *Healthcare policy-makers and commissioner participants:* individuals who may have influence on
205 uveitis care at the health system level e.g. through defining or implementing policy, regulatory
206 approvals related to NIU-PS.

207 **2.3 Recruitment**

208 Recruitment was as follows:
209 *Patient and caregiver participants:*

All eligible patients meeting the inclusion criteria attending the specialist uveitis clinics (Birmingham and Midland Eye Centre, Sandwell and West Birmingham Hospitals NHS Trust, UK; and Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, UK) from July-September 2018 were invited to take part in the study. Clinicians distributed the recruitment packs to the eligible participants. A recruitment pack included an invitation letter and a participant information sheet. Patients/caregivers were asked if they had any questions and whether they would be happy to be contacted regarding taking part in the research study. The clinical doctoral research fellow (MT) contacted potential participants 3-5 working days later asking if they were still interested in taking part the study. Agreement was confirmed with those who wished to participate, and details of the focus group discussions were sent at a later stage.

Participation in this study was voluntary, and therefore represents the views of those who were willing to engage with research. This may result in bias due to under-representation of certain groups. For patients and caregivers. We tried to attain sample diversity by purposively sampling with respect to age, ethnicity and gender. We did not undertake purposive sampling for all under-represented groups (e.g. higher levels of social deprivation). Focus groups were however continued until saturation of views was reached

Healthcare professional participants:

Ophthalmologists, health policy-makers and health commissioners were recruited via UK and international clinical, research and health service networks, such as the Uveitis National Clinical Study Group (UK) and the International Uveitis Study Group (IUSG), with purposive sampling to ensure a broad representation of geography and setting, supported by the COSUMO (Core Outcome Set in patients with posterior segment involving uveitis with and without Uveitic Macular Oedema) international advisory board; nurse practitioners involved in uveitis care were invited via an International Ophthalmic Nurses Group

Healthcare policy-makers and commissioner participants were identified through UK and international health service networks purposively sampling people in those roles who had been most

involved in uveitis policy decisions (e.g. regulators who had overseen policy on interventions in uveitis). For policy-makers we invited to ensure that at a minimum the major US and European regulators were included (FDA, EMA and MHRA). We recognize that there may be international variation in policy maker views that were not captured by this sampling.

Eligible participants were identified by consultant ophthalmologists (PIM and AD) and eligible participants were identified by consultant ophthalmologists (PIM and AD) and contacted via email, including a recruitment pack with an invitation letter and a participant information sheet. The clinical doctoral research fellow (MT) contacted all potential participants who had agreed to participate in the study, provided further information about the research and answered their enquiries prior to arranging an interview date. Participants were asked to provide their preferred method of contact and their telephone number for the interview. A convenient time and date were agreed and a reminder was sent two days prior. Verbal consent was obtained from each participant prior to commencing the interview.

Furthermore, for the Delphi study participants were given a unique ID number to gain access to the online Delphi survey. Informed consent was obtained prior to the study commencement. If a potential participant was no longer interested in taking part they were thanked for their time and interest in the study. All participants were asked to identify the key stakeholder group they belong to. Health professionals and health policy-makers were asked to provide their professional role and years of experience

2.4 Sampling of participants and sample size

We attempted to achieve a diverse sample with purposive criteria including patients of varying age, ethnicity and gender; with and without UME; with active and inactive disease: and with uveitis of different etiologies. For healthcare professionals, level of experience in ophthalmology/ uveitis and geographical area of work were considered. There is no consensus on the sample size used in Delphi methodology, however, the chosen sample size for both the Delphi exercise and the consensus

group is based upon previous Delphi studies (39, 40). Given the complexity of the topic, it was however considered that approximately 80 participants would be necessary for the Delphi exercise. In addition, approximately 25 participants would be approached for consensus meeting. A good representation from the key stakeholders (patients/ caregivers (54%), and healthcare professionals (46%) was considered which is generally regarded as good practice in terms of a COS being generalizable to future patients and in convincing other stakeholders of its value.

2.5 Ethical approval

Ethical approval for the study was granted by the UK National Research Ethics Service (NRES) West Midlands –South Birmingham Research Ethics Committee (Reference number 17-WM-0111).

Design and delivery of the Delphi Survey

The Delphi process was conducted in line with COMET recommendations (41). Participants' opinions were sought through two sequential rounds, with feedback from round 1 being provided anonymously to all participants prior to them completing round 2 (39). The Delphi was administered via an online survey (*Delphi Manager* Version 4.0, University of Liverpool, UK). Participants were asked to prioritize each outcome for inclusion in clinical trials of NIU-PS based on their level of importance using a nine-point Likert scale from 1 (no importance) to 9 (critically important). If a participant did not wish to complete the survey electronically, then a paper copy was provided; if participants had visual impairment, then the survey could be completed with assistance either via accessibility software (such as a 'screen reader') or from a cargiver or other individual who would read and record the responses without influencing them.

Delphi Rounds

Two Delphi rounds were conducted with all the stakeholder groups.

- **Delphi Round 1:**

Participants were asked to identify the stakeholder group that they belonged to and relevant additional features such as duration of uveitis (patients only); duration of caring for someone with

uveitis (caregivers only); and country of work, duration of experience in ophthalmology and uveitis (healthcare professionals and policy-makers/commissioners).

Participants were presented with a list of outcomes and were asked to rate the importance of each for inclusion in clinical trials for NIU-PS based on the nine-point Likert scale (1 = no importance; 9 = critically important). Participants were then also invited to answer the following questions in free text: (1) "Do you think there are any other outcomes relating to posterior segment involving uveitis that should be measured in research studies" and (2) "Any other comments?".

All new listed additional outcomes were reviewed by two researchers (MT, PIM) with a view to including in round 2 provided that they represented new outcomes. New outcomes were organized under appropriate existing outcome domains. All item scores in round 1 were summarized and retained for round 2.

- **Delphi Round 2:**

All participants from round 1 were invited to participate in round 2. All outcomes were again presented (including new outcomes from round 1) but accompanied by the results from round 1 including the number of responses and distributions of scores for each outcome, presented for both their own stakeholder and other stakeholder groups. Participants were asked to review their score and either keep it or amend if they wished to do.

2.6 Analysis of Delphi exercise

A statistical analysis using SPSS software 26 (IBM Corporation, Armonk, N.Y., USA) was conducted calculating total number of registrations; total number of participants in each stakeholder group; the response rate in each of the stakeholder groups and the proportion of respondents rating each outcome on the nine-point Likert scale. Partially completed questionnaires were excluded from the analysis process.

At the end of round 2, responses were analyzed to determine whether each outcome should be included in the final COS. The 9-point Likert scoring system where outcomes are graded in accordance to their level of importance is a common method used in COS. Typically, 1 to 3 signifies

an outcome is of limited importance, 4 to 6 important but not critical, and 7 to 9 critical (20, 42)This framework is recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group for assessing the level of importance about research evidence and has been widely adopted in other core outcome development research groups using Delphi methods (43).

All outcomes defined as 'consensus in' (an outcome was scored 7-9 by more than 70% of participants) were accepted and all outcomes defined as 'consensus out' (an outcome scored 1-3 by more than 70% of participants) were rejected. If discrepancy was noted among stakeholder groups about importance of outcome; further discussion was held at the consensus meeting. Attrition level following the closure of round 2 was assessed. Data analysis was summarized by the stakeholder group.

Phase 3: Consensus meeting

The consensus process concluded with a face-to-face meeting of key stakeholders and the research team. The meeting was led by an independent facilitator whose role was to lead, promote and mediate the discussion among the key stakeholders. Purposive sampling was used to ensure that there was appropriate balance of representation of the different stakeholder groups (patients, caregivers, ophthalmologists, nurse practitioners, health policy-makers and commissioners).
A list of outcomes were sent to all participants in advance of the meeting to make them aware of outcomes to be discussed in the meeting and enable them think independently what sort of outcomes they feel important to be included in the COS. The meeting included a summary of the work to date, discussion and voting on outcomes that have not achieved consensus through the Delphi exercise. The meeting then considered the outcomes as follows: (1) outcomes scored critically important (7-9) by over 90% of both patients/caregivers and professionals; (2) outcomes scored highly important (7-9) by over 70% overall, but where there was some disagreement between patients/caregivers and healthcare professionals (i.e. less than 60% of either patients/caregivers or professionals rated it critically important (7-9); (3) discussion and voting on

outcomes that have some degree of disagreement considering whether which of those outcomes should be included in COS when a clear rationale for inclusion is provided; (4) outcomes excluded during the Delphi process, and their rationale for exclusion.

Discussions were taken iteratively among the stakeholder groups before the final voting took place. All participants were asked to vote anonymously on those outcomes using an electronic voting software (Turning Technologies, Youngstown, Ohio, USA) highlighting the importance of each outcome on a nine-point Likert scale (1 =no importance; 9 = critically important). Outcomes were classified as 'Consensus In' if >70% of whole group voted 7-9 to retain in COS.

After voting was completed, all members including patients, caregivers and health professionals were then asked to ratify the final list of outcomes. Finally, all participants discussed and agreed the final categorization (outcome domains) for these retained outcomes in the final COS.

3. Results

Phase 1: Identification of long list of outcomes and development of survey questionnaire

A long list of items (n=142) was identified through systematic review, focus groups, and interviews. Items were reviewed, refined and amalgamated to form a single comprehensive list of 52 outcomes organized in 11 outcome domains comprising: (1) visual function, (2) symptoms, (3) functional ability, (4) impact on relationships, (5) financial impact, (6) psychological morbidity and emotional well-being (7) psychosocial adjustment to uveitis, (8) doctor/patient/interprofessional relationships and access to health care, (9) treatment burden, (10) treatment side effects, (11) disease control. Each domain was translated to generate a questionnaire item in the Delphi survey.

Phase 2: Prioritization of outcomes

Delphi Round 1:

A total of 116 participants were invited to participate in round 1; of those 80 (69%) responded, and 36 (31%) declined. A total of 33 patient/caregiver participants (41% of the total group) completed round 1 of the survey (28 patients; 5 caregivers). Participants in this group had a median age of 55

years (range 35-75 years); patients reported that they had uveitis for a mean of 14 years (range 5-28); caregivers reported that their duration of care was a mean of 11 years (range 5-25).

A total of 47 health professionals (59% of the total group) completed round 1 of the survey; of those 40 ophthalmologists (85%), 2 nurse practitioners (4%), 5 policy-makers (11%). Fifteen different countries from across the world were represented including: Australia (n=3), Austria (n=1), Belgium (n=1), Brazil (n=1), Canada (n=1), Germany (n=2), India (n=2), Italy (n=2), Japan (n=1), Singapore (n=1), South Africa (n=2), Switzerland (n=2), Tunisia (n=1), United States of America (n=6) and United Kingdom (n=22). Participants' demographic data for patients, caregivers and health professionals were similar between round 1 and round 2. All members (n=7) of the advisory group completed the Delphi exercise (Round 1 and 2). A more detailed profile on the socio-demographic details are reported in **Error! Reference source not found.**

Delphi Round 2:

A total of 74 participants completed round 2, comprising 26 patients (35%), 5 caregivers (7%), 36 ophthalmologists (49%), 2 nurse practitioner (3%) and 4 policy-makers (6%). Round 2 evaluated all 52 original items and five additional outcomes proposed during round 1 (**Error! Reference source not found.**). Nine outcomes were rated as critically important by over 90% of the participants and were recommended for inclusion in the COS; 33 outcomes were excluded based on the pre-specified thresholds; and 15 items were carried forward for discussion in consensus meeting. Summary of items scores and outcomes decision are reported in **Error! Reference source not found.**.

Phase 3: Consensus meeting

Of the 80 stakeholders who participated in the Delphi exercise, 24 participants attended the face-to-face consensus meeting that was held at the University of Birmingham on 23rd January 2020. These voting participants comprised 9 patients, 4 caregivers, 9 ophthalmologists, 1 nurse practitioner and 1 policy-maker; the ophthalmologists attending included members of the international advisory board (n=4) and represent current NIU-PS practice from around the world [including in Australia, Switzerland, Brazil, Germany and the UK].

The final COS of 16 outcomes was a conclusion of combined agreement across patients/caregivers and health professionals (is shown in **Error! Reference source not found.**. The meeting summarized the following

1. *Ratification of 'consensus in' items:* After review, the consensus group ratified all 9 items that had exceeded 90% of 7-9 scores by both patients/caregivers and professionals during the Delphi exercise.
2. *Discussion and voting of items that exceeded over 70% that had some degree of discordance between stakeholder groups during Delphi exercise:* After discussion the consensus group voted in 7 items from this category for inclusion into the COS. The consensus group advised that a number of items that were voted for inclusion should be incorporated into other items, notably:
    a. The outcome of continuing/maintaining education as a part of the outcome of work-related impact;
    b. The outcome of social and leisure activities as a part of day-to-day usual activities;
    c. The outcome of distortion of vision as part of visual disturbance.
3. *Review of any new items identified during Delphi round 2 or consensus meeting:* no new items were identified for evaluation or inclusion.
4. *Confirmation of 'consensus out' items:* The consensus group confirmed exclusion of all 33 items that had merited 'consensus out' on the prespecified threshold.
5. *Refining descriptions of items:* The consensus group advised a number of refinements including:
    a. The outcome 'retinitis' should be extended to include choroiditis and chorioretinitis in line with recent trial outcome definitions and the similarity of how these conditions would be experienced by a patient.

b. The outcome 'structural changes' should be extended to include retinal scarring, optic nerve damage (including glaucoma), formation or progression of band keratopathy, formation or progression of epiretinal membrane.

c. The definition of the outcome 'intraocular pressure' should be extended to include change in the pressure inside the eye above or below the normal range rather than raised intraocular pressure.

6. *Refining relations of items to domains and domain definitions:* The consensus group advised that:

a. The term 'Health Related Quality of Life (HRQoL)' was adopted as a domain title to include the following core outcomes: depression and mental well-being; work-/education-related impact, driving/commuting related impact, and day-to-day usual activities including social and leisure activities.

b. The domain 'Disease Control' should include clinical activity, structural changes and flare/relapse/recurrence.

c. The domain 'visual function' should include distance vision, near vision and visual disturbance

Discussion

This COS represents the culmination of a five-year program dedicated to discovering and defining the outcomes that are most important to patients with non-infectious NIU-PS, their caregivers and the healthcare professionals who are engaged with their medical care and the policies that support this care. COSs are increasingly recognized as a powerful tool for increasing relevance of studies and maximizing the value of clinical trials, both over the short and long term. In a health area such as uveitis where the number of clinical trials are few (44), there is perhaps an even greater ethical imperative to ensure that results from each trial counts and we measure the most relevant outcomes important to all stakeholders – is a key part of this.

A defining key feature of this first COS for NIU-PS, is the strong representation of different stakeholder groups. Empirically we recognize that there may be a diversity in the value that different stakeholders place on outcomes. We expect that for a patient or caregiver these outcomes are likely to reflect the lived experience of uveitis; for a clinician, the priority outcomes might be the measured visual acuity or the physical signs seen directly or on imaging; and for the policy-maker or commissioner, it may be the longer term functional impact or cost of care. In fact, it was striking that in our study there was relatively good concordance between stakeholder groups, although

differences were noted in round 2 of the Delphi exercise. For example, near vision was voted critically important by 93.5% of patients and caregivers while only 58% of healthcare professionals considered this important. A detailed discussion therefore concluded an agreement of inclusion by the vast majority of the key stakeholders. Furthermore, disagreement among the stakeholders was also noted for the item of formation of band keratopathy by which patients/caregivers were guided by the last part of the definition (that cause pain and a reduction in vision) and scored this as critically important (84%) compared to healthcare professionals (67%). However, following a detailed iterative discussion, both patients and caregivers developed a better understanding of the item and all agreed to exclude this item from the COS and keep it as a part of structural changes outcome.

Although systemic co-morbidities were scored highly by patients/cares (83.9%) and healthcare professionals (90.7%) in Delphi round 2, at the consensus meeting the vast majority of the stakeholders (90%) voted consensus out. This may have an impact on disease progression and could be linked to the uveitis etiology; however, this is not an outcome to be measured for clinical effectiveness of uveitis. A similar scenario was noted with the item "other ocular co-morbidities" that was scored highly by patients/caregivers (83.9%) and health professionals (93.0%) after Delphi round 2. However, when comorbidities were discussed in the consensus meeting the group considered that comorbidities were most relevant as an important parameter to record as an attribute of a patient going into a study (similar to demographic profile) rather than as an outcome. The group recognized that some comorbidities may arise as a consequence of an intervention, but advised that these would be captured by *Treatment Side Effects*. There was therefore consensus not to include comorbidities in the COS.

Although this is the first COS for NIU-PS, there have been previous initiatives with relevance to this area. For example, the Multinational Interdisciplinary Working Group for Uveitis in Childhood proposed an outcome set for JIA-associated uveitis (45), that has been registered on COMET database, although it is not explicitly described as a COS (41). This initiative has some similarities to

our study in that a long list of items were identified from a literature review, and that this underwent refinement through a Delphi process followed by a consensus meeting. Although of value, we would suggest that it has a number of limitations compared to our study, namely that the participants were all clinical experts without wider stakeholder representation, and there were no qualitative research elements to the study which might have generated outcomes that different stakeholders might deem important. However, it must be acknowledged that this study was conducted over a decade ago, and that even today the COS methodology and the incorporation of other voices (particularly the patient and caregiver) is still a relatively new phenomenon.

In this regard it is worth noting that the key Standardization of Uveitis Nomenclature (SUN) classification system was also based on clinical experts alone, however the lack of patient voice is less problematic here since SUN did not aim to be a comprehensive list of outcomes but rather an agreed set of definitions and its scope primarily covers the clinician's assessment of inflammatory activity within the eye (the SUN grading systems) (46).

Another strength was the study employed widely used consensus methods using a diverse sample including patients, caregivers, healthcare professionals and policy-makers from varied socio-demographic and clinical backgrounds. Furthermore, healthcare professional stakeholders were recruited from a wide geographical area including UK and other international countries. A robust consensus process therefore was achieved with a broad range of the key stakeholder representatives. Participants were actively involved in the consensus meeting discussion and the voting process.

There are some limitations to our study. We recognize that one could extend the systematic review stage of the study to include other types of studies of NIU-PS (including non-interventional), however our review focused on those studies where there is most intense research within uveitis, and where the adoption of a COS is likely to have maximal impact. Additionally, the qualitative stage within the COS process provided an opportunity for any outcomes not captured by the Systematic Review stage to be added.

Participation in this study was voluntary, and therefore represents the views of those who were willing to engage with research. This may result in bias due to under-representation of certain groups. For patients and caregivers we tried to address this by undertaking purposive sampling with respect to age, ethnicity and gender. We did not undertake purposive sampling for all under-represented groups (e.g. higher levels of social deprivation). Focus groups were continued until no new insights emerged for discussion at the final focus group and no new outcomes or relevant concepts were being identified with further data collection i.e. a point of code saturation had been reached. We therefore believe that our domain structure provides a comprehensive picture of the issues of importance to patients and their care givers and healthcare professionals. Although the clinical experts were gathered from the international community, patients and caregivers were only recruited from the UK. Since this is a single state-funded health care system it is possible that this might limit the wider generalizability of the results. On the other hand, the ophthalmologists engaged throughout the whole process of the COS development are a good representation of the international community from all types of health systems; early subgroup analysis suggested no difference between UK and international ophthalmologists. Although we have used a standard and recommended approach by COMET initiatives for gaining consensus, we also recognize that the results may be skewed by the mix of participant stakeholders. Therefore, we tried to balance levels of stakeholders across the whole consensus process to avoid one group being over-represented. We emphasize that results were consistent across stakeholders. Furthermore, running a heterogeneous consensus group meeting among all stakeholders is becoming more widely used in COS methodology, thus generalizability of results is improved based on the overall agreement rather than by specific stakeholder group (47, 48).

Implementation is critical to realizing the potential of a COS. This depends on a number of factors, including feasibility, methods of measurement and adoption. The COS provides standardization about 'what' to measure but not 'how' or 'when' to measure. The 'how' and 'when' to measure are usually a later stage in the process which is usually determined through a similar consensus process;

543 this will form the next phase of work. In terms of feasibility, a COS will only be widely adopted if the
544 burden of measurement is considered acceptable by all users, both patients and trial staff. In terms
545 of methods of measurement, it is a limitation of many COS – ours included – that outcomes may be
546 identified as important for which no reliable measure exists, or at least for which there is no agreed
547 measure. Our COS includes 16 outcomes, many of which are routinely measured during clinical trials
548 either as stand-alone clinical measures or investigations, or as part of a quality of life/visual function
549 assessment such as the National Eye Institute Visual Function Questionnaire – 25 Item (NEI-VFQ25)
550 questionnaire (49).

551 In our COS, most outcomes identified do have a standard method of measurement, but these
552 measures are often imperfect, for example our subjective measures of inflammation based on
553 clinician-estimate (46, 50) or the widespread use of the NEI-VFQ25 as a way to evaluate a number of
554 the HRQoL elements, despite the limitations of that questionnaire (51). Additionally, there are some
555 outcomes identified in our COS for which there is no agreement on the best way of measurement
556 (for example the measurement of near vision), and our COS does not resolve this issue. It is however
557 recognized that identification of unmet measurement needs is one of the values of COS
558 development and can be used to focus new research efforts on such areas.

559 In terms of adoption, any COS depends on the relevant community recognizing its value and
560 committing to incorporate into their trial design and reporting. It helps that the advantages of COS
561 are becoming more widely recognized, and indeed within ophthalmology, no COS has so far been
562 used in clinical trials for non-infectious uveitis of the posterior Segment. It is not clear, however, the
563 extent to which these COS have been adopted in areas with significant trial activity. In part this may
564 be for reasons of feasibility (overly burdensome numbers of outcomes) or availability of agreed
565 measurement methods, but in some cases it may also be a lack of engagement with the expert
566 community and a failure to communicate the value and importance of COS adoption
567 Building a COS is an investment by the community. This has been five years in the making and the
568 participation of the international community and active engagement of all groups of stakeholders

has been critical. For it to benefit patients we, as a community, now need to implement and start using it. It will however be a vital part of our next steps to communicate the COS more widely, and to provide resources that help the community adopt and implement it as a universal standard.

Conclusion

To our knowledge, this is the first published work worldwide that focused on developing a COS for NIU-PS clinical trials. The consensus process representing patients, caregivers and healthcare professionals identified a list of 16 outcomes of sufficient importance to be included in the COS, and thereby recommended for measurement in all future studies of NIU-PS. The COS is not restrictive since other data can be collected and does not constitute a single composite outcome measure but rather ensures that certain key outcomes are always collected in a standardized way. The development of a COS for NIU-PS provides for the first time a standardized set of outcomes that has value to all stakeholders (patients, caregivers, ophthalmologists, nurse practitioners, health policy-makers and commissioners) maximizing the value of each clinical trial since key outcomes are measured and reported in all relevant trials; ensuring that outcomes measured include those that are most important to each group of stakeholders, rather than just to one group. The adoption of the COS would lead to a richer, more consistent collection and reporting of data across clinical studies in NIU-PS. It is suitable across all settings regardless of whether the primary area of interest is reduction in flares of disease, long-term medication reduction, quality of life or some other aspect of the condition. By collecting the COS alongside the primary outcome of interest, it means that a study that was designed to address one outcome (e.g. effectiveness in reduction of flares defined by vitreous haze) can still contribute to evidence synthesis related to other outcomes (e.g. treatment side effects) due to their collection within the COS. The use of COS also helps to reduce outcome-selection bias and outcome-reporting bias since the whole COS is measured and reported, improving evidence synthesis and meta-analysis (20, 30). The next step will be to determine and validate the optimal measurement tool for each included outcome in the COS. COS will move us towards greater

595 consistency in outcome measurement for clinical trials in NIU-PS, and advance the care of patients
596 with this sight-threatening disease.

597 **Abbreviations**

BMEC	Birmingham and Midland Eye Centre
BUS	Birdshot Uveitis Society
CINAHL	Cumulative Index to Nursing and Allied Health Literature.
COMET	Core Outcome Measurement in Effectiveness Trials
COS	Core Outcome Set
COSUMO	Core Outcome Set in patients with posterior segment involving uveitis with and without Uveitic Macular Oedema
CPROR	Centre for Patient Reported Outcome Research
Embase	Excerpta Medica database
HRQoL	Health-Related Quality of Life
IRAS	Integrated Research Application System.
MEDLINE	Medical Literature analysis and Retrieval System Online
NIU-PS	Non-infectious uveitis of the posterior segment
PInGU	Patient Involvement Group in Uveitis
UIG	Uveitis Information Group
UME	Uveitic Macular Edema
RCT	Randomized Controlled Trials

598 **Ethical approval**

599 Ethical approval for the study has been granted by the National Research Ethics Service (NRES) West
600 Midlands –South Birmingham Research Ethics Committee (Reference number 17-WM-0111).

601 **Competing interests**

All named authors declare that they have no competing interests relating to this manuscript. MC receives funding from the National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre and NIHR ARC West Midlands at the at the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Health Data Research UK, Innovate UK (part of UK Research and Innovation), Macmillan Cancer Support, UCB Pharma . MC has received personal fees from Astellas, Takeda, Merck, Daiichi Sankyo, Glaukos, GSK and the Patient-Centered Outcomes Research Institute (PCORI) outside the submitted work.

Authors' contributions

All authors contributed to the study design. MT is the clinical research fellow and he is involved in all stages of the study design, data collection, and analysis of the focus group discussions and interviews. MT led the first draft of the manuscript. MT organized and conducted the Delphi exercise with supervision from AD, PIM, and MC. MT conducted the focus group discussions with facilitation from JM. MT ran the telephone interviews. MT, JM, PIM and AD were involved in identifying the list of outcomes and outcome domains and established definitions of outcomes and outcome domains. MT, PM and AD led the participant recruitment process. MT analyzed the Delphi exercise. MT chaired the consensus meeting and Sara Brookes facilitated the consensus meeting. All authors have read and approved the final manuscript.

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COSUMO Working Group

The COSUMO Working Group comprises the International uveitis Advisory Board and additional consensus group members.

Uveitis International Advisory Board

Prof Annabelle Okada	Kyorin University School of Medicine, Japan Professor of Ophthalmology and Director of the Ocular Inflammation Service and the Macular Disease Service
Prof Daniel Vasconcelos-Santos	Universidade Federal de Minas Gerais Belo Horizonte, Brazil
Prof Douglas A. Jabs	Director, Center for Clinical Trials and Evidence Synthesis Professor of Epidemiology, The Johns Hopkins University Bloomberg School of Public Health Professor of Ophthalmology, The Wilmer Eye Institute The Johns Hopkins University School of Medicine, USA
Prof Janet Davis	University of Miami, Miller School of Medicine, Bascom Palmer Eye Institute, USA
Prof Justine Smith	Matthew Flinders Distinguished Professor of Eye & Vision Health, Flinders University College of Medicine & Public Health
Prof Manfred Zierhut	Department of Ophthalmology, University of Tuebingen, Germany
Prof Marc D. de Smet	Leiden University, the Netherlands; MIOS, Lausanne, Switzerland

Additional consensus group members of the COSUMO Working Group

Mr David Maese	Patient, UK
Mrs Gaynor M Hollis	Patient, UK
Mr Graham Roberts	Patient, UK
Mrs Joanna Emerson	Patient, UK
Mr Joseph Quigley	Patient, UK
Miss Katie Cave	Patient, UK
Mr Kenneth Twigge	Patient, UK
Miss Maxine McCarthy	Patient, Olivia's Vision, UK
Ms Ruth Davis	Patient, UK

Mrs Eileen Twigge	Caregiver, UK
Mrs Helen Roberts	Caregiver, UK
Mr Martin Emerson	Caregiver, UK
Mrs Racheal Maese	Caregiver, UK
Dr Bashar Mohammed	Consultant Ophthalmologist, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham and Midland Eye Center, Dudley Road, Birmingham, UK
Dr Catey Bunce	Medical Statistician, King's College London, Moorfields Eye Hospitals NHSFT and London School of Hygiene and Tropical Medicine, UK
Dr Erika Damato	Consultant Medical Ophthalmologist, University Hospitals Cambridge NHS Foundation Trust, Hills Road, Cambridge UK
Prof Miles Stanford	Professor of Ophthalmology, St Thomas' Hospital, London UK
Mr Natraj Poonit	Clinical Nurse Specialist in Immunosuppression, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham and Midland Eye Center, Dudley Road, Birmingham, UK
Dr Richard Lee	Associate Professor in Ophthalmology, University of Bristol, consultant ophthalmologist University Hospitals Bristol NHS Foundation Trust, UK /Moorfields Eye Hospital NHS Foundation Trust, UK
Dr Srilakshmi M Sharma	Consultant Ophthalmologist, Oxford University Hospitals NHS Trust , John Radcliffe Hospital, Oxford Eye Hospital and NIHR Oxford Biomedical Research Centre, Oxford Headley Way, West Wing , UK

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Table 1: Demographics characteristics of participants in the Delphi survey

Patients and carers		Healthcare professionals	
Gender	**n (%)**	**Gender**	**n (%)**
Male	9 (27%)	Male	28 (60%)
Female	24 (73%)	Female	19 (40%)
Age		**Age**	
18-24 years	-	18-24 years	-
25-34 years	-	25-34 years	2
35-44 years	1	35-44 years	19
45-54 years	22	45-54 years	25
55-64 years	9	55-64 years	2
65-74 years	1	65-74 years	-
Duration of uveitis for patient		**Length of experience in uveitis**	
Less than 5 years	2	Less than 5 years	4
5-10 years	8	5-10 years	2
11-15 years	7	11-15 years	10
16-20 years	4	16-20 years	11
More than 20 years	12	More than 20 years	20
Duration of being a carer		**Job role**	
Less than 5 years	-	Ophthalmologist	40
5-10 years	2	Nurse practitioner	2
11-15 years	1	Policy maker/commissioner	5
16-20 years	1		
More than 20 years	1		
Role			
Patient	28		
Carer	5		

Table 2: Importance of outcome as indicated by percentage of stakeholder group rating the outcome as 'critically important' (7 to 9) during the Delphi process (round 2) and the consensus meeting

Outcomes	Percentage Scoring Outcome as 7-9			Items (In or carried forward to consensus meeting)	Consensus meeting voted in or incorporated into other item
	Patients/carers (n=33)	HCPs (n=74)	All participants (n=107)		
Distance vision	96.8%	93.0%	94.6%	Yes	In
Near vision	93.5%	58.1%	73.0%	Yes	In
Distortion of vision	87.1%	88.4%	87.8%	Yes	Part of visual disturbance
Visual disturbance	90.3%	86.0%	87.8%	Yes	In
Color vision	48.4%%	20.9%	32.4%	No	-
Contrast sensitivity	74.2%	23.3%	44.6%	No	-
Depth perception	71.0%	4.7%	32.4%	No	-
Peripheral vision	80.6%	55.8%	59.5%	No	-
Fatigue	61.3%	20.9%	37.8%	No	-
Floaters	54.8%	79.1%	68.9%	No	-
Headache	74.2%	30.2%	48.6%	No	-
Photosensitivity	83.9%	39.5%	58.1%	No	-
Redness	48.4%	18.6%	31.1%	No	-
An uncomfortable or painful eye/s	74.2%	48.8%	59.5%	No	-
Watery eye	48.4%	7.0%	24.3%	No	-
Day to day usual activities	90.3%	88.4%	89.2%	Yes	In
Driving/commuting	96.8%	86.0%	90.5%	Yes	In
Education related impact	67.7%	76.7%	73.0%	Yes	Part of work related impact
Social and Leisure activities	74.2%	74.4%	74.3%	Yes	Out
Work related impact	93.5%	90.7%	91.9%	Yes	In
Financial impact due to early retirement; the need to take a part-time job or redundancy	74.2%	69.8%	71.6%	No	-
Financial impact of treatments	67.7%	74.4%	71.6%	No	-
Desire to have children; able to conceive and lactate	54.8%	55.8%	55.4%	No	-
Relationships with family and/or friends	71.0%	41.9%	54.1%	No	-
Depression and mental illness	77.4%	79.1%	78.4%	Yes	
Frustration and Anger	74.2%	37.2%	52.7%	No	-
Stress	74.2%	62.8%	67.6%	No	-
Anxiety	67.7%	67.4%	67.6%	No	-
Access to uveitis clinic and/ facilities	80.6%	74.4%	77.0%	No	-
Access to counselling and psychotherapy services	51.6%	27.9%	37.8%	No	-
Access to physical aids and other resources	61.3%	25.6%	40.5%	No	-
Doctors-patient relationship/communication	83.9%	46.5%	62.2%	No	-
Inter-professional relationships	61.3%	39.5%	48.6%	No	-
Shared decision-making	67.7%	53.5%	59.5%	No	-
Overall wellbeing	64.5%	67.4%	66.2%	No	-
Coping	64.5%	37.2%	48.6%	No	-
Identity	51.6%	32.6%	40.5%	No	-

Normality	54.8%	37.2%	44.6%	No	-
Overall psychosocial adjustment	61.3%	41.9%	50.0%	No	-
Sense of self	64.5%	34.9%	47.3%	No	-
Adherence	67.7%	95.3%	83.8%	No	-
Amount of medications	61.3%	86.0%	75.7%	No	-
Number of hospital visits	45.2%	79.1%	64.9%	No	-
Treatment side effects	96.8%	97.7%	97.3%	Yes	In
Formation of band keratopathy	83.9%	67.4%	74.3%	Yes	Part of structural changes
Formation of Epiretinal membrane	90.3%	72.1%	79.7%	Yes	
Systemic co-morbidities	83.9%	90.7%	87.8%	Yes	Out
Anterior segment inflammation	87.1%	97.7%	93.2%	Yes	In
Cataract	80.6%	88.4%	85.1%	Yes	Out
Flare/relapse/ recurrence	100.0%	97.7%	98.6%	Yes	In
Other ocular co-morbidities	83.9%	93.0%	89.2%	Yes	Out
Raised intraocular pressure	83.9%	95.3%	90.5%	Yes	In
Retinal vasculitis	96.8%	100.0%	98.6%	Yes	In
Retinitis	96.8%	100.0%	98.6%	Yes	In
Structural changes	93.5%	97.7%	95.9%	Yes	In
Uveitic macular edema	93.5%	100.0%	97.3%	Yes	In
Vitreous inflammation/haze	96.8%	100.0%	98.6%	Yes	In

Table 3: Final Core Outcome Set (COS) for clinical trials in non-infectious uveitis of the posterior segment (NIU-PS)

Outcome	Definition
Issues relating to visual function	
Distance vision	*A person's ability to see objects/people clearly from distance (beyond arm's length) (e.g. road signs, TV, cinema)*
Near vision	*A person's ability to see near objects (e.g. reading, seeing prices on a menu, seeing phone numbers and other close-up tasks)*
Visual disturbance	*A person complains of seeing blurred, hazy, foggy, grainy vision, double vision, flashing/shimmering lights or that straight lines may appear bent, crooked or wavy*
Issues relating to Health related Quality of Life (HRQoL)	
Work/education related impact	*A person's performance and ability to maintain or continue work/employment or education*
Driving/commuting related impact	*A person's ability to maintain or continue driving a vehicle or commuting for example bicycle, train, bus, tram*
Day to day usual activities related impact	*A person's ability to maintain and continue engagement in day-to-day activities (e.g. care for own self, shaving beard, washing face, gardening, shopping, cooking and doing the washing etc.) including social and leisure activities*
Depression and mental wellbeing	*Feelings of severe sadness or feeling depressed with loss of interest or lack of enjoyment.*
Issues relating to treatment side effects	
Treatment side effects	*Describes undesired or unintended treatment effects that patients may experience*
Issues relating to disease control	
Anterior segment inflammation	*Inflammation in the front of the eye between the cornea and the iris*
Vitreous inflammation/haze	*Inflammation/haze/cloudiness of vitreous jelly located between the lens and the retina*
Retinal vasculitis	*Inflammation of the blood vessels of the retina (the light sensitive layer at the back of the eye)*
Retinitis/choroiditis/ chorioretinitis	*Inflammation of the retina and/or choroid layers (the light sensitive layer and the supporting blood vessel layer at the back of the eye)*
Flare/relapse/recurrence	*Recurrence or increase of inflammation in the front or back of the eye that may be associated with effects on vision*
Intraocular pressure	*Change in the pressure inside the eye above or below the normal range and if left untreated may permanently damage the sight*
Uveitic macular edema	*Fluid that builds up in the central part of the retina causing swelling of the macula. The macula is responsible for detailed central vision*
Structural changes	*Changes to the structure of the eye including:* *retinal scarring,* *optic nerve damage (including glaucoma),* *formation or progression of band keratopathy - white, chalky deposits on the surface of the cornea (the 'window' of the eye) that may cause pain and a reduction in vision,* *formation or progression of epiretinal membrane – a thin layer of scar tissue that forms on the surface of the retina usually at the macula (the sensitive central part of the retina) that may reduce vision*

Figure 1: Flow diagram illustrating the three-phase approach used to develop the core outcome set (COS) for non-infectious uveitis of the posterior segment (NIU-PS)

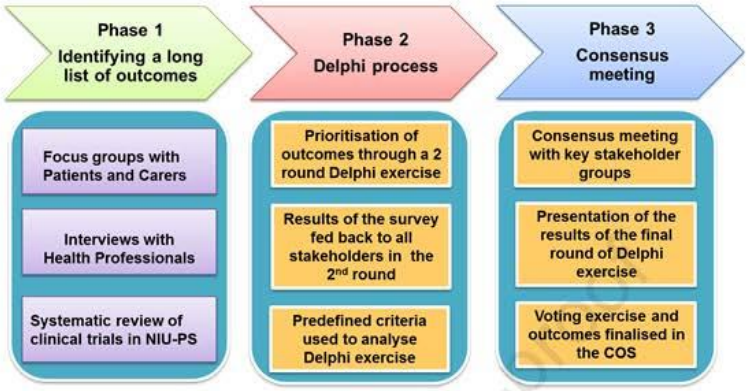
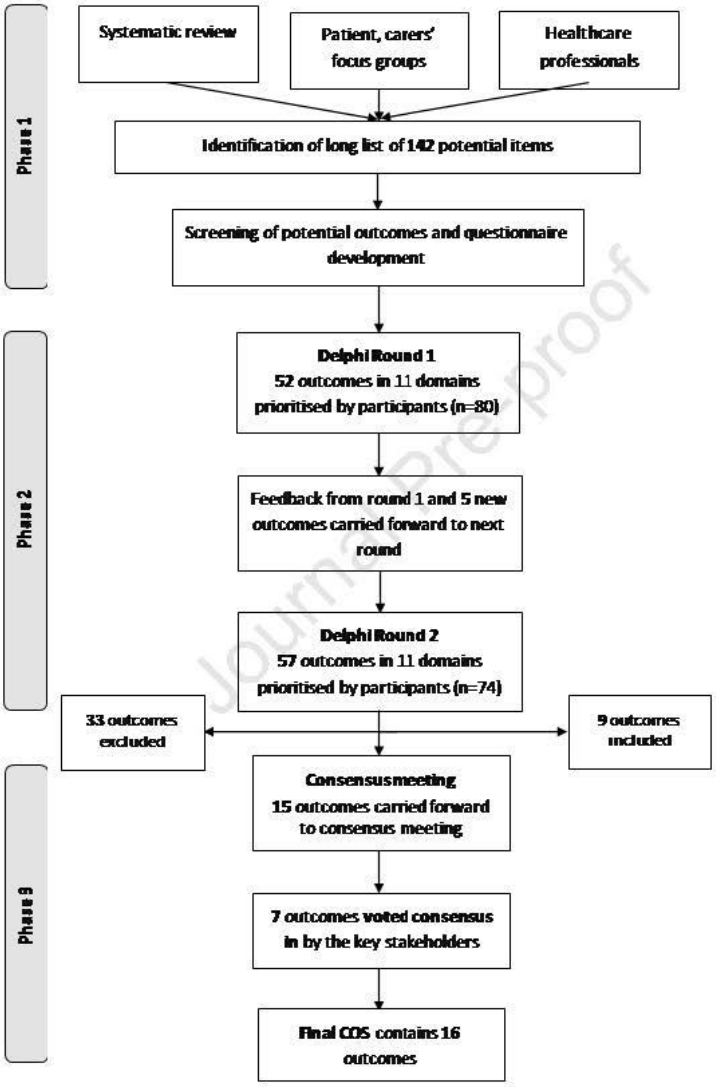


Figure 2: Summary of development of a Core Outcome Set for Effectiveness and Efficacy Trials in non-infectious uveitis of the posterior segment (NIU-PS)



Authors' contributions

All authors contributed to the study design. MT is the clinical research fellow and he is involved in all stages of the study design, data collection, and analysis of the focus group discussions and interviews. MT led the first draft of the manuscript. MT organized and conducted the Delphi exercise with supervision from AD, PIM, and MC. MT conducted the focus group discussions with facilitation from JM. MT ran the telephone interviews. MT, JM, PIM and AD were involved in identifying the list of outcomes and outcome domains and established definitions of outcomes and outcome domains. MT, PM and AD led the participant recruitment process. MT analyzed the Delphi exercise. MT chaired the consensus meeting and Sara Brookes facilitated the consensus meeting. All authors have read and approved the final manuscript.

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TITLE OF ARTICLE:

AUTHORS:

AUTHOR NAME	RESEARCH DESIGN	DATA ACQUISITION AND/OR RESEARCH EXECUTION	DATA ANALYSIS AND/OR INTERPRETATION	MANUSCRIPT PREPARATION
Mohammad O.Tallouzi	☒	☒	☒	☒
Alastair K.Denniston	☒	☒	☒	☒
Philip I. Murray	☒	☒	☒	☒
Melanie J. Calvert	☒	☒	☒	☒
Jonathan M. Mathers	☒	☒	☒	☒
David J. Moore	☒	☒	☒	☒
Nicholas Bucknall	☐	☐	☐	☒
COSUMO Working Group	☐	☐	☒	☒

OTHER CONTRIBUTIONS:

Precise:

This study presents the development of a core outcome set (COS) for non-infectious uveitis of the posterior segment (comprising intermediate, posterior and panuveitis) to ensure outcomes represent the priorities of all stakeholders, to enhance evidence synthesis and reduce research waste.

Chapter 9: Discussion

9.1 Introduction

This final chapter presents the key findings of the thesis, strengths and limitations, interpretation and implications of findings and identifies areas for future research. My thesis focused on the most sight-threatening forms of intraocular inflammation, PSIU, and its major complication, UMO. My thesis aimed to (i) assess the effectiveness of the available pharmacological therapies used in the treatment of UMO; (ii) develop an international consensus on a standardised set of outcomes using a multi methods approach to create a core outcome set (COS) for non-infectious PSIU

My thesis employed a systematic review to assess the effectiveness of the available pharmacological therapies used in the treatment of UMO. Furthermore, the COS development involved two main stages: First, relevant outcomes were identified through the systematic review (described in Chapters 3 and 4), and the qualitative research with key stakeholders: patients who had PSIU with or without macular oedema and their carers (described in chapter 6) and healthcare professionals (ophthalmologists, nurse practitioners and policy-makers/commissioners; described in chapter 7). Second, a Delphi exercise was undertaken to reach agreement on important outcomes and outcome domains. This was followed by a face-to-face consensus meeting with the key stakeholders to approve the final list of outcomes in the COS (described in Chapter 8).

The success of my work in achieving my aims is demonstrated by our publications of (1) the first, methodologically robust and most comprehensive overview of the available evidence of the pharmacological agents used to treat UMO (213); (2) the first qualitative research study to investigate patients and carers views regarding outcome domains relevant to outcome

assessment in non-infectious PSIU (348); and (3) to have submitted for publication the first core outcome set for use in clinical trials in adult non-infectious PSIU. This provides a holistic patient-engagement overview of the impact of uveitis and should be considered alongside the SUN criteria which define a number of grading tools to standardise several of the outcomes identified by our consensus group for inclusion in the COS. It is worth noting that COS is not restrictive since other data can be collected, but rather provides a minimum set of outcomes allowing further outcomes to be added if they are pertinent to the study (305).

9.2 Summary of key findings

9.2.1 Objective 1: To assess the effectiveness of the available pharmacological therapies used in the treatment of UMO

This systematic review summarised the available evidence of the pharmacological therapies used in the treatment of UMO across comparative studies of RCT and other comparative studies (e.g. non-randomised controlled trials, comparative observational studies). The review formed the basis of available evidence and recommended areas where further trials are needed (213).

The systematic review found corticosteroids to be the most frequently studied therapies, with various routes of administration being used. Corticosteroids are effective in UMO; however, significant adverse events (an increase of intraocular pressure and cataract) were reported in those studies, with the distribution between local and systemic adverse events being reflective of their route of administration

Additionally, a number of immunomodulatory agents have been used in treating UMO including anti-metabolites, alkylating agents, T-cell inhibitors and biological agents (anti-tumour necrosis factor (anti-TNF agents)). However, it was difficult to draw significant

conclusions from all those various subgroups. The findings indicated the need for further head-to-head studies for many of the major immunomodulatory drugs, and the need to conduct studies which are either exclusive to UMO or are designed to include stratification according to presence or absence of UMO and report the UMO-subgroup data (213).

Although a systematic review had been conducted in 2013 evaluating therapeutic interventions for UMO, our review provided a more methodologically robust, complete analysis that was able to include several emerging therapies that had not been evaluated at the time of the previous review (385).

9.2.2 Objective 2: To identify a comprehensive list of outcomes for inclusion in the Core Outcome Set (COS) based on:

(a) Systematic review of effectiveness trials in PSIU (Chapter 4)

The systematic review on the effectiveness of the pharmacological interventions in the treatment of UMO was used to summarise reported outcomes across included studies. The review identified the following outcomes and outcome domains: (1) visual function (Best Corrected Visual Acuity (BCVA)), (2) disease complication (e.g. UMO), (3) disease activity (anterior chamber (flares and cells) and vitreous activity (vitreous haze, vitreous cells, snowballs), retinal vasculitis, retinitis), (4) medication side effects, (5) quality of life, and (6) uveitis recurrence (flare-up/relapses), based on the previous outcomes.

(b) Qualitative research methods (Chapter 6, 7)

Qualitative research methods were used to understand the perspectives of the key stakeholders including patients with non-infectious PSIU and their carers; and healthcare professionals (ophthalmologists, nurse practitioners and policy-makers/commissioners) and

identify outcomes for inclusion in the COS.

Healthcare professionals' views were actually quite similar to patients and carers. This work identified eleven core domains comprising: (1) visual function, (2) symptoms, (3) functional ability, (4) impact on relationships, (5) financial impact, (6) psychological morbidity and emotional well-being (7) psychosocial adjustment to uveitis, (8) doctor/patient/interprofessional relationships and access to healthcare, (9) treatment burden, (10) treatment side effects, (11) disease control.

This work is the first in the field to take a multi-stakeholder approach to identifying outcomes and outcome domains to create a COS for PSIU. Some of those domains were familiar, being commonly used in clinical trials as identified by our systematic review (e.g. disease activity, BCVA) and in some cases have been standardised by SUN (disease activity). Other domains were, however, new to the field, having not been reported either by the SUN criteria or PSIU clinical trials (e.g. functional ability; the impact on relationships and finances; psychological morbidity and emotional well-being; psychosocial adjustment to uveitis; doctor-patient/inter-professional relationships and access to healthcare, and treatment burden). This qualitative research presents a broader picture of the impact of PSIU and related treatment on patients' lives that are not covered by simply using the outcomes provided by the SUN workshop (27).

9.2.3 Objective 3: To prioritise outcomes through a consensus process based on

(a) Delphi exercise with the key stakeholder groups (chapter 8).

This work described the Delphi exercise (an online web-based survey) that was used to reduce the range of potential outcomes for the core set. Two online Delphi rounds were conducted with the stakeholder groups to prioritise the collected list of outcomes identified in the systematic review and qualitative research. Participants were asked to rank those outcomes

based on their level of importance using a nine-point Likert scale (1=no importance; 9= critically important). Participants were also encouraged to add any further outcomes (n=5) they felt important for inclusion in the COS (Round 1) and re-evaluation of their responses in the light of this new data (Round 2). Delphi exercise presented 9 outcomes qualifying for inclusion in the COS.

(b) A face-to-face consensus meeting with the key stakeholder groups (chapter 8).

The Delphi exercise was concluded with a face-to-face consensus meeting with the key stakeholders. The consensus meeting invited key stakeholders to actively express their views and shape the final list of outcomes in the COS based on the final Delphi round. This resulted in the agreement of the first COS for use in all PSIU trials in an adult population – directly addressing the central aim of the thesis.

The final list in the COS included the following outcome domains:

I. Visual function comprising distance vision, near vision and visual disturbance
II. HRQoL comprising depression and mental well-being; work/education related impact, driving/commuting related impact, and day-to-day usual activities including social and leisure activities.
III. Disease Control comprising clinical activity (anterior segment inflammation, vitreous inflammation/haze, retinal vasculitis, retinitis/choroiditis/chorioretinitis); structural changes; UMO; IOP; and flare/relapse/recurrence.
IV. Treatment side effects

9.3 Strengths and Limitations

Strength and limitations to each part of the study have been discussed in detail in relevant

chapters. This section will consider the overall thesis strengths and limitations in the context of its most significant output, a COS for non-infectious PSIU in adult patients.

9.3.1 Strengths

The study design and underlying methodology for this COS was pre-specified, registered with and supported by COMET initiative with expert advice from COMET initiative management group members (Williamson/Blazeby). The study followed a robust methodology recommended by the COMET initiative comprising a systematic review and a programme of qualitative research with key stakeholders, followed by a consensus process (Delphi exercise and consensus meeting) (386).

The use of a multi methods approach in my thesis provides a broader perspective within the data collected. Results from the systematic review and data collected via qualitative research methods provided complementary information. Furthermore, using different qualitative research methods with different stakeholder groups was beneficial in providing a more complete set of outcomes.

The qualitative research (described in chapter 6 &7) is the first of its kind, exploring patients/carers' and health professionals' views on important outcomes for PSIU. It was successful in achieving code saturation, demonstrating that the number of participants recruited for the focus groups and interviews was sufficient. At the final focus group and interview, no new insights, no new outcomes and no new relevant concepts were being identified with further data collection (266, 352).

A key strength of the COS was our success in securing active involvement of a range of key stakeholders especially patients and carers. Under-involvement of patients and carers in determining the outcomes used in clinical trials has resulted in most reported outcomes in

clinical trials being determined by clinical experts and trialists, which may differ significantly to those that are important to patients and carers (388). The study was able to address patients' and other stakeholders' concerns, thereby, creating a COS that is relevant to all stakeholder groups. Recognition of patients' and carers' priorities is important in its own right to ensure that the outcomes we evaluate are those that matter to patients, but can have additional benefits such as potentially reducing NHS burden (cost, frequency of hospital visits) and enhancing effective healthcare. In terms of the professional participants within the Delphi process and the consensus meeting, we were successful in engaging international leaders in the field with influential positions on uveitis advisory groups, and who are actively involved in clinical trials. This group contain individuals who are well-placed to implement the COS in the design of future clinical trials.

Patient and public involvement was integral to the research from inception and has continued to be central to it (146). The study involved a patient representative (NB), who is a member both of the Patient Involvement Group in Uveitis (PInGU) West Midlands and the national Birdshot Uveitis Society (BUS). NB provided the patient-perspective to this work and also undertook a very important role of feeding back to the patient groups he represents, regarding the conduct, progress and findings of my study. Specific examples of his input include: co-designing the research questions and reviewing the wording of outcome definition. Table 10 reports examples of comments on outcome definitions identified by the patient representative.

Additionally, NB was on the steering group of this project, and he co-wrote the participant information sheet. NB was a co-author of the published papers arising from the project and patient groups were acknowledged for their contribution in all output. Numerous patient groups (e.g. Birdshot Uveitis Society, Olivia's Vision, and PInGU) were also consulted regarding

the study design (e.g. provided comment on patients' information sheet); their feedback was considered prior to submission to the ethics committee for approval. Furthermore, the survey questionnaire was piloted with members of PInGU including patients (n=4) and carers (n=2) to examine understanding, usability and highlight any potential practical issues prior to the next phase. Participants provided feedback on the pilot version of Delphi survey, and the Delphi was modified accordingly before being sent to all stakeholder groups (see Table 10).

Patients and carers attending the consensus meeting were involved in the subsequent publication and patients groups were acknowledged in all outputs. The research findings were presented to PInGU at their local meeting.

Patients were also central in defining the way the outcomes are expressed within the COS, to try to ensure that they felt immediately relevant and understandable to this group. The study used the patients' words and descriptions to describe the outcomes where possible, elicited through the qualitative work.

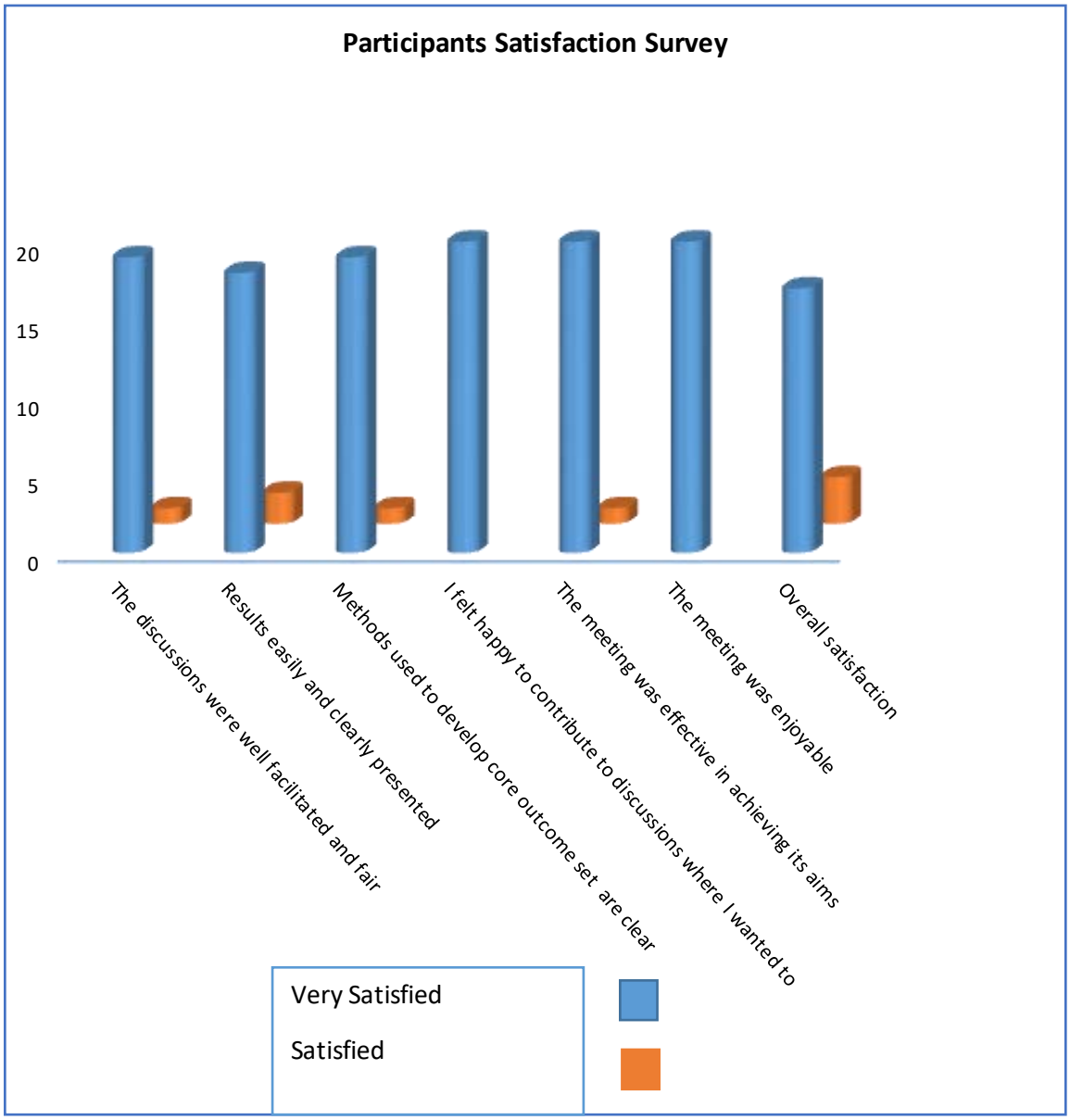
Finally, a participant satisfaction survey was conducted to evaluate the development process of the COS and the consensus meeting. A questionnaire was distributed to all the participants attended the consensus meeting (all stakeholder groups n=24). Of those 20 participants returned the completed survey. The aim of the survey was to investigate in-depth a number of elements and attributes of overall satisfaction with the process of COS development particularly the consensus meeting. Respondents were asked about their satisfaction with the organisation of the consensus meeting, facilitation of the discussion, clarity of the methods used to develop the core outcome set, their level of contribution to the discussion, how effective the meeting was in achieving its aims and whether the meeting was enjoyable or not. The results indicate positive satisfaction among all participants (85% very satisfied) and (15%

satisfied). Further details are illustrated in Figure 11.

Furthermore, the survey results concluded it had been a successful process reflecting the study team's observation that the dialogue between participants (including between patients/carers and healthcare professionals) had been effective, high-quality discussion had been achieved between stakeholders and that there had been active engagement from every participant. Active listening to patients' concerns makes it easier for patients and their carers to be at the centre of care. It was evident that patients and carers were looking to have support to develop their knowledge and skills and get involved in decision-making regarding their health related issues.

At the design stage we had considered whether to run two consensus meetings (one for healthcare professionals and one for patients/carers) or to combine all parties together in one meeting. Running a homogeneous consensus meeting may result in a COS that is relevant to a specific stakeholder group. However, conducting a consensus meeting combining heterogeneous groups can aid the process of considering outcomes based on the overall agreement rather than the stakeholder group. This can ensure that selected outcomes are deemed essential by all stakeholder groups (141). We decided to run one consensus meeting and include members of the key stakeholders and international uveitis advisory group considering a relative proportion of each stakeholder group

Figure 11: Participants Satisfaction Survey



It was extremely helpful for me as a researcher and other healthcare professionals to hear patients/carers concerns and provide advice/definition for outcomes prior to the voting process. I was able to present all potential outcomes (scored high in the Delphi exercise), followed by a definition for each outcome. Patients and carers were able to ask questions, discuss the outcomes and show their understanding of the definition, and justify the ranking.

In turn, healthcare professionals were able to clarify each outcome and give examples and where possible reach agreement and understanding upon those outcomes. The meeting described a process of active participation, effective communication and efficient engagement among all members leading to a full agreement to the final list of outcomes in the COS.

For me and other healthcare professionals, sitting with patients in the same meeting, discussing important issues regarding their PSIU and treatment was very impactful. This was the first time for most healthcare professionals present had experienced this kind of group discussion in which patients and their carers were talking about the impact of uveitis on their lives, and how this might be captured in clinical trial outcomes. This meeting was a great opportunity for ophthalmologists, nurse practitioners and policy-makers/commissioners to gain a better understanding of patient views and perceptions, highlighting this additional benefit of having all stakeholders in the same consensus.

Table 10: Suggested edits by patients in the pilot study

Items in the pilot survey	Addition suggested by participants
Depth perception A person's ability to perceive the world in three dimensions (3d) to judge distance of objects for example judging how far a step is	*Depth perception* A person's ability to perceive the world in three dimensions (3d) to judge distance of objects for example judging how far or *how high a step is*
Day to day usual activities A person's ability to maintain and continue engagement in day-to-day activities for example care for own self, shaving beard, washing face, gardening, shopping and cooking etc.	*Day to day usual activities* A person's ability to maintain and continue engagement in day-to-day activities for example care for one's self, shaving beard, washing face, gardening, shopping, cooking *and do the washing etc*.
Emotional and psychological Issues relating to person's emotional and psychological health in uveitis	*Emotional and psychological* Issues relating to a person's emotional and psychological health *with* uveitis
Stress Feeling of tension, mental or emotional strain and being under pressure	*Stress* *Feelings* of tension, mental or emotional strain and being under pressure
Access uveitis clinics and/ facilities Describes a person's ability to access uveitis clinics and care facilities	*Access to uveitis clinics and/ facilities* Describes a person's ability to access uveitis clinics and care facilities
Difficulties with psychosocial adjustment Describe things that individuals are having difficulty with adjusting to the life with uveitis (e.g. social anxiety, acceptance of the disease, social reaction, changing personal items, autonomy and independence)	*Difficulties with psychosocial adjustment* *Describes* things that individuals are having difficulty with adjusting to the life with uveitis (e.g. social anxiety, acceptance of the disease, social reaction, changing personal items, autonomy and independence)
Coping Specific things that individuals with uveitis are able to do in order to cope with disease effects.	*Coping* *Describes* specific Specifics things that individuals with uveitis are able to do in order to cope with the disease effects
How important is that treatment side effects are assessed in research studies?	How important *is it* that treatment side effects are assessed in research studies?
Adherence Describes whether people with uveitis follow treatment recommendations given by doctors e.g. taking medications at the recommended dose and time	*Adherence* *Describes a feeling of burden created by* the degree of which patients with uveitis follow treatment recommendations given ……
Medication side effects Describes the undesired secondary or unintended effects of treatments that people with uveitis may experience	*Treatment* side effects Describes the *undesired or unintended* treatment effects that people with uveitis may experience

Italic and underlined writing represent suggested amendments by patients in the pilot study

9.3.2 Limitations

There are a number of potential limitations to this study. First, the searches for the systematic review were conducted several years ago (February 2017) and will therefore not have included any studies reported since that date. This 'dating effect' is a feature of all systematic reviews, and is an argument for them being regularly updated to ensure that the latest evidence is available to inform decision-makers including clinicians, patients, and policy-makers. In terms of how this review contributed to the COS, I recognise that it is possible that these more recent studies might have included new outcomes of interest. However any new outcomes would be of such significant interest that it would be expected that they would have been suggested through our interviews with professionals (who include a number of chief investigators and principal investigators on international clinical trials in PSIU).

Secondly, the study limited the recruitment of patients and carers to the UK. Thus, such participants were representative of a single country with a single type of state health system. International recruitment for patients and carers was not possible due to time, cost and requirements for additional ethical approvals to recruit via other healthcare systems. Nonetheless, the study employed a broad range of participants in geographically diverse locations. Purposive sampling was achieved covering various characteristics of the population in the research question. International stakeholders (HCPs and policy-makers/commissioners) were involved representing members of the international uveitis advisory group. As such the COS is potentially transferable to international PSIU trials.

Thirdly, uveitis describes an intraocular inflammation that is highly linked to many forms of systemic disease including spondyloarthropathy, juvenile idiopathic arthritis, and Behcet's disease (389). Patients with such systemic issues are generally under the care of other specialists (such as rheumatologists) but these professional groups were not included in the

healthcare professionals' stakeholder group. We cannot, therefore, be sure that further outcomes would not have been identified if they had been included.

Finally, I wish to draw attention to the scope and boundaries of this COS. This COS was designed for non-infectious PSIU in adult patients. It cannot be assumed to be generalizable outside of this e.g. to infectious PSIU or to children. Thus, there may be a need to develop separate COS for these groups.

9.4 Interpretation and implications of findings

This is the first COS for use in clinical trials involving adult patients with non-infectious PSIU. My study provides a complementary effort to the SUN recommendations that have been essential in providing standard approaches to the quantification of selected clinical measures of inflammation in the eye. In contrast to SUN, this COS is a holistic, multi-stakeholder defined set of outcomes suitable for all clinical trials of non-infectious PSIU in adults (27). It can be argued that patients' perspective was less critical in the SUN workshop since the SUN's recommendations were established to help ophthalmologists to assess and record uveitis inflammatory activities (e.g. anterior chamber grading cells, vitreous grading cells/haze). The SUN also aimed to standardise the definitions and create a better understanding of uveitis common terminologies (active/inactive uveitis/remission) (27, 390).

SUN recommendations were reached following a consensus method of Nominal group technique; however, no qualitative methods were used to seek either patients or healthcare professionals' perspective. In contrast, patients reported outcomes were a major component of our COS that highlights their concerns and aids the development of such relevant outcomes in the field. It is worth noting that SUN was undertaken in 2005 and it is likely that some of the clinician-measured outcomes (such as anterior chamber cells) will be replaced by automated

instrument-based measures as the technology evolves.

9.5 Domains of PSIU COS

9.5.1 Visual function

Visual function was reported as an important outcome domain for PSIU comprising three outcomes: distance vision, near vision and visual disturbance. Those components were discussed in both focus group and interviews. Visual acuity (distance vision) is the most commonly reported outcome in both clinical trials and ophthalmology practice. Testing visual acuity is performed using a standard distance visual acuity chart (e.g. Snellen charts, Early Treatment Diabetic Retinopathy Study chart (ETDRS)). Variations in the way acuities were reported across these charts, i.e. Snellen charts are usually reported in metres in the UK and feet in the USA, while acuities from ETDRS charts are usually reported either as 'number of letters read' or converted into a LogMAR fraction (63).

It was agreed by the group that visual function is not only visual acuity and there are other important aspects of visual function to be included e.g. near vision and visual disturbance. Clinical reports suggested a positive correlation between uveitis and a patient's ability to read (near vision) (391), therefore providing a treatment for this underlying ocular condition may significantly improve patients function and reading ability (392). Patients' ability to perform a near vision function is more complex since the retinal performance is harder compared to reading single letters on the vision chart (391). Near vision is usually assessed using a handheld chart including a statement of various font size prints where LogMAR values are given for each paragraph based on the font size (393). It is worth mentioning that near vision is not a usual practice in either clinical trials or ophthalmology care clinics.

The final component of the visual function relates to patients visual disturbance describing

patients visual symptoms e.g. blurred, hazy, foggy, grainy vision, double vision, flashing/shimmering lights or that straight lines may appear bent, crooked or wavy

Visual disturbance is a subjective entity based on a patient's perceptions of the quality of their vision, comprising both their visual function and psychological aspects (394). A 30-item Quality of Vision (QoV) has been developed to assess patients quality of vision in non-uveitis patients including visual disturbance and distortion focusing on the frequency, severity, and how bothersome patients symptoms are (395).

9.5.2 Health Related Quality of Life (HRQoL)

Whilst HRQoL is influenced by visual function, this domain is distinct and describes patients' ability to perform day-to-day activities and reflects psychological, emotional and social well-being. Visual function and related HRQoL are an important component in evaluating the disease status, its progression and the impact of treatment (184). This domain is distinct and was highly expressed by patients/carers in focus groups and healthcare professionals in interviews. Vision related quality of life is an important outcome domain in our COS and there is a need to establish an agreed measurement tool for this domain so that in both clinical trials and routine clinical care, ophthalmologists record uveitis activity and its severity alongside its impact on vision related quality of life.

To measure the HRQoL-related outcomes, we need a suitable measurement tool. The National Eye Institute Visual Functioning (NEI-VFQ25) is the most common HRQoL questionnaire used in patients with ocular morbidity (158, 182). The NEI-VFQ25 was not originally designed for uveitis patients but is still the most widely used tool to assess the impact of the disease and vision-related on patients quality of life in this group of patients (187). The NEI-VFQ25 has various subscales related to patients' general health and general vision-related activities (e.g.

near activities, distance activities, dependency, driving, role difficulties, social functioning, colour vision, ocular pain, and peripheral vision) and general psychological and emotional health) (184-186).

In terms of implementing the COS for PSIU, The NEI-VFQ25 would be a reasonable tool to capture the four outcomes defined under the HRQoL Domain of our COS and additionally provide the patient's subjective assessment of their Distance vision, near vision, and some aspects of visual disturbance. Thus, the tool is considered to be a multi-faceted assessment of visual function in relation to every day to day activities e.g. driving, working, socialising, reading, etc.

9.5.3 Disease Control

There was consensus among all participants that control of the disease activity is an important outcome domain. Eight outcomes were identified in this domain including: (A) Direct measures of active inflammation comprising (1) anterior segment inflammation; (2) vitreous inflammation/haze; (3) retinal vasculitis; (4) retinitis/choroiditis/chorioretinitis); and (5) UMO; (B) Consequences of inflammation comprising (6) IOP and (7) structural changes; and (C) Overall summaries of inflammatory status comprising (8) flare/relapse/recurrence.

To measure these outcomes, we need suitable measurement tools. The SUN Working Group has helpfully provided measurement tools for some of these (anterior segment inflammation, vitreous inflammation/haze) which are based on subjective clinical measures but are standardised and already internationally adopted. OCT provides a sensitive, objective measure for measuring presence and severity of UMO (27). The main challenge therefore in direct measures of active inflammation from our COS is the lack of standardised systems for measuring retinal vasculitis and retinitis/choroiditis/chorioretinitis.

For IOP, Goldmann applanation tonometry remains the gold standard, although there are now a number of alternative instruments which are accepted in clinical practice and are often deemed equivalent in clinical trials. The SUN group stated the need to report IOP. There is no consensus about the outcomes to be used, but the following thresholds have been suggested for reporting: firstly, IOP>21mmHg (above the normal limit) and IOP >30mmHg (a level which clinicians would indicate treatment) should be reported; secondly, patients with elevated IOP>24mmHg increase the risk of glaucoma as the actual IOP increases beyond this level (27). It is worth mentioning that ocular hypotony was also agreed as an important outcome with substantial visual loss (27). Hypotony is a well-recognised ocular complication where IOP measurement ≤6mmHg is highly associated with acute intraocular inflammation and can be found in 3-10% of uveitis patients (396). This could happen due to a reduction in ciliary body secretion or increased uveoscleral outflow (397).

For structural changes we currently lack sensitive measurement tools. It is likely that instrument-based measures (notably OCT) will increasingly be able to provide an objective measure of their presence and absence, and quantify the severity, but for the moment these generally rely on subjective clinician assessment. The impact of these structural changes is, however, reflected in downstream impairment in visual function and consequent functional ability and QoL.

The development of new complications is usually a sign of ongoing disease activity. Complications such as UMO or ERM may be associated with impairment of central vision; complications such as retinal detachment may be associated with loss of peripheral vision; complications such as band keratopathy or cataract may be associated with reduction in contrast sensitivity and generalised reduction in vision (398). These in turn may be associated with impairment of visual function and quality of life (157, 158, 182).

The overall inflammatory status in terms of flare/relapse/recurrence has been defined by the SUN Working Group. They identified worsening activity as a two-step increase in the level of inflammation (e.g. anterior chamber cells, vitreous haze) or increase from grade 3+ to 4+, and improved activity as a two-step decrease in the level of inflammation (e.g. anterior chamber cells, vitreous haze) or decrease to grade 0. In addition they described remission as the period of having inactive disease for ≥3 months after discontinuing all uveitis treatments (27)

9.5.4 Treatment side effects

Participants agreed that treatment side effects are important outcomes to be reported in PSIU clinical trials, including ocular and/or systemic side effects. This domain is distinct and was highly expressed by patients/carers in focus groups and healthcare professionals in interviews. The most common ocular side effect is cataract formation which was agreed to be included within the treatment side effects' domain rather than having it as a separate outcome. Cataract formation is a common cause of visual impairment in uveitis due to both the underlying disease and the prolonged use of corticosteroids and/or repeated local corticosteroids (46). Cataract is a treatable condition usually through surgical removal of the cloudy lens followed by a lens implant (47). Raised IOP is another important ocular side effect that occurs as a result of uncontrolled and sustained ocular inflammation or the use of corticosteroids (399).

9.6 Summary of common COS in other eye-related disease in the context of our findings

To date, a number of COS have been developed in ophthalmology across various subspecialties including dry eyes (367), cataract (368), macular degeneration (346), glaucoma

(369), thyroid eye disease (370), strabismus and ocular motility disorders (400), with ongoing work in cerebral visual impairment (401). Proposed outcomes across various eye diseases are reported in Table 11.

The COS for dry eye disease was proposed by a multi-disciplinary team of patients, clinicians, researchers, industry representatives, and regulators. The study used a systematic review methodology followed by two rounds Delphi exercise to identify existing outcomes deemed important to patients with dry eye disease. Although multiple stakeholder groups were involved in the development process and the study focused on patient-centred outcomes for clinical research, however, the study did not use qualitative research methods to view patients perspectives and identify those important outcomes (367).

Further efforts were made to develop a COS in macular degeneration which is one of the main causes for visual loss in people aged 55 years and older across the United States of America (USA) and Europe (402). Again the study identified potential outcomes through searching existing registries and reported outcomes in major clinical trials. This was followed by four teleconferences to identify important outcomes supported by a Delphi exercise and concluded by another two teleconferences to refine and approve the final list of outcomes. Although the study focused on the impact of macular degeneration on patients and their relationship to good clinical care, the working group only included experts in the field representing 10 different countries without patients' perspectives being included that may have generated additional outcomes to those in the systematic review (346).

Previous work in macular degeneration was accomplished by further efforts around COS in patients with geographic atrophy following age-related macular degeneration disease that was published in 2019. Geographic atrophy describes permanent damage to the central part of the retina (macula) (403), leading to loss of retinal pigment epithelium (166) and damage to the

retinal photoreceptors (404). Geographic atrophy is usually associated with very poor visual function and subsequent functional ability (difficulties with reading and facial recognition) (405). The study was registered on the COMET database and used robust methodology with some similarities to our study. Focus group discussions with patients and relatives, and interviews with workers supporting patients were conducted, followed by a Delphi exercise with key stakeholders (e.g. patients, non-clinical scientists and clinicians). The study used the second round Delphi exercise to reach consensus on the final list of outcomes rather than using a consensus meeting to agree what was included in the COS (406).

Further COS were developed in inflammatory diseases including psoriatic arthritis, ulcerative colitis and inflammatory bowel disease. Whilst searching the COMET database a COS in Psoriatic Arthritis published in 2016 came to my attention (407). Psoriatic Arthritis is an autoimmune disease triggered by activation of immune cells and there is a strong association between the inflammatory process of uveitis and psoriatic arthritis especially the arthropathic form and psoriasis pustulosa. This initiative has some similarities to our study in that a long-list of outcomes was identified from a literature review, followed by focus groups discussions with psoriatic patients from several countries. Two rounds of Delphi exercises were conducted to achieve consensus over reported outcomes that was concluded with a nominal group technique meeting with patients and clinicians. The working group in Outcome Measures in Rheumatology (OMERACT) agreed the final list of outcomes in the COS and advised further work would be needed to evaluate outcome measures and aid the development of the Core Outcome Measurement Set (408).

In uveitis, there is only one other outcome set listed on the COMET site. This is for juvenile idiopathic arthritis associated uveitis (JIA-U) (236). There is however a number of important differences between this initiative and our COS (409). This initiative has some similarities to

our study in that searching was conducted on existing registries and major clinical trials to assess outcome measures used in studies of uveitis associated with JIA-U in childhood and adolescence. Collected outcomes and outcome domains were evaluated further through a Delphi exercise followed by a nominal group consensus meeting. Although the methodology used in the JIA-U study was close to ours, number of limitations were noted. First the participants in the study were limited to clinical experts consisting of ophthalmologists and paediatric rheumatologists; there was no representation of the service user (e.g. patients, carers). We recognise that the JIA-U initiative was conducted a number of years ago, and that the importance of involving public representatives (e.g. patients, carers, patient-support group representatives and service users) in COS development was less well-recognised at that time (410).

It is worth stopping to reflect on this increasing recognition of the central role of patient, carer and wider public on defining priorities in health service decisions including the creation of COS. OMERACT was one of the earliest to recognise the importance of patients perspectives in the COS development, highlighting what patients think are important and may differ to what clinicians think is important. OMERACT stresses that listening to patients and taking their perspectives on board is a priority rather than professionals making assumptions as to which outcomes are important to them (411). In the light of this, the COMET initiative introduced their People and Public Participation, Involvement, and Engagement (PoPPIE) working group that aims to ensure patients have their say in COS development and ensure that the final COS is relevant (412). A systematic review by Gargon et al. in 2014 reported public representatives in 18% of COS development; this had improved to 59% by the time of an update was conducted in 2016 (413). The latest version of the review was published in 2019, identified patients or their representatives in 77% of COS included (414, 415).

Another feature of our COS which is different to the older JIA-U study, is our appreciation of the role of qualitative research methods to elicit new outcomes from stakeholders including patients and carers. Without this, there is a potential of missing outcomes that may be important to key stakeholders. OMERACT highlighted the importance of qualitative research in clarifying terminologies and informing the meaning of each domain and its relationship to the others (416). Furthermore, the Gargon et al. systematic review reported the use of a qualitative research method with both healthcare professionals and patients' to explore their views and identify the list of outcomes for the COS in 53% of included COS (414, 415). Further details on reported outcome domains and instruments used are reported in Table 12

Table 11: Proposed Core outcomes proposed across various Eye conditions

Category	DE	Uv	Cat	MD	Gla	TED	Str
Visual acuity		✓	✓		✓	✓	✓
Grade of cells in anterior chamber		✓					
Grade of flare in anterior chamber		✓					
Structural damage/ Disease complications		✓		✓		✓	
Ocular surface damage	✓						
Treatment complication/adverse events			✓	✓			✓
Number of hospital visits		✓					
HRQOL		✓			✓		✓
VRQOL	✓		✓†	✓	✓		
Over all uveitis-related disability (Physical functional)		✓					
Psychosocial function							
Anti-inflammatory medication		✓		✓			
Number of treatment				✓			
Disease control							
Clinical symptoms	✓						
Treatment adherence/ compliance	✓						✓
Ophthalmic outcome	✓						
Intraocular pressure	✓				✓		
Visual field					✓		
Anatomic outcomes Retinal nerve fibre layer (RNFL) thickness					✓		
Safety					✓		
Global health							
Biomarkers						✓	
Imaging measures						✓	
Genetics						✓	
Refractive outcomes							✓
Ocular alignment							✓
Visual evoked potentials							✓
Economic data							✓

DE: Dry eyes UV: Uveitis Cat: Cataract MD: Macular degeneration Gla: glaucoma
TED: Thyroid eye disease Str: Strabismus

Table 12: Proposed outcomes and outcome domains in JIA-Study

Domain	Items in the domain	Instrument used
Visual function	Visual acuity	Snellen Chart
Disease activity	• Grade of cells in anterior chamber • Grade of flare in anterior chamber	• Slit lamp examination • Slit lamp examination • Laser flare photometry for prospective trials
Development of structural complications	• Synechiae • Ocular hypotony • Ocular hypertension, glaucoma • Cataract • Band keratopathy • Macular oedema • Epiretinal membrane formation	• Slit lamp examination • Slit lamp examination • Slit lamp examination • Slit lamp examination • Slit lamp examination • Slit lamp examination • Fundoscopy for routine clinical practice • Fundoscopy and optical coherence tomography for prospective trials
Number of hospital visits	Duration of activity over a minimum of 4 visits/year	Physician records
Overall uveitis-related disability	• HRQOL (Generic) • HRQOL (Specific)	• Childhood Health Assessment Questionnaire • Paediatric Quality of Life Inventory • Uveitis-specific quality of life instrument
Over all uveitis related disability (Physical functional)	• Overall assessment	• Assessment by parents, visual analogue scale • Assessment by children, visual analogue scale • Assessment by treating ophthalmologist, visual analogue scale • Assessment by treating paediatric rheumatologist, visual analogue scale
Psychosocial function	• School/kindergarten absence	• Assessment by parents
Anti-inflammatory medication	Reduction of corticosteroid dose • Topical dose • Systemic dose	• Assessment by treating ophthalmologist, rheumatologist and parents

9.7 Relevance of COS to PSIU

Who decides whether a treatment is 'successful'? Is it the patient, the carer, the ophthalmologist, the uveitis nurse practitioner, the trialist or the policy-maker/commissioner? Most clinical trials outcomes have been largely determined by clinicians and trialists with minimal or no engagement from patients and other stakeholders. The development of COS through a multi-stakeholder group with the patient at the centre, is an effective way of ensuring that any 'success' is meaningful to patients, and that the outcomes that are measured include those that are most important to all stakeholders (254). Our COS for PSIU includes measures traditionally measured by clinicians and trialists, and outcomes that have been identified by patients as being areas of concern. Together this COS provides a holistic picture of the impact of PSIU on the patient, and provides the outcomes that all stakeholders need to assess the effectiveness and safety of an intervention in PSIU (388).

This work provides an agreed standardised set of outcomes for use in non-infectious PSIU clinical trials. Outcomes in clinical trials are used in different ways by stakeholders: by patients and clinicians to inform shared decision-making and clinical management; regulators to inform licensing and labelling drug approvals; and policy-makers to inform clinical guidelines and reimbursement and use, locally and nationally.

9.8 Future implications of COS in PSIU

COS facilitates reporting and measuring of outcomes, providing an agreed set of outcomes that are important in clinical trials. COS aims to ensure standardised assessment and reporting of this set of important outcomes, improving the evaluation of a therapeutic intervention across trials and enabling the aggregation of data and avoidance of research waste (217). COS can therefore support the assessment of clinical efficacy (whether the drug works in ideal conditions) and effectiveness (whether the drug works in the real world) (417).

It can also be seen that COS may have a role in routine clinical practice, and not just in clinical trials. For example, the impact of PSIU on a person's emotional and psychological health is an important outcome in routine clinical care, but which is often overlooked in standard practice. Some uveitis care clinics have access to a clinical psychologist who takes referrals from ophthalmologists if any concerns are raised but this is very unusual. The presence of such outcomes in a COS highlights the priority areas that should be reflected in routine clinical practice, and can perhaps be used to realign service delivery to reflect the priorities of our patients.

A further advantage to using COS in routine clinical practice would be that such data would then routinely be available to support pragmatic trials without the need for major additional data collection. The International Consortium for Health Outcomes Measurement (ICHOM) argues for the use of COS in routine care, for example for lower back pain; coronary artery disease; Parkinson's disease; cleft lip and palate; stroke; and knee osteoarthritis (418, 419).

Consistency in reporting and measuring outcomes enables comparison between trials, the aggregation of data and improved evaluation of therapeutic interventions. The use of COS in non-infectious PSIU should encourage standardised outcome selection in such trials (even if there is variation in which outcome is the primary outcome), and enhance evidence synthesis. In consequence, selecting a subset of outcomes based on positive results (outcome reporting bias) should reduce (420). This in turn should provide more meaningful and consistent research outcomes that have value to all stakeholders (203), and reduce non-informative research that may include harmful or ineffective interventions.

Raising people's awareness about the value of a COS such as ours is essential if it is to make any impact on trials, improve clinical practice, and benefit patients. The Knowledge to Action Framework (the KTA Framework) is a framework that concerns knowledge translation and

linking evidence based to clinical practice. Knowledge translation has been defined *as "a process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve health, provide more effective health services and products and strengthen the health care system"* (421). The KTA framework helps the user understand how to communicate and implement knowledge, through engagement with stakeholders, understanding barriers to adoption, and appreciating local needs (422).

To encourage implementation of the COS, it will be helpful to engage with stakeholders who are involved in the design of clinical trials in PSIU, and to try to embed the COS within these studies as exemplars of good practice. This is assisted by the excellent engagement of the international advisory group as part of the COS development, but will require ongoing engagement.

The research group has considered various steps to achieve a future implementation of our COS. Initially, the COS has been registered on the COMET database and will be published on their webpage. Recently it has been submitted to the Ophthalmology Journal. The study will be presented to the International Uveitis Society Group and has support from this group (i.e. the 4th International Uveitis Study Group in Singapore). Highlighting COS has already taken place with other colleagues and relevant stakeholders who have shown an interest. Finally, the study has been funded by the National Institute for Health Research (NIHR) and will be presented at the next annual meeting in November 2020 to highlight the development process and the final list of outcomes in the COS

9.9 Recommendations for future work

This work presents a collaborative work among various stakeholder groups and members of the international uveitis advisory group presenting the first COS for non-infectious PSIU. It aims

to guide clinicians, policy-makers and researchers on *what* to measure and report in clinical trials. The COS establishes which outcomes to measure as a minimum in future PSIU trials but not *how/when* to measure those outcomes. Following this development, the next step is to agree on the measurement tool for each outcome in the COS

Consequently, future research is needed to determine the suitability of specific measurement tools for each outcome to be reported. Regardless of whether the measurement tool is a questionnaire, a clinical assessment or an instrument measurement, it should show validity (accuracy of a measure), reliability (consistency of a measure) and it should play a role in evaluating the disease status (184). This is a key requirement in the process of operationalizing this COS, and should be a priority if we are to ensure true standardisation across clinical trials in PSIU in the future. Whilst acknowledging that this implementation of the COS remains a work-in-progress, it is clear that creating this COS has a huge potential to improve the value of clinical trials, reduce research waste and to inform ophthalmology clinical practice.

9.10 Reflections on my research experience

Prior to starting my PhD, I had only clinical experience in general ophthalmology with limited contribution to ophthalmology research. A few years ago I was involved in two small corneal research projects; my role was to recruit patients meeting the inclusion criteria and collect corneal samples. I was a novice with no experience in research methods. My PhD was a successful journey of a positive learning curve that required good planning and management in a timely manner. My PhD taught me how to be consistent in my writing and how to communicate the story to my audience, reflecting the mantra of one of my supervisors: “speak to your audience”.

Conducting a systematic review enabled me to build my skills in running searches, screening

studies and extracting data using a pre-defined data extraction forms. Conducting a systematic review has been useful to identify the knowledge gap in the treatment of UMO. I have been able to translate these findings into clinical practice and find it enhance my discussion with clinical colleagues concerning the management of UMO. Furthermore, the review gave me the chance to discuss further treatment options with patients highlighting the advantages and the disadvantages of the available drugs. Conducting the systematic review reinforced me the need to update the searches as more trials are published and to keep myself aware of any new emerging medication in the field.

Furthermore, I was completely new to qualitative work. Facilitating focus group discussions and interviews was a new field to me. I have attended special workshops on focus group discussion and interviews followed by excellent advice from the supervisory team specially the qualitative researcher who supervised my focus group discussions. The discussion taught me how to be responsive and handle the discussion as the direction of discussion might change quickly and how to prompt for further clarification on issues raised by participants. To help with this, my supervisor suggested organising and running a mock focus group discussion with PhD students. This gave me a taste of how focus groups could be conducted. I have discovered the value of using ice-breaker questions to attract people to get involved and give them a comfortable and safe zone to be in, and the use of a flip chart to highlight the topic of discussion followed by a summary with participants. The focus group discussion was successfully conducted with the help of the supervisor and generated excellent and relevant data to the discussed topic.

Analysis of qualitative data was a new skill. I attended a training workshop on data analysis and received advice from the supervisory team on coding data using NVivo 12 software. Initially, data were partially coded by myself and checked for redundancy by one of my

supervisors. This was to help ensure that my interpretation was consistent with that of a non-clinical experienced qualitative supervisor. My interpretation to qualitative data was mirrored by my clinical experience which has helped in some ways. However, a constructive discussion with my supervisors enhanced my critical thinking and analytical interpretation to build a bigger picture. The analysis process made me very close to my data in a way I do remember where every single quote came from and in what situation this was mentioned.

The Delphi process was quite daunting at first, especially since the Delphi software used in this study was not very 'user-friendly'. I have received frequent advice from the COMET team at the University of Liverpool that enabled me to build my skills and complete this exercise. This success was reinforced when I was approached by another uveitis colleague who is planning to run a Delphi exercise to agree a set of outcomes in uveitic glaucoma and I was able to successfully advise them in this process.

Chairing a consensus meeting was a big challenge for me, being the first time I have run a multi-stakeholder meeting. I presented the study results covering the whole project and highlighting areas of discussion. Furthermore, I learnt to use the 'Turning Point' voting software to present the data effectively to the group for discussion and to provide them with a facility for voting. I worked hard to ensure I knew my data 'inside-out' and became very close to every single outcome I have used in my presentation. My presentation skills have developed, and my confidence has grown.

Overall, my PhD has been a positive learning experience. I have been able to identify my strengths and work on my weaknesses. I have been able to build my research skills in many aspects. First, my knowledge and skills about research methods (e.g. focus groups, interviews, Delphi exercise, etc.) have developed. Second, my knowledge about uveitis disease (i.e. classification, symptoms, and management) has increased. Third, I have recruited patients,

carers for my focus groups and listened to patients' concerns, trusting what their say and taking it seriously. I have learned to recognise that there are things that I may overlook as a clinician but which are very important to patients. The qualitative research methods helped me to actively listen to patients' concerns and act upon them where appropriate. A good example was noted in a patient whom I have seen in the follow-up clinic following his uveitis attack. This patient reported blurred vision in his left eye; however, there were no signs of active inflammation (resolved uveitis). Responding to his concern, I examined the back of the eye and was surprised to see a different condition affecting the macula - central serous retinopathy (CSR). Although this was not related to uveitis, it can be related to both steroid usage and stress, both of which were relevant to his condition. This also underlines how holistic factors need to be considered (423).

9.11 Conclusion

My thesis focused on the most sight-threatening forms of intraocular inflammation, PSIU, and its major complication, UMO. In the first part of the thesis I provided a comprehensive overview of the pharmacological agents used to treat UMO. The thesis highlights the need for further head-to-head studies for many of the major immunomodulatory drugs, and the need to conduct studies which are either exclusive to UMO or are designed to include stratification according to presence or absence of UMO and report the UMO-subgroup data.

Building on from this, I undertook a programme of work to develop a COS for clinical trials in non-infectious PSIU in adult patients. This COS comprises 16 outcomes grouped into 4 outcome domains. It is a standardised list of outcomes that has value to all stakeholders and provides a solution to the inconsistency and heterogeneity of reported and measured outcomes. The study was able to reach a consensus on *what* outcomes should be reported in PSIU trials and agree the definition of each reported outcome. This COS for PSIU ensures that outcomes

measured and reported are those most important to each group of stakeholders, rather than just to one group. We recommend the use of our COS as a minimum set of outcomes across PSIU clinical trials to reduce outcome-selection bias and outcome-reporting bias; thus, all outcomes are reported without deviation or being favoured to positively reported outcomes. The COS will enhance comparable results across PSIU and improve the statistical power of any meta-analysis since more studies can be included (217).

The next step is to determine the measurement tool for each included outcome in the COS and to promote consistency in outcome measurement across PSIU clinical trials. Additionally, it is important to evaluate the uptake of the COS in future PSIU clinical trials. The COS should be regularly reviewed following its implementation as a method of validation, to ensure the reported outcomes in the COS are still important and relevant to all stakeholder groups and to decide whether further outcomes should be included in the COS where necessary to cover emerging therapy and new evidence (254).

APPENDICES

Appendix 1: Invitation Letter (Focus group)

Invitation letter (Focus group)

(Version 1.4: 6th of February 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

Dear Participant,

As a valued member of the stakeholders (a patient with uveitis or a carer), I am writing to invite you to take part in a focus group discussion to help with a research study 'Defining a Core Outcome Set in patients with Uveitis both with and without Uveitic Macular Oedema' (COSUMO).

The aim of COSUMO is to understand the impact of uveitis on patients and carers to enable us to produce an agreed set of items (these are called 'outcomes' in these studies) that could be routinely assessed in research studies on treatments for uveitis.

We would like to seek your views on the importance of outcomes in the field of uveitis. We feel that your experience with uveitis will be extremely helpful and we would be very grateful if you would consider participating in this focus group discussion. If you require any further information, please contact me through my mobile phone or by email. The Clinical Doctoral Research Fellow will contact you in 3-5 days seeking your interest in taking part in the study.

Yours faithfully

Mohammad Tallouzi
Clinical Doctoral Research Fellow
Institute of Applied Health Research - University of Birmingham
Edgbaston, Birmingham, B15 2TT.
Mobile [redacted] - Email: [redacted]

Appendix 2: Invitation Letter (Telephone Interview)

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

Invitation letter (Telephone Interview)

(Version 1.4: 6th of February 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

Dear Participant,

I am writing to invite you to take part in a telephone interview to help with a research study 'Defining a Core Outcome Set in patients with Uveitis both with and without Uveitic Macular Oedema' (COSUMO). The aim of the COSUMO study is to understand the impact of uveitis on patients and carers to enable us to produce a core outcome set that could be used and reported in uveitis clinical trials. The use of a standardised set of outcomes would increase consistency in clinical trials and help ensure the relevance to stakeholders including patients. As a valued member of the stakeholders (health professionals or policy makers/commissioners), we would like to seek your views on the importance of outcomes in the field of uveitis.

We feel that your experience with uveitis/ health service would be extremely beneficial to develop a future value to the clinical trials of uveitis and would be very grateful if you would consider participating in this telephone interview. It is estimated the interview could take 45 minutes to complete. Further details are provided in the attached Participants Information Sheet.

The Clinical Doctoral Research Fellow will contact you in 3-5 days seeking your interest in taking

part in the study. Please do not hesitate to contact me if you require further information.

Please do not hesitate to contact me if you require further information.

Yours faithfully

Mohammad Tallouzi
Clinical Doctoral Research Fellow
Institute of Applied Health Research
University of Birmingham
Edgbaston, Birmingham - B15 2TT.
Mobile [redacted]
Email: [redacted]

Appendix 3: Invitation Letter (Delphi Exercise)

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

Invitation letter (Delphi process)

(Version 1.4: 6th of February 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

Dear Participant,

I am writing to invite you to take part in an online survey (known as a Delphi process) to help with a research study 'Defining a Core Outcome Set in patients with Uveitis both with and without Uveitic Macular Oedema' (COSUMO). The aim of the COSUMO is to understand the impact of uveitis on patients and carers to enable us to produce an agreed set of outcomes that could be used and reported in uveitis clinical trials. As a valued member of the stakeholders (patients with uveitis, carers, health professionals or health policy makers/commissioners), we would like to seek your views on the importance of outcomes in the field of uveitis.

We feel that your experience with uveitis would be extremely helpful and would be very grateful if you would consider participating in this Delphi process. It is estimated that there would be a minimum of two online Delphi surveys, 1 week apart that would each take 20 minutes to complete and further details are provided in the attached Participants Information Sheet

The use of a standardised set of outcomes would increase consistency in clinical trials and help ensure the relevance to stakeholders including patients. If you require any further information,

please contact me through my mobile phone or by email. The Clinical Doctoral Research Fellow will contact you in 3-5 days seeking your interest in taking part in the study.

Yours faithfully

Mohammad Tallouzi
Clinical Doctoral Research Fellow
Institute of Applied Health Research
University of Birmingham
Edgbaston – Birmingham - B15 2TT.
Mobile [redacted]
Email: [redacted]

Appendix 4: Invitation Letter (Consensus Meeting)

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

Invitation letter (Consensus Meeting)

(Version 1.4: 6th of February 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

Dear Participant,

I am writing to invite you to attend our consensus meeting as a final stage to the study: Defining a Core Outcome Set in patients with Uveitis both with and without Uveitic Macular Oedema (COSUMO). The aim of COSUMO is to develop a core outcome set that could be used and reported in uveitis clinical trials. The aim of the consensus meeting is to discuss the Delphi results presented in the final round and support the final outcomes that need to be included in the core outcome set.

Following the completion of the Delphi process, there is a face-to-face consensus meeting with the key stakeholders (patients, carers, clinicians, policy makers), and members of the research team which will take place (date, time and location). At this meeting the results of each round of the Delphi will be available with all final outcomes defined as 'consensus in' by stakeholders. The consensus meeting is anticipated to take approximately 1-2 hours. Further details are provided in the attached study information sheet.

We feel that your experience with uveitis would be extremely beneficial and we would be very grateful if you would consider participating in this consensus meeting. If you require any further information, please contact me through my mobile phone or by email. The Clinical

Doctoral Research Fellow will contact you in 3-5 days seeking your interest in taking part in the study.

Yours faithfully
Mohammad Tallouzi (Clinical Doctoral Research Fellow)
Institute of Applied Health Research
University of Birmingham
Edgbaston – Birmingham - B15 2TT.
Mobile [redacted]
[redacted]

Appendix 5: Participant Information Sheet for Focus groups

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

Participant Information Sheet for Focus groups

(Version 2.0: 12th of April 17)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

Clinical Doctoral Research Fellow: Mohammad Tallouzi

We would like to invite you to take part in our research study. Before you decide whether you want to take part in this study, it is important you understand why the research is being done and what we would be asking you to do. Please take your time to read the following information carefully and feel free to discuss or talk to anyone about this research. Contact us if there is anything that is not clear or if you would like more information about the study (Our contact details are provided at the end of this form).

Information about the study

Part 1: tells you the purpose of the study and what will happen if you decide to take part.

Part 2: gives you more detailed information about the conduct of the study.

If there is anything that is not clear about the study, please ask us (see contact details on page 6)

Part 1:

What is the purpose of the study?

The aim of the study is to ask patients with uveitis, like yourself, how the condition affects you in your everyday life. This will allow us to develop a list of factors that patients and those around them (e.g. companions or carers) feel are important and can be used in the future to provide a more complete assessment of whether a particular treatment is of benefit or not. These types of lists are known as a core outcome sets (COS). These factors are also valuable

when we are comparing different treatments for uveitis as they let us know if one treatment is better than another.

It is important that the way we measure uveitis outcomes includes those aspects of the disease that really matter to the patient, i.e. how do the patients themselves know whether they are getting better or worse over time? Without this happening, it could mean that doctors and other health professionals may underestimate how severely the uveitis is affecting somebody. It may also be a problem in clinical trials, where our assessment of whether a drug works or not may be based on measures that seem important to health professionals but may not make a real difference to patients.

COS will allow a comparison of treatments by ensuring that all clinical trials measure the same features of the disease. In summary, this research aims to identify what is most important to patients, carers, health professionals and those who are involved in decisions relating to healthcare.

What is a clinical trial?

A clinical trial is an experimental study that aims to help answer whether the available drug is safe to use, effective in treating the disease and whether it works better when it is compared to another drug.

What is uveitis and macular oedema?

Uveitis is a condition in which inflammation occurs inside the eye. It affects different people in many different ways but can often affect vision. One fairly common cause of reduced vision in people with uveitis is macular oedema. Macular oedema is where there is fluid leakage into the central part of the retina (the light sensitive layer at the back of the eye), an area known as the macula. It is the macula that is responsible for your central vision which you use for things like reading.

Part 2:

Who are we?

My name is Mohammad Tallouzi a Clinical Doctoral Research Fellow undertaking a PhD at the University of Birmingham. My PhD study is being supervised by experienced ophthalmologists and researchers who are interested in uveitis and people's ability to carry out everyday tasks.

Why we are approaching you?

We wish to learn how people are affected by uveitis. You are being invited to participate in this study, either because you have uveitis yourself or because you have been identified as a companion or carer for someone with uveitis who is participating in this study. For this study, a 'carer' is a person who is at least 18 years of age (e.g. friend, family member or spouse) who provides unpaid and informal care to the patient during his/her illness.

Do I have to take part?

Taking part in the study is completely voluntary. If you agreed to take part, then you will be asked to sign a consent form. If you are a patient, we will seek your permission to access your medical records that would be relevant to this study.

What will happen to me if I take part?

If you decide to take part in this study, then you need to leave your contact details with the researcher. You will be contacted to discuss it further and to ask any questions you may have. You will then be invited to participate in focus groups made up of people with uveitis and in some cases their carers with the purpose of finding out what is most important to them about uveitis and its impact.

Focus groups

A 'focus group' discussion will include you and 3-5 other participants (patients and their carers) who will participate in a discussion of how uveitis impacts on life. This will be led by a facilitator who is not involved in your clinical care. The discussions will be recorded on audio tape. The group discussion will take up to two hours. Refreshments will be provided. The focus group discussion will be conducted at the University of Birmingham or Birmingham and Midland Eye Centre/Queen Elizabeth Hospital. A map to the location, along with information about parking will be sent to you prior to the discussion.

Study Reimbursement

Each participant will receive a reimbursement for their travel expenses.

Withdrawal from the study

You will be able to withdraw from the study at any point and this will not affect your future medical care. You do not have to give a reason for withdrawing. Any data collected before the focus group discussion will be destroyed. If you withdraw after taking part in a focus group, your data (which is anonymised) will be used up to that point. You are welcome to speak to the research team if you would like any further information (please see contact details on page 6).

What are the possible benefits of taking part?

We cannot promise that our research will help you directly but it is very likely to improve the way we care for patients with uveitis generally. Additionally, the 'core outcome set' for uveitis would reflect the actual impact of the disease on patients and those around them, helping eye specialists and patients to make better-informed decisions about treatments. Having a standard 'core outcome set, would enhance to create comparisons between treatments for uveitis and help to draw a meaningful conclusion for the treatment effects. This may directly impact whether new drugs become available for use in uveitis.

What are the possible disadvantages and risks of taking part?

We do not believe that this study carries any significant risks. However, when talking about what it is like to have uveitis and its impact on your life, it is possible that you may become upset during the discussion. If this happens, the discussion will be paused and the facilitators will ask if you wish to continue or withdraw from the discussion. The facilitator will also assess the situation and ensure any distress is handled appropriately. The experienced facilitator will be available to help making any judgements and provide the most appropriate course of action needed to be put in place. Participants will be directed to the relevant support services available. If a participant is still upset and does not wish to continue the focus group, he/she may withdraw from the study and further support will be provided as needed.

What will happen to results of the research study?

All collected data will be analysed in order to feed into the development of the Core Outcome Set for Uveitis research. The summary results will be published in peer reviewed journals, conference presentations, and the Core Outcome Measures in Effectiveness Trials (COMET) Initiative website. Results will also be disseminated via patients' groups, such as Patient Involvement Group in Uveitis, (PINGU), Olivia's Vision and the Birdshot Uveitis Society. None

of the participants will be identified in any of their outputs and anonymity is guaranteed. We will also feed anonymised results back to participants. If you are interested, we would be pleased to provide you with a report summarising the whole study once it has been completed.

Will my taking part in the study be kept confidential?

All information and responses which were collected about you during the course of the research will be kept strictly confidential and will be handled as dictated by the Data Protection Act 1998, NHS code of confidentiality (2003) and University of Birmingham code of practice for research (2015-2016). The discussions will be recorded on audio tape and held on a secure encrypted and password protected computers and networks at the University of Birmingham. All patients based data (paper and electronic records) will be securely stored in locked cabinets and password protected computers and networks at the University of Birmingham. Data will be marked with a unique study ID and all personal identifiers will be removed from hard copy interview transcripts.

Who is organising and funding the research?

The study is being funded by the Department of National Institute of Health Research (NIHR) and the sponsor organization for the study is Sandwell & West Birmingham Hospitals NHS Trust. The study will be conducted by Mohammad Tallouzi a Clinical Doctoral Research Fellow under the supervision of the research team at the University of Birmingham.

Who has reviewed the study?

This study has been reviewed by the West Midlands - South Birmingham Research Ethics Committee

What if I have any comments?

If you have a concern about any aspect of this study, you should contact the [Local Principal Investigator on [redacted]]. If you wish to discuss independently please contact the hospital's Patient Advice and Liaison Services on 0121 507 5836 or swbh.complaints@nhs.net. For further information about the study or should you have any concern about your involvement or any aspect of the study, please contact

Clinical Research Fellow	Chief investigator	Investigator
Mr Mohammad Tallouzi Clinical Doctoral Research Fellow Academic Unit of Ophthalmology Birmingham and Midland Eye Centre City Hospital Dudley Road Birmingham B18 7QH	**Prof. Philip I. Murray** Professor of Ophthalmology Academic Unit of Ophthalmology Birmingham and Midland Eye Centre City Hospital Birmingham Dudley Road B18 7QH	**Prof. Alastair Denniston** Consultant Ophthalmologist Department of Ophthalmology Queen Elizabeth Hospital Birmingham Mindelson Way Edgbaston Birmingham B15 2TH
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Thanking you for considering taking part in the study

Appendix 6: Participant Information Sheet for Interviews

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

Participant Information Sheet for Interviews

(Version 2.0: 12th of April 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

Clinical Doctoral Research Fellow (CDRF): Mohammad Tallouzi

We would like to invite you to take part in our research project on defining a core outcome set in patients with uveitis both with and without uveitic macular oedema.

Who are we?

My name is Mohammad Tallouzi a Clinical Doctoral Research Fellow undertaking a PhD at the University of Birmingham. My PhD study is being supervised by experienced ophthalmologists and researchers who are interested in how inflammation inside the eye (uveitis) may affect people's ability to carry out everyday tasks.

What is the purpose of the study?

The aim of the study is to establish agreement on which features of the uveitis disease and associated macular oedema should be measured and reported in all clinical trials. Researchers refer to this list of features as a core outcome set (COS).

This study will focus on issues that are important to patients, and have major impacts on patients' life. However, it is also important that we capture such issues that could be used by health professionals and health policy makers/commissioners to complete their roles when trying to decide whether treatment is helping or not.

Evidence suggests that insufficient attention was given to the selection of outcomes to be measured in clinical trials. However, this issue could have been dealt with through the development and use of an agreed standardised set of outcomes, known as a core outcome set, which should be measured and reported as a minimum in all trials of specific clinical area. The aim of the project is to define a core outcome set in uveitis that could be used and reported

in clinical trials.

Currently there is no consensus as to what outcome measures should be collected in uveitis and macular oedema associated uveitis trials. The development of a core outcome set for uveitis would provide for the first time a standardised set of outcome measures that has value to all the stakeholders of patients, carers, health professionals and health policy makers and can be used in all efficacy trials in uveitis. Additionally, involving all parts of the stakeholders in the core outcome set for clinical trials would maximise the relevance and consistency of the outcomes to be included.

Why have I been invited?

You have been invited to participate in this research study because either you are a health professional involved in managing patients with uveitis or you are part of the health commissioning group involved in commissioning health service.

Do I have to take part?

Taking part in the study is completely voluntary. You can change your mind at any time and withdraw from the study without giving a reason. You are welcome to speak to the research team if you would like any further information (please see contact details on page 4).

What will you be asked to do?

If you have agreed to take part in the study you would be asked to provide some data related to your work and expertise in uveitis and discuss the impact uveitis and uveitic macular oedema on a person's life. You will be invited to a telephone interview, which is estimated to take up to 45 minutes and will be audio-recorded on audio tape. The phone call will be made to a convenient number at a mutually agreed time. The investigators will also make sure that they talk to you from a place where maintaining the privacy of your participation can be assured.

Will my taking part in the study be kept confidential?

All information and responses which were collected about you during the course of the research will be kept strictly confidential and will be handled as dictated by the Data Protection Act 1998, NHS code of confidentiality (2003) and University of Birmingham code of practice for

research (2015-2016).

All collected data will be strictly confidential, and your identity will not be divulged. All participants' emails and names and collected data will be securely stored in locked cabinets and password protected computers and networks at the University of Birmingham. The summary results will be published in peer-reviewed journals, conference presentations, and the Core Outcome Measures in Effectiveness Trials (COMET) Initiative website

Who is organising and funding the research?

The study is being funded by the Department of National Institute of Health Research (NIHR) and the sponsor organization for the study is Sandwell & West Birmingham Hospitals NHS Trust. The study will be conducted by Mohammad Tallouzi a Clinical Doctoral Research Fellow under the supervision of the research team at the University of Birmingham.

Who has reviewed the study?

This study has been reviewed by reviewed by the West Midlands - South Birmingham Research Ethics Committee

What if I have any comments?

Thank you for taking time to read this information sheet and for considering taking part in the study. If you wish to participate we would be very grateful if you could leave your contact with the clinical doctoral research fellow. If you have a concern about any aspect of this study, you should contact the [Local Principal Investigator on [redacted]]. If you wish to discuss independently please contact the hospital's Patient Advice and Liaison Services on 0121 507 5836 or swbh.complaints@nhs.net. For further information about the study or should you have any concern about your involvement or any aspect of the study, please contact

Clinical Research Fellow	**Chief investigator**	**Investigator**
Mr Mohammad Tallouzi Clinical Doctoral Research Fellow Academic Unit of Ophthalmology Birmingham and Midland Eye Centre City Hospital- Dudley Road Birmingham B18 7QH	Prof. Philip I. Murray Professor of Ophthalmology Academic Unit of Ophthalmology Birmingham and Midland Eye Centre - City Hospital Birmingham Dudley Road B18 7QH	Prof. Alastair Denniston Consultant Ophthalmologist Department of Ophthalmology Queen Elizabeth Hospital Birmingham Mindelson Way - Edgbaston Birmingham B15 2TH
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Thanking you for considering taking part in the study

Appendix 7: Participant Information Sheet for Delphi Study

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

Participant Information Sheet for Delphi Study

(Version 2.0: 12th of April 17)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

Clinical Doctoral Research Fellow: Mohammad Tallouzi

We would like to invite you to take part in a special series of surveys which will help us determine what outcomes are important to patients with uveitis. Before you decide whether or not you would like to take part, it is important for you to consider why the research is being done and what it will involve. Please read this information sheet carefully.

What is the study about?

The study aims to use a special series of surveys (known as the Delphi process) to develop a list of the most important factors (or 'outcomes') which help us decide whether a treatment is beneficial or not. Importantly this list will be compiled and agreed on by patients, those around them (e.g. carers), health professionals and people involved in health policy. These types of lists are known as core outcome sets (COS). These factors are also valuable when we are comparing different treatments for uveitis as they let us know if one treatment is better than another.

The development of a core outcome set for uveitis would provide for the first time a standardised set of outcomes that has value to all the stakeholders of patients, carers, health professionals and health policy makers/commissioners and can be used in all uveitis treatment trials. Additionally, engaging all the stakeholders in this process ensures that reported outcomes in clinical trials as are relevant to patients and carers as to health professionals and health policy makers/commissioners.

What is a Delphi process?

A Delphi process is a technique which seeks to obtain agreement on the opinions of stakeholders (patients with uveitis, carers, health professionals or health policy makers/commissioners) through a series of structured survey questionnaires. As part of the process, the responses from each round are fed back in a summarised form to the participants who are then given an opportunity to respond again to the results. The Delphi process combines individual opinion into a group agreement.

Who are we?

My name is Mohammad Tallouzi a Clinical Doctoral Research Fellow undertaking a PhD at the University of Birmingham. My PhD study is being supervised by experienced ophthalmologists and researchers who are interested in how inflammation inside the eye (uveitis) may affect people's ability to carry out everyday tasks.

Why have I been invited?

You have been invited to participate in this Delphi process because you have been identified as a valued member of the stakeholder group (a patient with uveitis or a carer, a health professional involved in managing patients with uveitis or you are part of the health commissioning group involved in commissioning health service). We are keen to gain your views about which issues may be important in defining outcomes in patients with posterior segment involving uveitis

Do I have to take part?

Taking part in the study is completely voluntary. You can change your mind at any time and withdraw from the study without giving a reason. If you read the information sheet and you choose not to participate in the study this will not affect your future medical care. In case you participated in the study and submitted your responses to Round 1 then decided to withdraw from the study, please inform the researcher. However, the data you submitted from the start of the study to the date you decided to withdraw will still be included in the study. If you would like to have any further information, please contact the research team (please see contact details on page 4).

What will you be asked to do?

You are invited to participate in the Delphi process and this would involve completing a brief survey questionnaire, rating the importance of outcomes provided using an online survey. It is estimated to take approximately 20 minutes to complete the survey. However, this will vary between participants and will be dependent on the amount of information you are happy to provide. It is important to remember that the researcher is interested in your opinion and there is no right or wrong answer. In each round of the survey, participants' views on the relative importance of each item will be sought and scored on a nine-point scale. Participants' responses in each round will be collated and feedback anonymously to the stakeholders. This process would continue until a group consensus is achieved. A minimum of two Delphi rounds will be conducted with the stakeholders. In order to allow timely conclusion of the study, we would respectfully request a response time of 1 week for completion of each round.

Who is organising and funding the research?

The study is being funded by the Department of National Institute of Health Research (NIHR) and the sponsor organization for the study is Sandwell & West Birmingham Hospitals NHS Trust. The study will be conducted by Mohammad Tallouzi a Clinical Doctoral Research Fellow under the supervision of the research team at the University of Birmingham.

Will my taking part in the study be kept confidential?

All collected information and responses about you during the research will be kept strictly confidential and will be handled as dictated by the Data Protection Act 1998, NHS code of confidentiality (2003) and University of Birmingham code of practice for research (2015-2016.

The information collected will be securely stored in locked cabinets and password protected computers and networks at the University of Birmingham. The only personal data to be collected are participants' emails and names which will be securely stored in locked cabinets and password protected computers and networks at the University of Birmingham. The survey responses will be allocated anonymously using an identifying ID number and all personal identifiers will not be used. The summary results will be published in peer-reviewed journals, conference presentations, and the Core Outcome Measures in Effectiveness Trials (COMET) Initiative website.

Who has reviewed the study?

This study has been reviewed by the West Midlands - South Birmingham Research Ethics Committee.

What if I have any comments?

Thank you for taking time to read this information sheet and for considering taking part in this research. Please let us know if you would like to take part by replying to this email [redacted]. If you have a concern about any aspect of this study, you should contact the [Local Principal Investigator on [redacted]]. If you wish to discuss independently please contact the hospital's Patient Advice and Liaison Services on 0121 507 5836 or swbh.complaints@nhs.net. For further information about the study or should you have any concern about your involvement or any aspect of the study, please contact.

Clinical Doctoral Research Fellow	**Chief investigator**	**Chief investigator**
Mr Mohammad Tallouzi Clinical Doctoral Research Fellow Academic Unit of Ophthalmology Birmingham and Midland Eye Centre City Hospital Dudley Road Birmingham B18 7QH	Prof. Philip I. Murray Professor of Ophthalmology Academic Unit of Ophthalmology Birmingham and Midland Eye Centre City Hospital Birmingham Dudley Road B18 7QH	Prof. Alastair Denniston Consultant Ophthalmologist Department of Ophthalmology Queen Elizabeth Hospital Birmingham Mindelson Way Edgbaston, Birmingham B15 2TH
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Thanking you for considering taking part in the study

Appendix 8: Participant Information Sheet for Consensus Meeting

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

Participant Information Sheet for Consensus Meeting

(Version 2.0: 12th of April 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

Clinical Doctoral Research Fellow (CDRF): Mohammad Tallouzi

We would like to invite you to take part in the final stage of the study and attend our consensus meeting in order to support defining a core outcome set in patients with uveitis both with and without uveitic macular oedema. Before you decide whether or not you would like to take part, it is important for you to consider why the research is being done and what it will involve. Please read this information sheet carefully.

What is the purpose of the study?

The aim of the study is to agree a list of the most important features or impacts of uveitis which should be measured and reported in all clinical trials. Researchers refer to this list of features as a core outcome set (COS).

The development of a core outcome set for uveitis would provide for the first time a standardised set of outcome measures that has value to all those who it matters to (known as 'stakeholders') including patients, carers, health professionals and health policy makers/commissioners and can be used in all trials in uveitis to measure whether a treatment is a benefit or not. Additionally, engaging all the stakeholders in the COS development and making sure that reported outcomes in clinical trials are as relevant to patients and carers as to health professionals and health policy makers and researchers, will help ensure that the COS is relevant to all those stakeholders.

Who are we?

My name is Mohammad Tallouzi a Clinical Doctoral Research Fellow undertaking a PhD at the University of Birmingham. My PhD study is being supervised by experienced ophthalmologists and researchers who are interested in how inflammation inside the eye (uveitis) may affect people's ability to carry out everyday life.

What is a consensus meeting?

Consensus meeting is a face-to-face meeting with the key stakeholders (patients, carers, health professionals, health policy makers/commissioners), and members of the research team. The aim of the consensus meeting is to discuss the Delphi results presented and ratify the final outcome set to be included in clinical trials of uveitis. At this meeting, we will be presenting the results of the final round of the Delphi, which were defined as 'consensus in' by stakeholders. The final format of the meeting will be decided upon at the end of the Delphi exercise and after the advice of COMET (Core Outcome Measures in Effectiveness Trials) members.

Why have I been invited?

You have been invited to participate in this consensus meeting because you have been identified as a valued member of the key stakeholder group (a patient with uveitis or a carer, a health professional involved in managing patients with uveitis or you are part of the health commissioning group involved in commissioning health service). We feel that your experience with uveitis would be extremely beneficial to develop a credible value to the future clinical trials of uveitis and would provide a crucial step in finalising what outcomes should be included.

Do I have to take part?

Taking part in the study is completely voluntary. If you read the information sheet and you choose not to participate in the study you will not be affected in any way. However, if you agree to take part in the consensus meeting then you will be asked to sign a consent form. If you would like to have any further information, please contact the research team (please see contact details on page 3).

What will you be asked to do?

If you decide to take part in the consensus meeting, then you need to leave your contact details with the clinical doctoral research fellow and you will be contacted via the preferred contact method to discuss it further and answer any questions you may have. The meeting will be held at (date and location); map to the location will be attached. The meeting is anticipated to take approximately 1-2 hours.

Who is organising and funding the research?

The study is being funded by the Department of National Institute of Health Research (NIHR) and the sponsor organization for the study is Sandwell & West Birmingham Hospitals NHS Trust. The study will be conducted by Mohammad Tallouzi a Clinical Doctoral Research Fellow under the supervision of the research team at the University of Birmingham.

Will my taking part in the study be kept confidential?

All collected information and responses about you during the course of the research will be kept strictly confidential and will be handled as dictated by the Data Protection Act 1998, NHS code of confidentiality (2003) and University of Birmingham code of practice for research (2015-2016). All responses received in the study will be strictly confidential, and your identity will not be divulged. All participants' emails and names will be securely stored in locked cabinets and password protected computers and networks at the University of Birmingham.

The summary results will be published in peer-reviewed journals, conference presentations, and the Core Outcome Measures in Effectiveness Trials (COMET) Initiative website.

Who has reviewed the study?

This study has been reviewed by the West Midlands - South Birmingham Research Ethics Committee.

What if I have any comments?

Thank you for taking time to read this information sheet and for considering taking part in this consensus meeting). If you wish to participate we would be very grateful if you could leave your contact with the clinical doctoral research fellow. If you have a concern about any aspect of this study, you should contact the [Local Principal Investigator on [redacted]51]. If you wish to discuss independently please contact the hospital's Patient Advice and Liaison Services

on 0121 507 5836 or swbh.complaints@nhs.net. For further information about the study or should you have any concern about your involvement or any aspect of the study, please contact

Clinical Doctoral Research Fellow	**Chief investigator**	**Investigator**
Mr Mohammad Tallouzi Clinical Doctoral Research Fellow Academic Unit of Ophthalmology Birmingham and Midland Eye Centre City Hospital Dudley Road Birmingham B18 7QH	Prof. Philip I. Murray Professor of Ophthalmology Academic Unit of Ophthalmology Birmingham and Midland Eye Centre City Hospital Birmingham Dudley Road B18 7QH	Prof. Alastair Denniston Consultant Ophthalmologist Department of Ophthalmology Queen Elizabeth Hospital Birmingham Mindelson Way Edgbaston Birmingham B15 2TH
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Thanking you for considering taking part in the study

Appendix 9: Topic Guide for Focus Group

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

Topic guide for focus groups – patients and carers

(Version 2.0, 5th of December 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

Doctoral Researcher: Mohammad Tallouzi

- **What I need to bring on the day**
- Ground rules
- Focus group topic guide
- Consent forms and pens
- Background survey questionnaire and pens to complete them
- ID badges
- Flip chart and marker pens
- Two Digital audio recorder
- Spare batteries
- Watch or clock
- Refreshments, cakes and fruits
- Preparation and setup the venue
- The focus group discussion will take place at Sandwell and West Birmingham Hospital NHS trust (Birmingham and Midland eye centre. Research unit, D46, Sheldon Block, City Hospital- B18 7QH)

- Signage to the venue will be placed.
- Inform the front desk receptionist that there will some guests coming to the meeting.
- Informed security that there is a meeting running in the evening
- If possible arrange the furniture so that the participants are facing each other.
- Set up your audio recording device and decide the best place to set up the recorder (middle of the table in order to capture everyone's voice).
- Place the ground rules up on the wall in away all participants are able to see them.
- Set up refreshments at the side of the room.

- **Arrival of participants**
- Meet participants in the reception area and take them to the focus group venue (use lifts where available). Strategies

- **Arrival in the room**

- Once participants begin to arrive, participants will be welcomed
- Ask participants to introduce themselves (patient or a companion)
- Provide name badges for all involved people.
- Please help yourself with a drink; we have tea, coffee, juice and water. Please make yourself comfortable anywhere. We are expecting more people today. I might need to leave the room but if you have any questions Jonathan is here to help you.
- **Signing of consent forms:** Mohammad will give out two copies of consent forms for each participant to complete; one copy is for participant and the other for researcher. (*Please let us know if you require any help in completing the consent form).*
- **Completion of questionnaire:** Mohammad will distribute the survey

questionnaire and ask each participant to complete it. Section A to be completed by uveitis sufferers and section B to be completed by the companion. All the provided details are completely confidential as there are no identifiers on it. (*Please let us know if you require help in completing the questionnaire).*

All completed consent forms and questionnaires will be collected before starting discussion.

- **Prior to start of Focus Group**
    - Housekeeping – Toilets, exits, fire alarms (we are not expecting a fire alarm test today so if the alarm sounds goes on then we will need to evacuate the building (point the direction)
    - If you need to use the toilets, please just get up and excuse yourself.
    - If anyone needs a break from the discussion for any reason please let us know.

Introduction

Thank you for coming today and for agreeing to take part in our study. I will start by introducing myself and the co-facilitator. My name is Mohammad Tallouzi. I am a clinical research fellow undertaking a PhD at the University of Birmingham to understand how the eye condition uveitis impacts on patients' life. I will also introduce the co-facilitators present at the meeting. This is Jonathan who will introduce himself.

Purpose:

Explain purpose of the focus group:

- You may have read the participant information leaflet but I would just like to briefly explain a little more about my research to you.
- We are here today to talk about the impact of the inflammation inside the eye (uveitis) and the treatment you have received and whether this has matched your

expectations. Clinical research is looking at how good the treatment is and is it achieving what is intended to achieve. However, we are interested to hear how people with uveitis and those around them (e.g. partners, family members, friends etc.) are affected by the condition and what the most important impacts and issues are in your view. This is because we need to be sure that the care provided is focused on what is important to people with uveitis and those around them. The purpose of this particular study is to develop a list of the major impacts of uveitis. This list could then be used by doctors and patients when trying to decide whether treatment is helping or not.

- **It is important that we focus on things that are important to you and how uveitis/UMO affects your life.**
- We are running a number of groups like this and the end goal is to have a clear idea of what is important to people with a clinical diagnosis of uveitis both with and without swelling to the back of the eye (macular oedema) so we can look at measuring those things when we assess new ways of supporting people.

So far does anyone have any questions?

Confidentiality:

This discussion will be completely confidential. The session will be audio-recorded (to allow me having accurate records of the discussion to review later) and we will ensure that all transcripts are anonymised and your names will NOT be used in any publication of this research. The audio tapes and transcripts will be kept securely at the University of Birmingham.

Ground rules for the focus group:

- The aim is to fully explore all views, opinions, points and possibly even

generate new ideas based on your different experiences.

- I am here to help guide the conversation but we want you to discuss points made by other people in the group.
- This is an open discussion between participants
- This is not a Question and Answer session.
- There are no right or wrong answers.
- Please respect others' contributions so we don't want to interrupt or start up side conversations, but you should feel free to respond to each other's comments. You don't need to wait for me to invite you.
- Listen to others. Please be mindful that people may have discussed things in this group that they may not necessarily want discussed or shared outside of this group. There is no need to speak into the recorder as it will record everything quite clearly provided we are not speaking at the same time as each other.
- I would like to reiterate that the discussion is completely confidential so all comments will be anonymous.
- We will be writing-up notes to make sure we do not miss anything you have to say.

Does anyone have any questions?
Are you all happy to start the discussion?

Turn on the recorder

Discussion

Thanks again to all of you and it's great to see you all here. Let's start with everyone sharing their name and where they have come from. Please tell us whether you are a uveitis sufferer or a companion ('carer'). If you are here as someone with uveitis can you please tell us how

long you have been diagnosed with uveitis. If you are accompanying someone with uveitis can you tell us what your relationship to them is and how long you have known each other? We'll go around the room this way (indicate direction so that co-facilitator is next). I'll start

I'm Mohammad and I'm a PhD student here at the University of Birmingham and I'm here today because I think that your experience about the disease of uveitis will be really helpful for my research.

We will have three questions

There are three questions to be discussed (*Mohammad and Jonathan will be taking notes).*

Looking at the flip chart, the first question is

Question 1:

1. ***Tell me about uveitis and how the disease has changed your life?***

Discussion on this activity is anticipated to last for 15-20 minutes.

After discussion: Thank you for your contributions, I think we've had an excellent discussion. The facilitator will go through and summarise the points raised by the discussion and write them on the flip chart.

Is there anything else anyone would like to add before we move onto the next topic?
Is there anything Jonathan would like to ask?

Question 2:

2. ***How do you know when the uveitis is under control?***

Discussion on this activity is anticipated to last for 15-20 minutes.

After discussion: Thank you for your contributions, I think we've had an excellent discussion on disease under control. The facilitator will go and summarise the points raised by the group

discussion and write them on the flip chart.

Is there anything else anyone would like to add before we move onto the next topic?

Is there anything Jonathan would like to ask?

Question 3:

3. What do you hope for /expect from the treatment?

Discussion for each activity is anticipated to last for 15-20 minutes.

After discussion: Thank you for your contributions, I think we've had an excellent discussion on the expectation form the treatment. The facilitator will go and summarise the points raised by the group discussion and write them on the flip chart.

Is there anything else anyone would like to add?

Is there anything Jonathan would like to ask?

NB: *If the discussed points are focused on patients' only, then I we say "We have talked about patients and what is important to them, is there anything specific to you people as a husband, wife, daughter or a son".*

Summary of the discussion

The group has raised a lot of different ideas about uveitis and its impact on your life, getting the disease back under control and the treatment issues and expectations. So let's summarise the main points raised by the group to make sure we have covered all the topics.

Mohammad will also ask participants to reflect on those points and identify the things that are most important to them from all the discussed topics.

Closure

- We have reached near to the end of the discussion.
- Has this discussion made any difference to what you think about this issue?

Anybody see the issue differently?

- Thank you for coming to this meeting and participating in the discussion. I hope you have found the discussion interesting and informative.
- I would just like to remind you that this session is confidential and should not be discussed outside this room
- Free parking tickets will be given to participants.
- Travel expenses will be reimbursed to all participants

Appendix 10: Topic guide for (Clinicians and Policy-makers/Commissioners)

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

Topic guide for (Health professionals and Policy-makers/Commissioners)

(Draft version 1.4: 6th of February 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

Clinical Doctoral Research Fellow (CDRF): Mohammad Tallouzi

Introduction

Thank you for agreeing to take part in our study. I will start the interview by introducing myself. My name is Mohammad Tallouzi. I am a Clinical Research Fellow undertaking a PhD at the University of Birmingham.

Purpose:

You may have read the participant information leaflet but I would just like to briefly explain a little more about my research to you. My research project focuses on the eye condition uveitis and I am developing what is called a core outcome set for uveitis. This core outcome set would be a clearly defined minimum set of outcomes that would be recommended for use in clinical trials for treatments of uveitis. Core outcome sets are intended to help with the consistency of reporting of outcomes in clinical trials, reducing reporting bias and helping users of trial research to be able to compare the results across different treatments and trials. In this part of my study I am talking to a range of healthcare professionals and other key stakeholders with an interest in the treatment of uveitis to understand what sort of outcomes might potentially

be included in a core outcome set for uveitis.

Does that make sense? Are there any questions so far?

During our today's discussion I would like to try to understand how you think that uveitis impacts on patients' lives and therefore what sort of outcomes you believe are most important and should be included in a core outcome set. Once we get going I've got a few questions to try to understand your views on this. There are no right or wrong answers and I really just want to try to understand what you think are the most important outcomes for patients that have uveitis.

Confidentiality:

This discussion will be completely confidential. The session will be audio-recorded (to allow me having accurate records of the discussion to review later) and I will ensure that all transcripts are anonymised. The audio tapes and transcripts will be kept securely at the University of Birmingham.

Do you have any question?

Prior to the start of the interview

- Take verbal consent from the participants.
- **Completion of the survey questionnaire:** Mohammad will make sure that all participants have completed the survey questionnaire before starting the interview and if not will ask them to complete it and email it back later.
- The interviews will be audio-recorded and might take up to 45 minutes. And check that participants are ok with the time
- I can stop the interview at any time if participant want to withdraw from the interview.
- Set up your audio recording device and connect to the phone handset

- *Do you have any question?*
- *Are you happy to start the interview?*

Turn on the recorder

Discussion

Thanks again for accepting to take part in this interview. Would you please say your name and where do you work, your current role and level of experience in uveitis?

Topics for discussion

There are few topics that will be discussed. Discussion on each topic is anticipated to take 5-7 minutes. After discussion: participants will be thanked for their contributions.

If speaking to clinicians and policy makers/commissioners:

- How does the posterior segment involving uveitis affect a patient's life?
- What outcomes are clinicians looking to achieve from the treatments provided for posterior segment uveitis patients?
- Are those outcomes that you are trying to achieve reflect clinical practice or clinical trials or both? Are there any examples where those outcomes are different?
- What do patients and carers expect from their treatments? Are there examples of where patients' expectations are different to what clinicians are trying to achieve? Are there other examples of where patients' and clinicians' priorities differ?"
- As you are aware uveitis can be either with or without macular oedema. Do these issues differ between uveitis with and without macular oedema?
- We have discussed the impact of the disease on patients, does uveitis affect carers of patients, and if so how?"

Additional topics if speaking to a policy maker/commissioner:

- Are there outcomes and measures you would consider important within policy or commissioning for uveitis services?

Prompts and probes will be used to enhance a detailed and in-depth discussion (e.g. ''Can you say a bit more about that?"; "Can you give me an example?" "What do you mean by

this''; "Why this is important do you think?"; "Is there anything else that is relevant?" etc.

Closing

- Tell the interviewee that I have reached the end of the interview.
- The researcher would recap issues discussed and check that there is nothing else participants feel is relevant.
- Is there any other information regarding your expertise with uveitis you think would be useful to share?
- Thank the interviewee for taking part in the interview and participating in the discussion

Appendix 11: Background Questionnaire (Focus Groups)

UNIVERSITY OF BIRMINGHAM | Sandwell & West Birmingham Hospitals NHS Trust | University Hospitals Birmingham NHS Foundation Trust

Background Questionnaire (Focus Groups)

(Version 1.4: 6th of February 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

PLEASE COMPLETE PART A IF YOU ARE A PATIENT

PLEASE COMPLETE PART B IF YOU ARE A CARER

A. BACKGROUND INFORMATION FOR PATIENTS

1. What is your gender?

☐ Male ☐ Female

2. What is your age group?

☐ 18-30 ☐ 31-45 ☐ 46-60 ☐ Over 60

3. What is your ethnic group?

☐ White ☐ Mixed/ multiple ethnic groups

☐ Asian/ Asian British ☐ Black/ African/ Caribbean/ Black British

☐ Other _____ (please specify)

4. What is your working status? (Please tick only one box)

☐ Employed ☐ Unemployed incl.

☐ Housewife/husehusband ☐ Student ☐ Retired

☐ If you are employed, please state your occupation here: _____

5. Have you ever smoked

☐ Never smoked ☐ In the past ☐ Current smoker

6. Have you ever driven

☐ Never driven ☐ In the past ☐ Current driver

7. Which hospital do you normally attend?

☐ Birmingham and Midland Eye Centre ☐ Queen Elizabeth Hospital

B. BACKGROUND INFORMATION FOR CARERS

1. What is your gender?

☐ Male ☐ Female

2. What is your age group?

☐ 18-30 ☐ 31-45 ☐ 46-60 ☐ Over 60

3. What is your ethnic group?

☐ White ☐ Mixed/ multiple ethnic groups

☐ Asian/ Asian British ☐ Black/ African/ Caribbean/ Black British

☐ Other _____

(please specify.

4. What is your relationship to the person you care for?

☐ Spouse/Partner ☐ Other family member (please specify) _____

☐ Friend ☐ Other (please specify)

_____

5. How long have you been a carer for?

_____Months _____ (Years)

6. Do you live with the person you care for?

☐ Yes ☐ No

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE

Appendix 12: Background Questionnaire (Interviews)

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

Background Questionnaire (Interviews)

(Version 1.4: 6th of February 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

1. What is your job title / role?

☐ Ophthalmologist ☐ Policy-Maker/Commissioner ☐ Nurse practitioner ☐

Other (Specify) _____

2. Are you currently

☐ Employed ☐ Self-employed ☐ Retired

3. Where is your Country of work?

_____ (please specify)

4. How many years of experience do you have in the area of ophthalmology?

_____

5. How many years of experience do you have in uveitis and UMO?

_____

6. Have you contributed to clinical trials in uveitis?

☐ Yes; if yes, please specify how many

_____ ☐ No

7. Do you have any experience in ophthalmology commissioning?

☐ Yes; if yes, please specify your involvement_____

☐ No

8. Have you been involved with uveitis patient groups?

☐ Yes (if yes please specify which group(s) _____

☐ No

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE

Appendix 13: Focus Group Participants Consent Form

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS Trust

University Hospitals Birmingham NHS Foundation Trust

FOCUS GROUP PARTICIPANTS CONSENT FORM

(Version 2.0: 12th of April 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

		Please write your initial in the Box
1.	I confirm that I have read the information sheet dated 11th April 2017 (Version 2.0) for the above-named study and understand the purpose described.	☐
2.	I confirm that I have had the opportunity to ask questions and had my questions answered to my satisfactioN	☐
3.	I understand that my participation is voluntary and will not affect my clinical care / the clinical care of the person for whom I am the carer	☐
4.	I understand that I am free to withdraw at any time, without giving reason and no subsequent data will be gathered but data given freely before my withdrawal can continue to be used for research purposes.	☐
5.	I understand that my participation in this study will involve me taking part in focus group discussion which will be audio-recorded.	☐
6.	I understand that the data gathered may be presented at a conference or published in journals, provided it is anonymised.	
7.	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Birmingham, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in the research. I give permission for these individuals to have access to my records	☐
8.	I freely agree to take part in this study	☐
9.	I agree that any data collected may be used for future research purposes	☐

Name of Participant	Date	Signature
Name of Researcher	Date	Signature

Appendix 14: Participants Consent Form (Consensus Meeting)

UNIVERSITY OF BIRMINGHAM | Sandwell & West Birmingham Hospitals NHS Trust | University Hospitals Birmingham NHS Foundation Trust

PARTICIPANTS CONSENT FORM (CONSENSUS MEETING)

(Version 2.0: 12th of April 2017)

Study title: Defining a core outcome set in patients with uveitis both with and without uveitic macular oedema (COSUMO)

	Please write your initial in the Box
1. I confirm that I have read the information sheet dated 11th April 2017 (Version 2.0) for the above-named study and understand the purpose described.	☐
2. I confirm that I have had the opportunity to ask questions and had my questions answered to my satisfactioN	☐
3. I understand that my participation is voluntary and will not affect my clinical care / the clinical care of the person for whom I am the carer	☐
4. I understand that I am free to withdraw at any time, without giving reason and no subsequent data will be gathered but data given freely before my withdrawal can continue to be used for research purposes.	☐
5. I understand that my participation in this study will involve me taking part in consensus meeting which will be audio-recorded.	☐
6. I understand that the data gathered may be presented at a conference or published in journals, provided it is anonymised.	
7. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Birmingham, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in the research. I give permission for these individuals to have access to my records	☐
8. I freely agree to take part in this study	☐
9. I agree that any data collected may be used for future research purposes	☐

Name of Participant	Date	Signature
Name of Researcher	Date	Signature

Appendix 15: Delphi Survey (Round 1)

Development of a Core Outcome Set for Efficacy and Effectiveness Trials in Posterior Segment-Involving Uveitis (COSUMO).

Round 1 questionnaire

Thank you for agreeing to take part in our online survey (known as a Delphi process) to help with a research study 'Development Of A Core Outcome Set For Efficacy And Effectiveness Trials In Posterior Segment-Involving Uveitis' (COSUMO). The aim of the COSUMO is to understand the impact of uveitis on patients and carers to enable us to produce an agreed set of outcomes that could be used and reported in uveitis clinical trials. As a valued member of the stakeholders (patients with uveitis, carers, health professionals or health policy makers/commissioners), we would like to seek your views on the importance of outcomes to be assessed in future research studies of posterior segment involving uveitis i.e. inflammation affecting the back of the eye.

This questionnaire is the first of two questionnaires in our Delphi process and we are calling

this Round One. It is really important that you take part in both rounds. Please answer all the questions. We thank you for your time in completing this and assure you that your input is valuable.

In order to carry out the research project described above, we will need to collect information about you, and some of this information will be your personal data. Under data protection law, we have to provide you with very specific information about what we do with your data and about your rights. We have set out below the key information you need to know about how we will use your personal data. The University of Birmingham's web page 'Data Protection- how the university uses your data' sets out much of this information, including how to ask any questions you may have about how your personal data is used, exercise any of your rights or complain about the way your data is being handled.

Please read the following statements and click on the button below to proceed with the Delphi questionnaire.

1. I confirm that I have read (or have had read to me) and understood the research information sheet (Participant Information Sheet for Delphi Study Version 2.0: 12th of April 17) and have been given the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected

3. I give my consent to take part in this Delphi questionnaire.

4. If you agree with the all of the above statements and would like to proceed with the Delphi questionnaire please write your initial in the Box ☐

A few things about you

To allow us to analyse the results of the study, we need some brief information about you and your clinical expertise. Please tick the most appropriate box.

1. What is your age group?

☐ 18-24 ☐ 25-34 ☐ 35-44

☐ 45-54 ☐ 55-64 ☐ 65-74

☐ 75 and over

2. What is your gender?

☐ Male ☐ Female

3. What is your ethnic group?

☐ White ☐ Mixed/Multiple ethnic groups

☐ Asian/Asian British ☐ Black/African/ Caribbean/ Black British

☐ Other ethnic group

4. Which of the following describes your primary role?

☐ Patient ☐ Carer

☐ Ophthalmologist ☐ Nurse practitioner

☐ Policy maker or commissioner

☐ Other (Specify) _____

5. If you are a patient how long have you had uveitis?

☐ Less than 5 years ☐ 5-10 years

☐ 11-15 years ☐ 16-20 years

☐ More than 20 years

6. If you are a carer how long have you been a carer?

☐ Less than 5 years ☐ 5-10 years

☐ 11-15 years ☐ 16-20 years

☐ More than 20 years

7. What is your relationship to the person you care for?

☐ Spouse/Partner ☐ Other family member (please specify)

_____

☐ Daughter ☐ Son

☐ Friend ☐ Other (please specify)

_____

8. If you are a health care professional

a. Where is your country of work?

_____ (please specify)

b. How many years of experience do you have in the area of ophthalmology?

☐ Less than 5 years ☐ 5-10 years

☐ 11-15 years ☐ 16-20 years

☐ More than 20 years

c. How many years of experience do you have in uveitis?

☐ Less than 5 years ☐ 5-10 years

☐ 11-15 years ☐ 16-20 years

☐ More than 20 years

B. Things that may be important to assess posterior segment involving uveitis

Please rate how **important** you think it is that each of the following issues (outcomes) are assessed in ***research studies on patients with posterior segment involving uveitis?***
The ***term*** describing each outcome is stated in **bold** and the definition of each term explained in ***italics***. This allows us to use the same questionnaire for patients/carers and healthcare professionals. Please circle the number that best represents your opinion.

Not 1 2 3 4 5 6 7 8 9 Extremely

B1. Issues relating to visual function

B1 How important is it that the following aspects of vision are assessed in research studies on posterior segment involving uveitis?

		Not important (Please circle) Extremely important								
B1a)	**Distance vision** *A patient's ability to see objects/people clearly from distance (beyond arm's length) (e.g. road signs, TV, cinema)*	1	2	3	4	5	6	7	8	9
B1b)	**Near vision** *A patient's ability to see near objects (e.g. reading, seeing prices on a menu, seeing phone numbers and other close-up tasks)*	1	2	3	4	5	6	7	8	9
B1c)	**Colour vision** *A patient's ability to distinguish colours accurately (e.g. choosing items of clothing that match)*	1	2	3	4	5	6	7	8	9
B1d)	**Peripheral vision** *A patient's ability to see towards the edge of their vision (e.g. seeing people or objects at the side)*	1	2	3	4	5	6	7	8	9
B1e)	**Contrast sensitivity** *A patient's ability to distinguish objects from the background (e.g. in low light, fog or glare)*	1	2	3	4	5	6	7	8	9
B1f)	**Depth perception** *A patient's ability to perceive the world in three dimensions (3D) to judge distance of objects (e.g. judging how far away or how high a step is)*	1	2	3	4	5	6	7	8	9

B2. Symptoms that may occur during the disease process

B2. How important is it that the following symptoms are assessed in research studies on posterior segment involving uveitis?

		Not important	(Please circle)							Extremely Important
B2a)	**Uncomfortable or painful eye** *A person complains of eye pain that may be severe and seem sharp, aching, or throbbing, or a person may feel only mild irritation of the eye surface or the sensation of a foreign object in the eye (foreign body sensation)*	1	2	3	4	5	6	7	8	9
B2b)	**Watery Eye** *A person experiences a watery or a runny eye (excess tears)*									
B2c)	**Redness** *A person experiences a visible bloodshot or redness to the white part of the eye*									
B2d)	**Photosensitivity** *A person experiences light intolerance or the eye is over sensitive to light (e.g. in sun light, fluorescent light, headlights, street lights)*									
B2e)	**Floaters** *A person complains of seeing moving dark or grey spots, specks, strands, or cobwebs*									
B1f)	**Visual disturbance** *A person complains of seeing blurred, hazy, foggy, grainy vision, flashing/shimmering lights or double vision*									
B1g)	**Distortion of vision** *A person complains that straight lines may appear bent, crooked or wavy*									
B1h)	**Headache** *A person experiences a severe or throbbing headache*									
B1J)	**Fatigue** *A person experiences fatigue, exhaustion, a feeling of tiredness or a general lack of energy*									

B3. Issues relating to functional ability

B3. How important is it that the following aspects of functional ability are assessed in research studies on posterior segment involving uveitis?

		Not Important			(Please circle)					Extremely Important
B3a)	**Work related impact** *A person's performance and ability to maintain or continue work/employment*	1	2	3	4	5	6	7	8	9
B3b)	**Driving/commuting related impact** *A person's ability to maintain or continue driving or commuting*	1	2	3	4	5	6	7	8	9
B3c)	**Education related impact** *A person's ability to maintain education (e.g. attend college or university)*	1	2	3	4	5	6	7	8	9
B3d)	**Day to day usual activities related impact** *A person's ability to maintain and continue engagement in day-to-day activities (e.g. care for own self, shaving beard, washing face, gardening, shopping, cooking and doing the washing etc.)*	1	2	3	4	5	6	7	8	9
B3e)	**Social and Leisure activities related impact** *A person's ability to participate, maintain and continue social or leisure activities*	1	2	3	4	5	6	7	8	9

B4. Issues relating to relationships with family members and friends

B4. How important is it that the following aspects of relationships are assessed in research studies on posterior segment involving uveitis?

		Not Important			(Please circle)					Extremely Important
B4a)	**Impact on relationships with family and/or friends** *A person's ability to maintain valued relationships with family members, friends or colleagues*	1	2	3	4	5	6	7	8	9

B.5 Issues relating to financial cost

B5. How important is it that the following financial impacts are assessed in research studies on posterior segment involving uveitis?

		Not Important			(Please circle)					Extremely Important
B5a)	**Financial impact due to early retirement, the need to take a part-time job or redundancy** *Describes the financial implications/costs of having uveitis and the experience of financial loss due to loss of work, early retirement, the need to take a part-time job or redundancy*	1	2	3	4	5	6	7	8	9
B5b)	**Financial impact of treatments** *Describes other financial costs including treatment related costs (e.g. prescriptions costs, travel, parking etc.)*	1	2	3	4	5	6	7	8	9

B6. Issues relating to a person's emotional and psychological health

B6. How important is it that the following aspects of emotional and psychological health are assessed in research studies on posterior segment involving uveitis?

B7. Issues relating to psychosocial adjustment		Not Important			(Please circle)					Extremely Important
B6a)	***Depression and mental illness*** *Feelings of severe sadness or feeling depressed with loss of interest or lack of enjoyment*	1	2	3	4	5	6	7	8	9
B6b)	**Anxiety** *Feelings of constant worry and being anxious*	1	2	3	4	5	6	7	8	9
B6c)	**Stress** *Feelings of tension, mental or emotional strain and being under pressure*	1	2	3	4	5	6	7	8	9
B6d)	**Frustration and Anger** *Feeling upset or annoyed as a result of being not able to achieve something*	1	2	3	4	5	6	7	8	9

B7. How important is it that the following aspects of psychosocial adjustment are assessed in research studies on posterior segment involving uveitis?

		Not Important	(Please circle)						Extremely Important
B7a)	**Overall psychosocial adjustment** *Describes difficulties that a person has in adjusting his/her life (e.g. social anxiety, acceptance of the disease, social reaction, autonomy and independence)*	1	2	3	4	5	6	7	8	9
B7b)	**Coping** *Describes specific things that a person is able to do in order to cope with the effect of the disease. These can include a mix of psychological (e.g. positive attitudes and good mind-set, positive spiritual beliefs) and behavioural strategies (e.g. changing driving, reading or working behaviours or change in day to day life patterns etc.)*	1	2	3	4	5	6	7	8	9
B7c)	**Sense of self** *Describes how a person views him/herself (i.e. their self-image). This could be positive or negative, or mixed*	1	2	3	4	5	6	7	8	9
B7d)	**Identity** *Describes how a person is viewed by and relates to others, including family and friends*	1	2	3	4	5	6	7	8	9
B7e)	**Normality** *Describes a person's ability to retain or regain some sense of normality within life*	1	2	3	4	5	6	7	8	9

B8. Issues relating to doctor/patient/inter professional relationship and access to health care (Service outcomes)

B8. How important is it that the following aspects of service outcomes are assessed in research studies on posterior segment involving uveitis?

		Not Important				(Please circle)				Extremely Important
B8a)	**Doctors-patient relationship/communication** *Describes how effective the communication process between doctors and patients with uveitis is (listening and speaking)*	1	2	3	4	5	6	7	8	9
B8b)	**Inter-professional relationships** *Describes how effective the communication process between health care professionals is (e.g. whether GPs and hospital doctors communicate effectively)*	1	2	3	4	5	6	7	8	9
B8c)	**Shared decision-making** *Describes the process of actively involving people with uveitis in decisions that are made regarding their treatment plan*	1	2	3	4	5	6	7	8	9
B8d)	**Access to uveitis clinics and/facilities** *Describes a person's ability to access uveitis clinics and care facilities*	1	2	3	4	5	6	7	8	9
B8e)	**Access to physical aids and other resources** *Describes a person's ability to access physical and visual aids (e.g. getting a white stick, light bulbs that reduce glare, a water level indicator, a guide dog, smartphone apps etc.)*	1	2	3	4	5	6	7	8	9
B8f)	**Access to counselling and psychotherapy services** *Describes a person's ability to access psychotherapy, counselling and clinical psychology services*	1	2	3	4	5	6	7	8	9

B9. Issues relating to treatment burden

Describes the workload of healthcare and its effect on the functioning and wellbeing of patients with posterior segment involving uveitis. This includes the burden of attending clinic appointments and taking medications.

B9. How important is it that the following aspects of treatment burden are assessed in research studies on posterior segment involving uveitis?

		Not Important			(Please circle)					Extremely Important
B9a)	**Number of hospital visits** *Describes a feeling of burden created by frequent hospital visits to monitor the disease and treatment*	1	2	3	4	5	6	7	8	9
B9b)	**Amount of medications** *Describes a feeling of burden created by the amount of the prescribed medications*	1	2	3	4	5	6	7	8	9
B9c)	**Adherence** *Describes a feeling of burden following treatment recommendations given by doctors (e.g. taking medications at the recommended dose and time)*	1	2	3	4	5	6	7	8	9

B10. Issues relating to treatment side effects

B10. How important is it that treatment side effects are assessed in research studies on posterior segment involving uveitis?

		Not Important			(Please circle)					Extremely Important
B10a)	**Treatment side effects** *Describes undesired or unintended treatment effects that patients may experience*	1	2	3	4	5	6	7	8	9

B11. Issues relating to disease control

B11. How important is it that the following aspects of disease control are assessed in research studies on posterior segment involving uveitis?

		Not Important								Extremely Important
		(Please circle)								
B11a)	**Anterior segment inflammation** *Inflammation in the front of the eye between the cornea and the iris*	1	2	3	4	5	6	7	8	9
B11b)	**Vitreous inflammation/haze** *Inflammation/haze/cloudiness of vitreous jelly located between the lens and the retina*	1	2	3	4	5	6	7	8	9
B11c)	**Retinal vasculitis** *Inflammation of the blood vessels of the retina (the light sensitive layer at the back of the eye)*	1	2	3	4	5	6	7	8	9
B11d)	**Retinitis** *Inflammation of the retina (the light sensitive layer at the back of the eye)*	1	2	3	4	5	6	7	8	9
B11e)	**Flare/relapse/recurrence** *Recurrence or increase of inflammation in the front or back of the eye that may be associated with effects on vision*	1	2	3	4	5	6	7	8	9
B11f)	**Raised intraocular pressure** *Increase in the pressure inside the eye above the normal range and if left untreated may permanently damage the sight*	1	2	3	4	5	6	7	8	9
B11g)	**Uveitic macular oedema** *Fluid that builds up in the central part of the retina causing swelling of the macula. The macula is responsible for detailed central vision*	1	2	3	4	5	6	7	8	9
B11h)	**Cataract** *Clouding of the normally transparent lens of the eye*	1	2	3	4	5	6	7	8	9

B11i)	**Structural changes** *Changes to the structure of the eye including retinal scarring and optic nerve damage (including glaucoma)*	1	2	3	4	5	6	7	8	9
B11j)	**Other ocular co-morbidities** *Manage other eye problems not directly related to uveitis (e.g. dry eyes)*	1	2	3	4	5	6	7	8	9

B12. Please write down any outcomes relating to posterior segment involving uveitis not included above, which you think would be important to assess in research studies. Please click on 'Add Outcome Row' and add your text.

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B13. Any other comments. We welcome all your views.

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Thank you for your contribution to this round of the survey.
We look forward to providing you with the results in the next round

Appendix 16: Additional outcomes identified by the Delphi participants in Round 1

Outcomes	Definition	Outcome domain
Overall well-being	*How uveitis affects one's overall health status*	**Psychological adjustment**
Band keratopathy	*White, chalky deposits on the surface of the cornea (front window of the eye) that may cause pain and a reduction in vision*	**Disease Control**
Epiretinal membrane	*A thin layer of scar tissue that forms on the surface of the retina usually at the macula (the sensitive central part of the retina) reducing vision*	**Disease Control**
Systemic co-morbidities	*Manage other systemic (general) health problems that are related to the uveitis (e.g. sarcoidosis, Behcet's disease)*	**Disease Control**
Desire to have children, able to conceive and lactate	*Describes wanting to have children and the ability to get pregnant and breast feed*	**Relationships with family members and friends**

Appendix 17: Welcome Letter (Consensus Meeting)

COSUMO Posterior Segment-Involving Uveitis Core Outcome Set Consensus Meeting

Date: Thursday 23rd January 2020, 9:20am- 5pm

Venue: Liberty Room in Winterbourne House & Gardens, University of Birmingham, Edgbaston, B15 2TT, UK (G12 University of Birmingham campus map)

Dear Attendees,

Welcome to Birmingham!

We are delighted to welcome you to our COSUMO Consensus meeting.

On behalf of the COSUMO team, we would like to thank you for your valuable contribution to this important study and for joining us for this meeting.

The consensus meeting is the final step to compile a core outcome set for Posterior Segment-Involving Uveitis and the findings of this will be used to advise all studies of Posterior Segment-Involving Uveitis when choosing outcomes to measure in trials.

Previous to this stage, we have completed a comprehensive systematic review of existing uveitis studies, four focus groups, twelve interviews and two rounds of a Delphi exercise to

gain insight into what health care professionals, policy makers, carers and, importantly, patients who have to live with uveitis believe to be most important outcomes for them. The results will be presented and discussed at the meeting and the aim is to agree the final list of outcomes in the core outcome set.

Prior to the Meeting

We have prepared a summary document of outcomes scores that are sent out to you nearer the date of the meeting. We ask you to familiarise yourself with outcomes achieved consensus >70% before the meeting. As a key stakeholder, we need your thoughts and feelings about these outcomes, and we would value your input.

Meeting Details

Meeting registration will commence at 9:20 am on the 23rd January 2020 at the Liberty room in Winterbourne House & Gardens, University of Birmingham, Edgbaston, B15 2TT, UK. The meeting will start at 9.45am. Please refer to the agenda for further details about the schedule of the day. There will be refreshments such as tea and coffee available from 9.20am throughout the day. We will also be providing a buffet lunch

Finding Liberty Room

Winterbourne is located on the University of Birmingham campus (G12) in Edgbaston, Birmingham (see attached map). Only a few miles from the city centre, it is just off the main A38 route leaving the city towards the South West.

Train

Direct trains from Birmingham New Street on the Cross-City line to University station then a 10 minute walk across campus. Winterbourne House & Gardens is shown as G12 on the attached university campus map.

Bus

The X20, X21 and X22 buses stop just around the corner from Winterbourne. They pick up from the city centre by Moor Street Station. More details about frequency and other stops can be found on the National Express Bus website www.nxbus.co.uk.

Car

Winterbourne is off Edgbaston Park Road. You can enter the postcode B15 2RT into your satnav. Few parking spaces are available in front of Winterbourne House that is accessed by bearing left around the central island and in the front of Winterbourne. There are three blue badge parking spaces located in this alternative parking area. Alternatively, North east car park can be used (5minutes walk), B15 2SA, charges applied and can be reimbursed. There are also cycle racks available.

Hotel

A two-night reservation (22nd and 23rd January) has been made for you at the Edgbaston Park Hotel, 53 Edgbaston Park Road, Birmingham, B15 2RS, UK. Telephone No: +44 121 414 8888 https://www.edgbastonparkhotel.com/ (G23 on the Campus map, a few hundred metres from Winterbourne). Details of the room booking will be sent at a later stage. Breakfast will be provided at the hotel. Following the meeting we would be delighted to invite you to be our guest at an evening meal on the 23rd January at Asha's Restaurant, 12-22 Newhall St, Birmingham B3 3LX, https://ashasbirmingham.co.uk/. Transport will be provided and there will be an informal pre-dinner drink before the meal (venue to be decided)

Reimbursement

We will cover the transport costs e.g. economy air fare, economy train fare/taxi/car mileage. The cost of the 2-night stay at the Edgbaston Park Hotel will also be covered by us. Please retain your receipts as these will be required for any claim. Claim forms will be provided at the meeting or via email.

Enquiries

Please let us know if you need any support with your visit. For any urgent requests/enquiries please contact Mohammad Tallouzi (or any of us)

We hope you look forward to a playing a vital role in creating a core outcome set for use in future studies of Posterior Segment-Involving Uveitis.

Kind regard

Mr Mohammad Tallouzi	**Prof. Philip I. Murray**	**Prof. Alastair Denniston**
Clinical Research Fellow Institute of Applied Health Research Academic Unit of Ophthalmology Birmingham and Midland Eye Centre City Hospital Dudley Road Birmingham B18 7QU [redacted] (Work) [redacted] (Mobile) Email **:** [redacted] [redacted]	Professor of Ophthalmology Academic Unit of Ophthalmology Birmingham and Midland Eye Centre City Hospital Birmingham Dudley Road B18 7QH [redacted] (Work) [redacted] (Mobile) Email: [redacted]	Consultant Ophthalmologist Department of Ophthalmology Queen Elizabeth Hospital Birmingham Mindelson Way Edgbaston Birmingham B15 2TH [redacted] Email: [redacted]

Edgbaston Campus Map

Index to buildings by zone

Red Zone
- R0 The Harding Building
- R1 Law Building
- R2 Frankland Building
- R3 Hills Building
- R4 Aston Webb – Lapworth Museum
- R5 Aston Webb – B Block
- R6 Aston Webb – Great Hall
- R7 Aston Webb – Student Hub
- R8 Physics West
- R9 Nuffield
- R10 Physics East
- R11 Medical Physics
- R12 Bramall Music Building
- R13 Poynting Building
- R14 Barber Institute of Fine Arts
- R15 Watson Building
- R16 Arts Building
- R17 Ashley Building
- R18 Strathcona Building
- R19 Education Building
- R20 J G Smith Building
- R21 Muirhead Tower
- R23 University Centre
- R24 Staff House
- R26 Geography
- R27 Biosciences Building
- R28 Murray Learning Centre
- R29 The Alan Walters Building
- R30 Main Library
- R31 Collaborative Teaching Laboratory
- R32 Teaching and Learning Building
- R33 Fry Building
- R34 Cuore

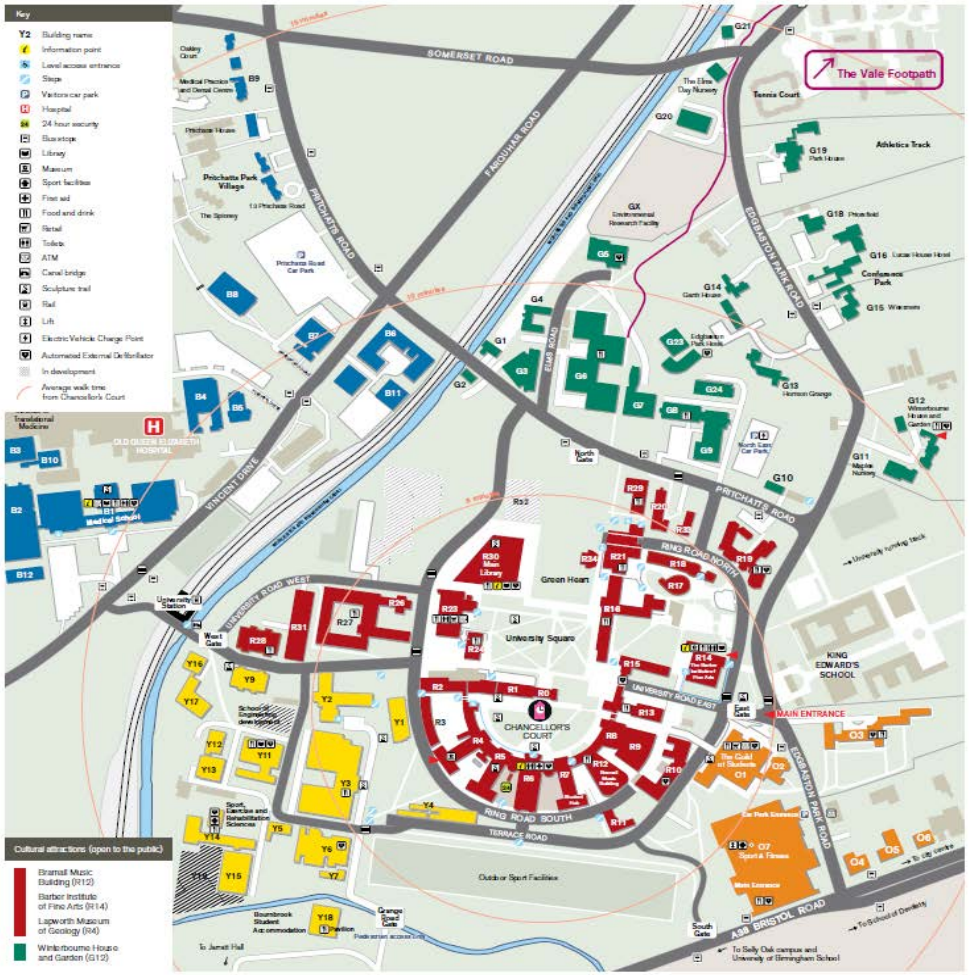
Blue Zone
- B1 Medical School
- B2 Institute of Biomedical Research including IBR West
- B3 Wellcome Clinical Research Facility
- B4 Robert Aitken Institute for Clinical Research
- B5 CRUK Institute for Cancer Studies and Denis Howell Building
- B6 Research Park
- B7 90 Vincent Drive
- B8 Henry Wellcome Building for Biomolecular NMR Spectroscopy
- B9 Medical Practice and Dental Centre
- B10 Advanced Therapies Facility
- B11 BioHub Birmingham
- B12 Health Sciences Research Centre (HSRC)

Orange Zone
- O1 The Guild of Students
- O2 St Francis Hall
- O3 University House
- O4 Ash House
- O5 Beech House
- O6 Cedar House
- O7 Sport & Fitness

Green Zone
- G1 32 Pritchatts Road
- G2 31 Pritchatts Road
- G3 European Research Institute
- G4 3 Elms Road
- G5 Computer Centre
- G6 Metallurgy and Materials
- G7 IRC Net Shape Laboratory
- G8 Gisbert Kapp Building
- G9 52 Pritchatts Road
- G10 54 Pritchatts Road – Institute for Global Innovation
- G11 Maples Nursery
- G12 Winterbourne House and Garden
- G15 Westmere
- G16 Lucas House Hotel
- G18 Priorsfield
- G19 Park House
- G20 Elms Plant
- G22 Elms Day Nursery
- G24 Centre for Human Brain Health

Green Zone Conference Park
- G13 Hornton Grange
- G14 Garth House
- G23 Edgbaston Park Hotel and Conference Centre
- G24 Centre for Human Brain Health

Yellow Zone
- Y1 The Old Gym
- Y2 Haworth Building
- Y3 Engineering Building
- Y4 Terrace Huts
- Y5 Estates West
- Y6 Maintenance Building
- Y7 Grounds and Gardens
- Y9 Computer Science
- Y11 Chemical Engineering
- Y12 Biochemical Engineering
- Y13 Chemical Engineering Workshop
- Y14 Sport, Exercise and Rehabilitation Sciences
- Y15 Civil Engineering Laboratories
- Y16 Institute of Occupational and Environmental Medicine
- Y17 Public Health
- Y18 Bournbrook Student Accommodation and Pavillion



Appendix 18: COSUMO Consensus Meeting Agenda

COSUMO Posterior Segment-Involving Uveitis Core Outcome Set Consensus Meeting Agenda

Thursday 23rd January 2020

Liberty room in Winterbourne House & Gardens, University of Birmingham

Meeting Agenda	
9:00-9:15	Refreshments on arrival
9:15-9:45	Meeting patients and carers
9:45-9:55	Welcome, orientation from the facilitator (Sara Brookes)
9:55-10:25	Introduction (60 minutes) • Background to project • What is a COS • Methods used to develop COSUMO • Delphi consensus results
10:25-11:25	Session 1 Discussion of outcomes (60 minutes)
11:25-11:40	Refreshment break (15minutes)
11:40-12:40	Session 1 to continue Discussion of outcomes (60 minutes)
12:40-13:20	Lunch break (40 minutes)
13:20-15:00	Session 2 Discussion of outcomes (100 minutes)
15:00-15:15	Coffee break (15 minutes)
15:15-16:20	Session 3 Discussion of potential groupings of items (65 minutes)
16:20-16:45	Summary of key points from discussions
16:45-17:00	Closing and final remarks

Appendix 19: Consensus meeting Evaluation form

UNIVERSITY OF BIRMINGHAM

Sandwell & West Birmingham Hospitals NHS
NHS Trust

COSUMO Posterior Segment-Involving Uveitis Core Outcome Set Consensus Meeting

Many thanks for attending the meeting today and for your contribution to the development of a core outcome set. We would really value your feedback on the day.

Please rate the following statements by ticking the appropriate box

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
I was happy with the organisation for the day					
The aims of the meeting were communicated clearly					
The discussions were well facilitated and fair					
Results easily and clearly presented					
Methods used to develop core outcome set are clear					
I felt happy to contribute to discussions where I wanted to					
The meeting was effective in achieving its aims					
The meeting was enjoyable					

Overall satisfaction

	Very satisfied	Satisfied	Neutral	Jnsatisfied	Very unsatisfied
Overall satisfaction					

What did you enjoy most about the meeting?

……

……

……

……

……

How could the meeting have been improved?

……

……

……

……

……

Appendix 20: HRA Approval Letter

NHS
Health Research Authority

Prof Philip I. Murray
Professor of Ophthalmology, Consultant Ophthalmologist
Sandwell and West Birmingham NHS Trust
Birmingham and Midland Eye Centre
Academic unit
Birmingham- Dudley Road
B18 7QH

Email: hra.approval@nhs.net

25 April 2017

Dear Professor Murray,

Letter of HRA Approval

Study title:	**Defining a Core Outcome Set in patients with Uveitis both with and without Uveitic Macular Oedema (COSUMO).**
IRAS project ID:	**221333**
REC reference:	**17/WM/0111**
Sponsor	**Sandwell and West Birmingham NHS Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **221333**. Please quote this on all correspondence.

Yours sincerely,

Steph Blacklock
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Dr Jocelyn Bell, Sandwell and west Birmingham NHS trust*

IRAS project ID	221333

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Interview schedules or topic guides for participants [Topic guide for focus group discussion- 060217 .docx]	1.4	06 February 2017
IRAS Application Form [IRAS_Form_21022017]		21 February 2017
Letter from funder [Letter from funder]		
Letter from sponsor [Sponsor Letter]	NA	16 February 2017
Letters of invitation to participant [Invitation letter for Focus group (patients & carers) 060217]	1.4	06 February 2017
Non-validated questionnaire [Background survey questionnaire for focus groups (patients & carers) 060217]	1.4	06 February 2017
Other [D.Moore CV(supervisor)]	NA	16 February 2017
Other [A.Denniston CV(supervisor)]	NA	16 February 2017
Other [J. Mathers CV(supervisor)]	NA	16 February 2017
Other [HRA statement of activities]	NA	17 February 2017
Other [HRA schedule events]	NA	17 February 2017
Other [Participant Information Sheet for interviews (health profs & policy makers) 060217.docx]	1.4	06 February 2017
Other [Participant Information Sheet for Delphi (all participants) 060217.docx]	1.4	06 February 2017
Other [Participant Information Sheet for Consensus meeting (all participants) 060217]	1.4	06 February 2017
Other [Invitation letter for interview (health professionals & policy makers) 060217]	1.4	06 February 2017
Other [Invitation letter for Delphi (all participants) 060217.docx]	1.4	06 February 2017
Other [Invitation letter for consensus meeting (all participants) 060217]	1.4	06 February 2017
Other [Consent Form for consensus meeting (all stakeholders) 060217]	1.4	06 February 2017
Other [Topic guide for health professionals and policy makers 060217]	1.4	06 February 2017
Other [Background survey Questionnaire for Interviews (health professionals & policy makers) 060217]	1.4	06 February 2017
Other [Consent Form for consensus meeting (all stakeholders) V2.0-]	2.0	12 April 2017
Other [Consent Form for focus group (patients carers) V2.0-]	2	12 April 2017
Other [COSUMO Protocol]	2.0	12 April 2017
Other [Participant Information Sheet for Consensus meeting (all participants)]	2.0	12 April 2017
Other [Participant Information Sheet for Delphi (all participants)]	2.0	12 April 2017
Other [Participant Information Sheet for focus group (patients carers) V2.]	2.0	12 April 2017
Other [Participant Information Sheet for interviews (health profs policy makers)]	2.0	12 April 2017
Summary CV for Chief Investigator (CI) [Philip Murray's CV- Chief Investigator]	NA	07 February 2017
Summary CV for student [Mohammad Tallouzi CV (Student)]	NA	16 February 2017
Summary CV for supervisor (student research) [Mel Calvert CV]	NA	16 February 2017

IRAS project ID	221333

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Dr Mohd Tallouzi

Email: [redacted]

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	Applicant has included PALS details in the participant information sheet(s) and confirmed that details regarding transcription services will be added to the participant information sheet.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	This is a single site, same sponsor study with no third party involvement and therefore no additional agreements are required.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	The study is funded by NIHR.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Yes	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
This is a single site, same sponsor questionnaire/interview study with one site type. If this study is subsequently extended to other NHS organisation(s) in England, an amendment should be submitted to the HRA, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at

hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.
This is a single site study sponsored by the site. The R&D office will confirm to the CI when the study can start.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
HRA would expect a local collaborator to be in place for this study. GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
Where arrangements are not already in place, network staff (or similar) undertaking any of the research activities listed in A18 or A19 of the IRAS form, would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
• The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio..

Appendix 21: Ethics Approval Letter

NHS
Health Research Authority
West Midlands - South Birmingham Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

24 April 2017

Professor Philip I. Murray
Sandwell and West Birmingham NHS Trust
Birmingham and Midland Eye Centre
Academic unit
Birmingham- Dudley Road
B18 7QH

Dear Professor Murray,

Study title:	**Defining a Core Outcome Set in patients with Uveitis both with and without Uveitic Macular Oedema (COSUMO).**
REC reference:	**17/WM/0111**
IRAS project ID:	**221333**

Thank you for your letter of 12 April 2017, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Recommendations:

- Although it was not stipulated in the minutes of the REC meeting, nor in the letter of provisional opinion, it is asked the applicants consider after transcriptions, the audio recording would then be destroyed or kept in an encrypted way.
- It was also commented that the point in the Protocol concerning understanding English rather than reading and writing was because it was imagined the visual defects of the patients might cause difficulty for some of them from reading and writing anything, but should not be excluded from the study. in their case the PIS cold be read to them or given via an audio tape. It was asked the applicants take the above into consideration.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Interview schedules or topic guides for participants [Topic guide for focus group discussion- 060217 .docx]	1.4	06 February 2017
IRAS Application Form [IRAS_Form_21022017]		21 February 2017
IRAS Application Form XML file [IRAS_Form_21022017]		21 February 2017
IRAS Checklist XML [Checklist_22022017]		22 February 2017
IRAS Checklist XML [Checklist_12042017]		12 April 2017
Letter from funder [Letter from funder]		
Letter from sponsor [Sponsor Letter]	NA	16 February 2017
Letters of invitation to participant [Invitation letter for Focus group (patients & carers) 060217]	1.4	06 February 2017
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Summary CV for student [Mohammad Tallouzi CV (Student)]	NA	16 February 2017
Summary CV for supervisor (student research) [Mel Calvert CV]	NA	16 February 2017

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/WM/0111	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely,

[redacted]

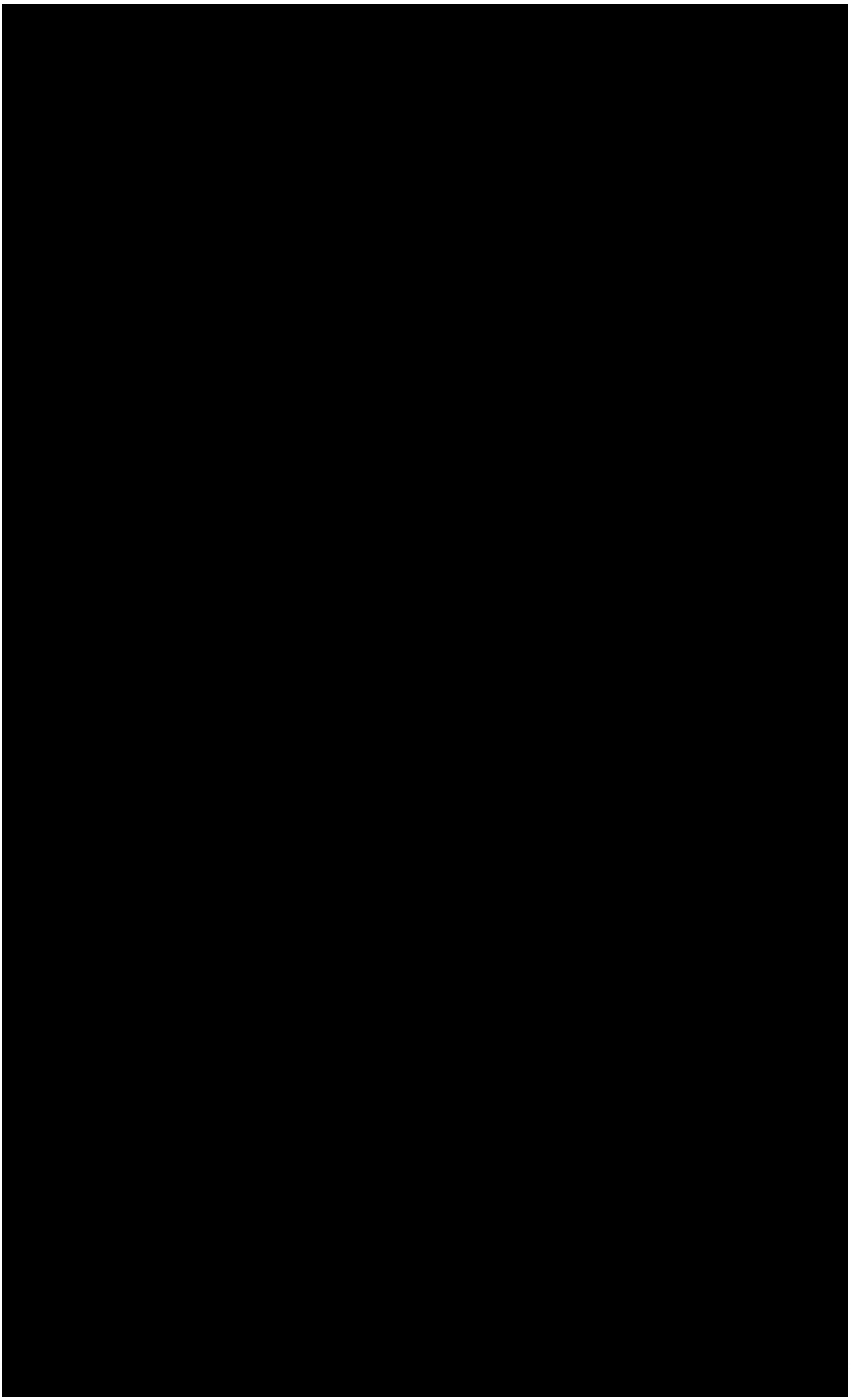
Dr John Cochrane
Vice Chair

Email:NRESCommittee.WestMidlands-SouthBirmingham@nhs.net

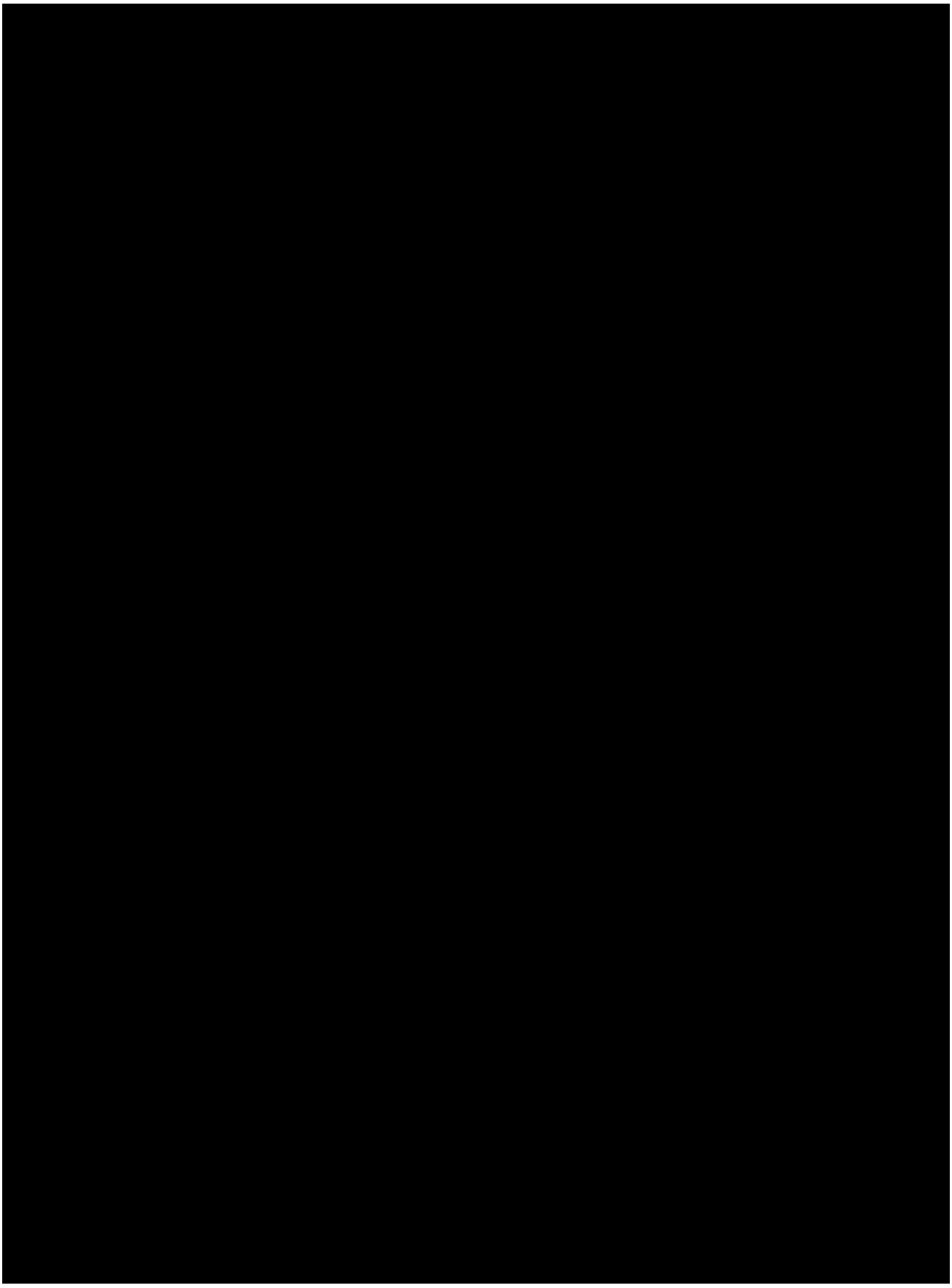
Enclosures: "After ethical review – guidance for researchers"

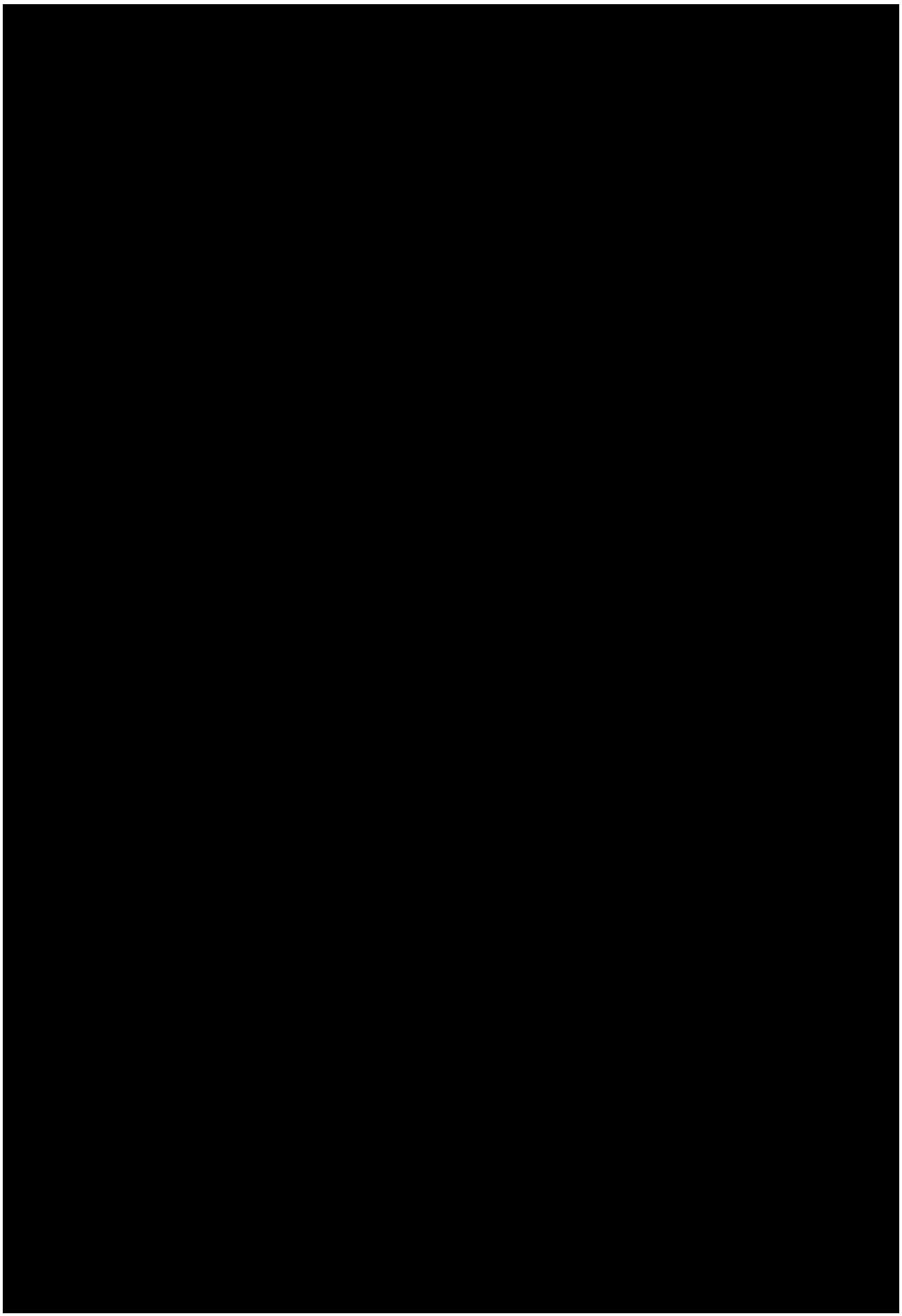
Copy to: *Dr Jocelyn Bell, Sandwell and west Birmingham NHS trust*

Appendix 22: NHS to NHS Access



Appendix 23: CRN Portfolio Applications





Appendix 24: Alternative approaches considered

Nominal group Technique

This is a structured technique which aims to seek participants' opinions and determine their priorities, highlighting any discrepancy and agree on the most important one. A successful nominal group technique comprises four stages as follows (424-426).

I. *Silent generation:* the technique is chaired by a facilitator who would highlight the research question and give participants around 20 minutes of silent thinking. This would enable them to consider and generate ideas in relevance to the topic. Generated ideas are usually supplemented by data already identified via literature review.

II. *Round robin:* at this stage facilitator will then ask each participant to state one idea in a 'round robin' fashion. This will allow participants to have critical thinking and have the opportunity to state more than one idea during this process when their turn comes. All participants will have the chance to provide their say in confidence. All generated ideas will be written on a chart and are presented to all participants.

III. *Clarification:* this is a useful stage to clarify the meaning and provide a definition to given ideas; and removing duplicates, merging ideas together if they are similar and agree to group them as required. Listening to participants is the key principle of this stage, by which participants are encouraged to discuss in detail their ideas and to say what is meant by. The role of the facilitator is to steer the group and make sure every member of the group has the opportunity to talk. Worth mentioning, as a facilitator, it is important not to guide participants in their responses.

IV. *Voting*: this is the final stage of the technique where participants are asked to rank all generated ideas on a Likert scale based on their level of importance (e.g. a 5-point Likert scale of 1 is the least important item and 5 is the greatest important item). It is important

to specify which Likert scale will be used as numerous scales have been used as per discussion earlier.

- **Strengths and Limitations of Nominal group Technique**

Nominal group technique is usually run in a comfortable atmosphere to enable participants making their informed decision about items on the generated list, even though they may not agree on all reported items. Communication between the facilitator and participants is very important and considered the key to having a successful meeting and consensus over reported outcomes. Thus, participants need to be informed on every stage of the technique, time of each stage and what is expected to happen at each stage. It is one of the common consensus meetings in healthcare that is based on balanced participation between the stakeholder groups. It is also characterised by structure and formality for decision-making in clinical practice and health setting and results could be obtained in a short period of time. Nominal group technique is an effective technique that is not only used to seek consensus but also helps to explore and generate new ideas (427, 428).

Challenges in the nominal group technique include the duration of each stage in the technique, which will be sensitive to the sample size and the complexity of the topic. The number of participants for nominal group technique is generally smaller than Delphi techniques, with examples ranging from 2 to 14 participants. Additionally, it may be quite sensitive to the level of experience of participants on a specified topic, with less experienced people may not have the ability to contradict the views of those experienced or even contribute to the meeting. Thus, this type of meeting may work best with a reasonably homogenous sample; and if there is a need to run two separate meetings to accommodate the stakeholders based on their background experience (426). Another area of challenge in the nominal technique is around the difficulty in collecting ideas together in the clarification stage.

Variations have been reported in the ranking process and scales used in the nominal technique. Thus, participants are usually asked to use a Likert scale to rank generated ideas and consensus is reached, however, in circumstances where consensus was not obtained studies have asked participants to revise their responses and then re-rank them again via a secondary survey (429). Validation of nominal group results is sometimes demonstrated by conducting a survey to a different group of participants (430). Nominal group technique costs relate to participants' travel, accommodation, catering, and venue, reflecting the size of the group and whether international participants are invited to take part or not. It is still a widely used technique to determine priorities among participants over discussed topics (426) and enhance decision-making and consensus. Nominal group technique formed the basis of Standardisation of Uveitis Nomenclature (SUN) workshop in 2005 (431).

Survey questionnaire

Survey questionnaire is a quantitative research tool that is widely used to collect information related to people's knowledge, opinions and experience over a specific subject. It is also a useful method to collect observable data (e.g. patient's mobility), measurable data (recorded vision) or patients feeling (psychological and emotional well-being) (432). Survey questionnaires can either be completed face-to-face, or via phone, email or could be posted as a hard copy to the participant's home address. Thus, the survey questionnaires can easily reach a wide range of people in any geographical area over a short period of time. It is therefore the most practical and cheapest method to run compared to other qualitative methods. Survey questionnaire usually use a random sample to generate findings even though the sample is small, therefore it is an efficient method to express the range of people's knowledge and experience (433).

Survey questionnaires usually provide a range of multiple-choice answers on different levels

of Likert scales.

- **Strengths and limitations of survey questionnaire**

Survey questionnaires are able to provide data on the level of agreement or disagreement of participants on each item, however, they have been criticized for using multiple choice questions that do not explain why people acted or responded in a particular way. Some surveys do also include open-ended question(s) which may give participants the opportunity to say more, however these are less effective in this capacity than other qualitative methods such as focus groups and interviews (434).

Length of questions is a major issue in the design and structure of the survey that may lead to misinterpretations of questions, skipping items and providing inaccurate answers. Therefore, it is recommended to have a short survey with clear structure and reasonable question length. Furthermore, surveys should be written in plain language that enables participants having a better understanding and similar interpretations to questions. Consistency and grouping of items throughout the survey need to be maintained (435).

Questionnaires have two important concepts to be considered; validity (ability to measure what it is meant to measure) and reliability (consistency of a measure). Validity is more critical in most of the survey questionnaires (436). Thus, having a reliable and valid questionnaire adds more value to the collected data.

References

1. Bradford CA. Basic Ophthalmology: American Academy of Ophthalmology; 2004.

2. Snell RS, Lemp MA. Clinical Anatomy of the Eye: John Wiley & Sons; 2013.

3. Foster CS, de la Maza MS. The Sclera: Springer Science & Business Media; 2013.

4. Aurosiksha. Anatomy and Physiology of Uvea 2012. Available From: Https://Www.Aurosiksha.Org [

5. Hunchawiia. Anatomy of the Eye 2018. Available From: Https://Www.Hnchawaii.Org/ [

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