THE METHODOLOGICAL AND ETHICAL ISSUES ASSOCIATED WITH PATIENT-REPORTED OUTCOME MEASUREMENT IN CLINICAL TRIALS

by

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Abstract

The doctoral research forming this thesis used mixed-methods to explore methodological issues associated with patient-reported outcome (PRO) measurement in clinical trials and to identify ethical issues requiring considered debate. The thesis investigates anecdotal reports from research nurses and data managers of: (1) inconsistencies in the administration of PROs in trials; (2) difficulties associated with the management of 'concerning' PRO data (i.e. that which raises concern for the wellbeing of the trial participant); and (3) a lack of PRO-specific trial protocol content, trial training and guidance. The primary aim was to establish whether these reports were generalizable to the wider community of trial staff and management. The secondary aim was to explore the methodological and ethical issues faced by trial staff involved in PRO data collection in trials. The tertiary aim was to evaluate current PRO-specific protocol content, trial training and guidance to determine whether, and if so which, areas were in need of improvement. A series of novel studies were undertaken to address these aims.

A qualitative study of trial staff suggested there are perceived inconsistencies in the administration and management of PROs in some UK trials which could undermine PRO trial results and introduce bias. In addition, the study found that staff reported intermittently encountering 'concerning' PRO data in trials, but were unsure how it should be managed. A theoretical viewpoint paper further explored the ethical and methodological issues associated with the previously unreported phenomenon of 'concerning' PRO data in trials; for the first time introducing the term 'PRO Alert' to describe the exposure of data collection staff to PRO information displaying:

‘concerning levels of psychological distress or physical symptoms that may require an immediate response’.

A large-scale survey of UK-based trial staff and management involved in PRO assessment was then undertaken. This study demonstrated the above qualitative findings could be generalised to the wider community of trial staff.

PRO trial guidance was investigated in three systematic reviews. A review of PRO literature for front-line data collection staff found guidance was lacking. A large-scale review of PRO-specific literature for trial protocol developers suggested guidelines were inconsistent and difficult to access. Finally, using a novel PRO protocol checklist, a systematic review of the PRO components of National Institute for Health Research (NIHR) Health Technology Assessment (HTA) trial protocols found that PRO information was commonly absent from trial protocols, even where a PRO was the primary outcome.

In conclusion, the thesis highlights a need for the development of comprehensive consensus-based PRO guidelines addressing protocol development, training and the management of PRO alerts in trials. Guidelines should aim to facilitate improvements in PRO protocol content and PRO assessment, whilst protecting the interests of trial participants, to enhance the credibility of PROs as an important trial outcome and optimise their ability to inform patient care and policy.

Dedication

To Rachel, my soul mate, thanks for your love, patience and support.

To Ellie May, thanks for brightening every day.

To Mum and Dad, thanks for always being there.

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Contributorship statement

Chapters 1, 2, 3, 4, 5, 6, 8 and 9 are entirely the product of my own work, assisted by continuous guidance from my supervisors: Prof. Melanie Calvert (MC), Prof. Heather Draper (HD) and Dr. Jonathan Ives (JI). Additional contributions are detailed below.

Tom Keeley (PhD candidate, University of Birmingham) piloted interview topic guide questions and was involved in the review of the final manuscript of the qualitative study reported in Chapter 2.

Prof. Ethan Basch (UNC Lineberger Comprehensive Cancer Center) (EB) and MC helped conceive the idea for the Viewpoint presented in Chapter 3. The concept of PRO alerts from an ethical perspective was developed in part by JI and HD. EB, Prof. Michael Brundage (Queen's University, Ontario, Canada) (MB) and Prof. Madeleine King (University of Sydney, Australia) (MK) assisted in providing an international trials perspective. DK wrote the first draft of the manuscript. HD, MC, JI, EB, MB and MK all provided edits and critiqued the manuscript for intellectual content.

Adrian Gheorghe (PhD candidate, University of Birmingham) (AG) was involved in the identification of eligible studies for the systematic review presented in Chapter 6 and Clive Liles (Lecturer in Physiotherapy, University of Birmingham) contributed to the analysis phase; both provided edits and critiqued the manuscript for intellectual content.

The systematic review presented in Chapter 7 was designed primarily by MC and DK. AG and Helen Duffy (project officer, University of Birmingham) (HDu) searched the literature and, with MC and DK, screened for eligible papers. Rebecca Mercieca-Bebber (PhD candidate, University of Sydney, Australia) (RMB), MB, Prof. Jane Blazeby (University of Bristol) (JB) and MK assisted with the identification of grey literature. MC and DK extracted data from the included publications and conducted the analysis. MC wrote the first draft of the manuscript. DK, HDu, AG, RMB, JI, HD, MB, JB, MK all provided edits and critiqued the manuscript for intellectual content.

The review of PRO protocol content, presented in Chapter 8, was designed primarily by DK and MC. Benjamin Fletcher (PhD candidate, University of Oxford) (BF) and HDu searched for eligible trial HTA protocols, with input from DK and MC when necessary. DK and HDu extracted data from included protocols. DK and HDu evaluated the content of included protocols using the SPIRIT and PRO-specific checklists, with assistance from MC where necessary. MC and DK produced the PRO-specific checklist with input from the international advisory panel (MB, JB, MK and RMB) and all approved the final version. DK conducted the main analysis. DK wrote the first draft of the manuscript. HDu, BF, AG, RMB, MK, HD, JI, MB, JB and MC all provided edits and critiqued the manuscript for intellectual content.

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List of abbreviations

PROs	Patient-Reported Outcomes
RCT	Randomized Controlled Trial
SOPs	Standard Operating Procedures
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
GCP	Good Clinical Practice
UK	United Kingdom
REC	Research Ethics Committee
US	United States
IRBs	Institutional Review Boards
PROMs	Patient-Reported Outcome Measures
HRQL	Health-Related Quality of Life
EQ-5D	Five Dimension European Quality of Life Instrument
HUI	Health Utilities Index
CARE-HF	Cardiac Resynchronisation in Heart Failure Trial
NICE	National Institute for Health and Care Excellence
MRC	Medical Research Council
NIHR	National Institute for Health Research
SPCR	School for Primary Care Research
HTA	Health Technology Assessment
QCA	Qualitative Content Analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
IF	Impact Factor
CPIs	Chief and Principal Investigators
CRC-RCTUs	Clinical Research Collaboration Registered Clinical Trials Units
CLRNs	Comprehensive Local Research Networks
HADs	Hospital Anxiety and Depression scale
SF-12	Short-Form Health Survey 12-item questionnaire
SF-36	Short-Form Health Survey 36-item questionnaire
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
HAQ	Health Assessment Questionnaire
CRFs	Case Report Forms
HTA	Health Technology Assessment
PROMIS	Patient Reported Outcomes Measurement Information System
COSMIN	Consensus-based Standards for the selection of health Measurement Instruments
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
IF	Incidental Finding
AE	Adverse Events
SAE	Serious Adverse Events
CTCAE	Common Terminology Criteria for Adverse Events
ASyMS	Advanced Symptom Management System
eRAPID	Electronic Patient Self-Reporting of Adverse-Events: Patient Information and Advice
PICs	Participant Identification Centres

Formatting

This thesis has been formatted according to the University of Birmingham 'Alternative Format Thesis Guidelines'.

The Alternative Format thesis allows incorporation of chapters that are in a format suitable for submission for publication in a peer-reviewed journal.

Please note:

- This thesis includes three published journal articles, which already have page numbers; these are not included in the pagination sequence of the submission (see the extract below for further details).
- The thesis also includes 4 chapters written in paper format. For consistency these are presented in the PLoS One submission style (manuscript guidelines available at: http://www.plosone.org/static/guidelines).
- Reference lists are included at the end of each chapter (rather than at the end of the thesis) to provide consistency and aid clarity.

Extract from the University of Birmingham Alternative Format Thesis Guidelines:

7) Since the alternative format thesis includes copies or offprints of journal articles, book chapters etc, which already have page numbers, the pages of the publications themselves will not be included in the pagination sequence of the submission. Candidates should insert a sheet of A4 before each publication on which is displayed the publication number, publication title, and the page number of the thesis. For example, if the publications section starts on p75, insert an A4 sheet before the first publication on which is printed the name and number of the publication and p75. The first publication will then follow, with its own pagination. Before the second publication insert another A4 sheet on which is printed the name and number of the second publication and p76, and so on. This applies equally to the print and electronic thesis…

10) The incorporation of publication-style chapters in the thesis will inevitably lead to some duplication since each publication-style chapter will have self-contained components that will overlap with parts of the other sections of the thesis…

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Chapter 1. Introduction and background

1.1 Introduction to the thesis

Patient-reported outcomes (PROs) are defined as: "… any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[1] PROs are increasingly used in clinical trials and provide important information for researchers, patients, regulatory authorities and policy-makers.[2] This thesis describes a programme of research investigating anecdotal reports from researchers, which outlined concerns regarding the consistency of PRO data collection and management in trials, and highlighted a purported lack of PRO-specific guidance for trial staff.

The following Chapter presents the background to the research, outlines the thesis aims and structure, and discusses the selection of methods.

1.2 Background

1.2.1 Clinical trials

Clinical trials represent the 'gold standard' in assessing the effectiveness of health care interventions.[3-5] Trials set out to determine if a particular treatment or intervention of interest is superior to a comparator, or a series of comparators: commonly an alternative treatment or a control.[5] The purpose of a trial is to prove or disprove the null hypothesis; i.e. that there will be no difference in the outcomes of participants in differing treatment arms. The null hypothesis may be rejected if the difference in outcomes between groups is determined to be statistically significant; i.e. the probability of observing such a difference by chance is less than a pre-determined threshold (commonly five per cent for two-tailed hypotheses).[6]

Clinical trials usually evaluate one 'primary' outcome, also known as a primary endpoint, that should provide 'the most clinically relevant and convincing evidence directly related to the primary objective of the trial'.[7] The primary outcome is used to determine the number of participants required to investigate the trial hypothesis and, crucially, it is analysis of the primary outcome that is used to decide the overall result of the study.[6] Other 'secondary' outcomes are also commonly included in trials. These outcomes may be important in improving understanding of the experimental intervention under investigation, or in evaluating effects related to the secondary objectives of the study, and may also help in generating additional research hypotheses.[7,8]

Trials should possess both internal and external validity in order to effectively inform decisions surrounding the treatment of patients.[9] Internal validity speaks to the trustworthiness of the study data and describes the extent to which differences in the outcomes of trial participants may be ascribed to 'genuine' treatment effects.[9,10] External validity describes the extent to which trial findings may be generalized to the population under investigation.[9,10]

In a randomized controlled trial (RCT), the participants are randomly allocated to study groups, ensuring that systematic bias does not affect the results of the study and promoting both internal and external validity.[6,10] Bias is defined as any deviation of the study results from the 'truth', also referred to as systematic error.[11] Such bias can occur in both directions, therefore its presence in a trial may lead to erroneous under- or over-estimations of treatment effect.[11] In a properly designed RCT, the risk of bias is minimized and observed differences in the outcomes between treatment arms may

only be explained as either 'real' differences (i.e. treatment effects), or those due to the play of chance.[3] Non-randomized clinical trials may also provide valuable information regarding the effectiveness of therapeutic treatments, however, as participants are not randomly allocated to treatment groups, such trials are potentially subject to bias and confounding.[3] A confounder is a factor external to the research question posed by the trial, which influences the outcome of interest and may be unequally distributed between study arms.[5]

1.2.2 Prevention of bias in clinical trials

Trial data plays an important role in informing patient management, drug evaluation and health policy, therefore, it should be trustworthy.[12] Clinical trials attempt to ensure that the only difference between study groups, other than that due to the play of chance, is whether they receive the treatment under investigation or not.[9] Thus, scientifically rigorous methods should be used to minimize any potential differences in study group characteristics, or inconsistencies in the way that participants are dealt with in the trial, to reduce the risk of bias.[3,6]

There are a number of methods that are commonly utilized in trials to reduce the risk of bias. For instance, the use of appropriate randomisation and allocation concealment helps to minimize differences caused by the selection of participants to study groups on the basis of their baseline characteristics, known as selection bias.[11] The use of intention to treat analysis ensures that participants are analysed according to the study interventions they were randomised to, irrespective of the treatment they actually received in the trial, this helps to preserve randomization.[13] Adequate blinding of patients and/or researchers may reduce differences in the care that is provided

between groups, commonly referred to as performance bias.[11] Minimizing loss to follow-up in a study may help to reduce differences between groups due to study withdrawals or missing data, known as attrition bias.[11]

Other potential sources of bias may still arise, however, such as inconsistencies in the way outcome data are collected across study sites.[11] To mitigate the risk of this kind of bias, trial data should be collected using standardised methods.[14] Ideally, the same data collection processes should be applied at all study sites and across all study groups; with the standardised methods that will be employed during the trial clearly outlined in the study protocol, and communicated to research staff through in-house training and supporting trial documentation, for example, standard operating procedures (SOPs).[14-16]

1.2.3 The trial protocol, trial training and SOPs

All clinical trials are based on a protocol: 'A procedure for carrying out a scientific experiment'.[17] The trial protocol is a key document, which includes information on the background and rationale for the study, a description of the methods and organizational aspects, and an overview of the ethical considerations.[14] The protocol should provide sufficient detail to ensure that all trial personnel understand the important design and administrative elements of the study - ensuring they carry out trial procedures uniformly - and also enable appraisal of the trial's scientific, methodological and ethical rigor by funders, journal reviewers, regulatory bodies and ethics committees.[14,18] Despite their importance, evidence suggests information relating to study design, implementation and dissemination is often omitted from trial protocols.[19-22] This has led to the development of international

guidance for protocol developers and reviewers, in the form of the 'Standard Protocol Items: Recommendations for Interventional Trials' (SPIRIT) 2013 statement, which is aimed at enhancing general study design, conduct, reporting and external review.[14,18]

In the UK, all trial personnel are required to attend regular 'Good Clinical Practice' (GCP) training to ensure they are aware of the ethical and quality standards for trials involving human participants.[23,24] GCP training addresses generic issues common to all such trials and is normally conducted outside of the in-house, study-specific, training delivered in most studies. Such in-house training, usually provided to research personnel at each site taking part in a study, is an important part of the information transfer process within a trial.[14] The purpose of such training is to facilitate uniformity across the study, by ensuring that all staff are aware of the standardized trial procedures that are in-place, so that all trial participants are managed in the same, pre-agreed, way.[14] Trial training also offers staff an important opportunity to discuss protocol content which they feel requires clarification, increasing the likelihood that trial procedures are correctly implemented.[25]

Supporting information surrounding trial conduct, supplementary to the study protocol and trial training, may also be available to trial staff in the form of SOPs. SOPs provide written instructions for trial personnel and include all the information they require to carry out a trial procedure in a consistent and uniform way, regardless of the setting or time-point within the trial, enhancing the reliability of the resulting data.[16]

1.2.4 Clinical trials and ethical approval

It is a legal requirement for clinical trials based in the United Kingdom (UK) to obtain a favourable opinion from a research ethics committee (REC) prior to the start of participant recruitment.[26,27] Similarly, in the United States (US) ethical review is undertaken by Institutional Review Boards (IRBs). The role of the REC is to review the study protocol to determine if the proposed research adheres to ethical standards.[28] REC members must therefore determine if the research will be conducted in such a way as to protect the 'health, well-being and rights'[29] of participants. In addition, they must be satisfied that participant risks are minimised in a trial, and that the benefits of trial participation, whether to the participants' themselves and/or to society as a whole, outweigh these potential risks.[28] Once the study commences, participants enrolling onto a trial should be made aware of the potential risks and benefits and allowed sufficient time to decide for themselves whether or not to take part.[26,27,29,30] During the lifetime of the study, all trial personnel have a responsibility to continue to protect and uphold the interests of the participant over and above the interests of the trial.[26,27,29,30]

1.2.5 Clinical trials and PROs

Clinical trial outcomes have traditionally focused on biomedical indicators of mortality and morbidity, for instance, survival and hospitalization.[31] Increasingly, however, the importance of investigating experiences reported directly by patients is being recognized.[2] PROs are therefore now commonly included in contemporary trials. PRO data is collected using specific questionnaires, known as PRO measures or PROMs. Trial participants are normally asked to self-complete these PROMs (on paper or electronically) at specific time-points during the study. Questionnaires are

usually designed to focus on one or more specific elements of a patient's wellbeing. For example, some PROMs used in health care may measure a combination of physical, mental and social aspects, collectively known as health-related quality of life (HRQL), whilst others may evaluate a single dimension of health, for example, levels of physical activity.[31,32]

'PRO' is an 'umbrella' term which covers a number of different specific outcomes included in trials, for instance, whilst some PROs may measure HRQL, others may measure symptom severity, or satisfaction with care[33] PROs are also often used to evaluate health utilities - preferences for different health states - for the purposes of cost-effectiveness analysis.[34] Common PROMs used to measure utilities in trials include the five dimension European Quality of Life instrument (EQ-5D) and Health Utilities Index (HUI).[34]

The specific questions within a PROM (known as 'items') are usually grouped together to form appropriate sub-categories, or 'domains', for example, several questions regarding ambulation may be grouped within the domain 'mobility'. The answers given by the patient in these sub-categories provide individual domain scores, often combined to generate an overall score for the PROM.[33] The resulting data is then aggregated with that provided by other participants, before being analysed to determine if there is a statistically (and clinically) significant difference between study groups.[31] PROs may be used as the primary outcome in a trial to compare the effectiveness of different treatments, but more commonly, they are included as secondary or exploratory outcomes and used to provide a patient-focused evaluation of treatment benefits and risks.[8,35]

1.2.6 The importance of PROs in trials

The importance of including PROs in clinical trials has been recognized by major international health policy makers, regulatory authorities and patients[1,2,36-46]; with some organizations arguing that they should be incorporated into all comparative effectiveness studies, unless there exists a justifiable reason for not doing so.[2,8] This is because PROs provide additional 'patient-centred' data in trials which is unique in capturing the patient's own opinion on the impact of their disease or disorder, and its treatment, on their life.[31] This information provides a snapshot of what it is like for patients to personally experience an intervention and its effects, over and above aspects surrounding treatment effectiveness or the potential risks and side-effects that are observable by others. This is important, as evidence suggests more traditional 'clinician-reported' outcomes, when used in isolation, may underestimate the impact of a disease upon the individual.[47,48]

PROs are used in claims supporting medical product labelling and may provide evidence underpinning the adoption of new drugs.[1] Patients also value PRO information and may use it to inform complex healthcare decisions.[38,43] For instance, PRO trial results may help patients to assess whether the survival benefits of a new drug may be worth the potential side effects and associated cost to their overall HRQL.[8,49] Alternatively, they may assist patients and their clinicians in choosing between treatment options offering similar survival rates. For example, in a prostate cancer trial of chemotherapy with mitoxantrone plus prednisone or prednisone alone[50], whilst there was no difference in survival between study arms, PRO data

demonstrated significant benefits in the mitoxantrone group in-terms of pain intensity and other patient-reported secondary outcomes including global HRQL.[8]

PROs are also used to influence healthcare policy and change clinical practice. For instance, the cardiac resynchronisation in heart failure trial (CARE-HF) demonstrated that the use of an implantable pacemaker was associated with both a significant reduction in the risk of death and improvement in HRQL.[51] The cost effectiveness of the CARE-HF intervention was also supported in follow-up studies using the EQ-5D PROM.[52,53] PRO data from the CARE-HF trial has helped inform health policy, and the findings have been incorporated into a number of high impact international clinical guidelines[54-57] - notably in National Institute for Health and Care Excellence (NICE) guidance[58] - which has led to a significant increase in the use of cardiac resynchronisation therapy in the UK.

1.2.7 Minimising PRO measurement bias in trials

PRO data may inform the health-care decisions made by patients and their clinicians, support licensing claims for new medicines and influence the development of health policy, including decisions about cost effectiveness.[1,31,59] In view of their potential importance, as with any trial outcome, PROs should be captured in a scientifically rigorous way. Reducing the risk of bias associated with PROM collection is therefore a key consideration during trial design. Three main potential sources of bias have received attention in the literature.

First, for PROs collected in the clinic environment, it may be important that the trial participant is asked to complete the PROM *prior* to their clinical consultation. If the

participant receives bad news during a consultation, or is subjected to an invasive and/or uncomfortable procedure, this may negatively affect the answers they provide on the PROM, leading to data contamination.[60,61] Second, marked differences in the level of assistance given to trial participants by data collection staff during PRO assessment may lead to response bias: where some participants answer questions in accordance with what they think the data collector wants to hear, rather than what they actually feel.[62] Third, missing data has been highlighted as a particular problem affecting PROM measurement in trials.[1,15,25,63,64] Both individual PRO items and whole questionnaires can be missing in a trial. Evidence suggests that missing PRO data may not be missing at random; rather, data is more likely to be missing from those participants in a trial with the poorest outcomes.[63] This could result in bias if such participants are concentrated in a particular arm of the trial, for example, where one intervention in the study results in greater levels of side effects or toxicity.[12]

To mitigate the risk of these kinds of bias, PRO trial data should be collected using standardised methods.[1] Trial design literature advises that: (1) data collection staff should administer the PROM prior to clinical encounters that may influence completion; (2) staff across trial sites should provide comparable levels of assistance to participants during PROM assessment and emphasize that participants should answer questions based entirely on their own viewpoint; and (3) trial personnel should check complete PRO questionnaires for missing items, and also screen for missing questionnaires, subsequently following-up with the participant to rectify any omissions.[65] Ideally, the same data collection processes should be applied at all study sites and across all study groups; with the standardised methods that will be employed during the trial clearly outlined in the study protocol, and communicated to all trial

personnel through in-house training and supporting trial documentation such as SOPs.[14,16,25]

1.3 Genesis of the thesis

As previously stated, there is a need to ensure that PROs are collected with rigour in trials, as they inform important health care decisions. It is of concern, therefore, that in 2010, anecdotal reports from trial personnel at UK-based HRQL training days (run by the Medical Research Council (MRC) Midland Hub for Trials Methodology) outlined:

- Inconsistencies in the standards of PRO data collection and management in some trials, which appeared to risk potential bias: for example differing approaches to the management of missing data.
- A general lack of PRO-specific protocol content, trial training and guidance available in trials.

Furthermore, data collection staff reported difficulties in dealing with HRQL data which raised concern for the well-being of the trial participant in some way. Such data typically presented as extreme PROM scores, or in additional comments recorded on the questionnaire, and was commonly discovered on collection of the completed PROM from the participant or at the point of data entry. Some researchers reported responding to this 'concerning' data with *ad-hoc*, off-protocol, interventions to aid the trial participant: for example, referral of a participant with potential depression to a counselling service. These 'co-interventions', i.e. "any intervention other than the experimental manoeuvre that alters the frequency of a trial's outcome of interest"[66], may lead to bias if they are administered differently across trial arms. Unless PRO related co-interventions in a trial are formally reported and the associated costs

captured, under- or over-estimates of clinical efficacy and cost-effectiveness could result.

As PRO trial data are valued and utilised so widely, and may inform important healthcare decisions, any threat to the integrity of PRO results should be comprehensively explored. Thus, in 2011, the PRO Research Group at the University of Birmingham successfully applied for funding from the National Institute for Health Research (NIHR) School for Primary Care Research (SPCR), to support a PhD project investigating the aforementioned anecdotal reports.[a] In 2013, the team were awarded additional funding by the SPCR to extend the scope of the investigation to include the evaluation of the PRO content of trial protocols.[b] This thesis details the methods, results and findings of a series of studies, supported by these funding streams, which sought to determine the generalizability of the anecdotal reports outlined above and explore the potential ethical and methodological issues associated with their content.

[a] **Kyte D**, Calvert M, Draper H, Ives J. The Methodological and Ethical Issues Associated with Health-Related Quality of Life Measurement in Clinical Trials. NIHR School for Primary Care Research Studentship. £85,196

[b] Calvert M, **Kyte D**, Draper H, Ives J, Gheorghe A, Brundage M, King M, Mercieca-Bebber R. Evaluation of patient reported outcomes in clinical trials: systematic review of trial protocols. NIHR School for Primary Care Research Funding Round 7. £23,976

1.4 Thesis aims and structure

1.4.1 Research Question

The thesis considered the following research question:

- Do anecdotal reports of: (1) inconsistencies in PRO trial administration; (2) difficulties associated with the management of 'concerning' PRO data; and (3) a lack of PRO-specific protocol content, trial training and guidance available in trials; represent isolated experiences, or are they indicative of a potentially wider problem?

1.4.2 Aims

The primary aim of the thesis, therefore, was to establish whether the anecdotal reports outlined above were generalizable to the wider community of trial staff.

The secondary aim was to explore the methodological issues associated with PRO measurement in clinical trials and to identify ethical issues requiring considered debate.

A tertiary aim was to explore current PRO-specific trial guidance and determine whether, and if so which, areas were in need of improvement.

Initially, a fourth aim was to also investigate trial participants' perspectives surrounding the management of PRO assessment in trials. However, significant

recruitment problems meant that data collection for the study addressing this aim was incomplete. This will be further discussed in Chapter 9 (section 9.3.4).

1.4.3 Structure

The thesis presents a series of studies addressing the primary, secondary and tertiary aims outlined above and is structured as follows. Chapters 2 to 5 focus primarily on the primary and secondary thesis aims. Chapter 2 presents a qualitative study (published in PLoS One in 2013) exploring the thoughts and experiences of 26 UK-based research nurses, data managers, trial coordinators and research facilitators involved in the collection and entry of PRO data in clinical trials. Chapter 3 presents a theoretical viewpoint (published in JAMA in 2013) exploring in greater detail the potential difficulties associated with the management of 'concerning' PRO data. Chapter 4 presents the first part of a large-scale cross-sectional survey of UK-based trial staff and management, focused on the administration of PROs in trials. Chapter 5 presents the second part of the survey, which focuses on the management of 'concerning' PRO data in trials.

Chapters 6 to 8 are primarily concerned with the tertiary thesis aim and therefore focus on the PRO-specific guidance available to trial staff and management. Chapter 6 presents a systematic review of 'in-trial' guidance for front-line data collection staff involved in the administration of PROs (published in PLoS One in 2013). Chapters 7 and 8 present two papers detailing work supported by a NIHR SPCR grant and conducted in collaboration with researchers in the UK, US and Australia. Chapter 7 presents a systematic review of PRO guidance for trial protocol writers, led by Prof. Calvert (Kyte second author, paper under review at time of writing), and is presented

in the thesis to provide context for the paper presented in Chapter 8. Chapter 8 presents a systematic review of the PRO content of NIHR Health Technology Assessment (HTA) protocols (Kyte first author, paper under review at time of writing).

Finally, Chapter 9 contains a discussion of the principle findings of the research and their implications, highlights the strengths and limitations of the work and provides suggestions for future research in this area, before presenting the overall conclusions.

1.5 Selection of methods

In the absence of existing research, the anecdotal reports outlined in section 1.2, which led to the genesis of the research question, represented the sole source of data on the subject. In research terms, such data could be considered 'shallow' as they may only address the surface of a topic.[67] Therefore, before the primary aim of the thesis could be addressed, it was deemed necessary to gain a greater understanding of the nature and demands of PRO assessment in trials, and to explore, in greater depth, the issues that had been raised. Thus, qualitative methods were utilized to examine the views and experiences of trial staff involved in PRO data collection, in order to generate 'richer' data which can facilitate a deeper understanding of both the known and unexpected aspects in an area under investigation.[67] In-depth, semi-structured, interviews were conducted according to established guidelines.[68-71] Iterative content analysis of the data drew upon principles of grounded theory[72] and utilised both constant comparison[73] and deviant case analysis.[74] The aim was to construct a hierarchical network of themes, which captured the essence of the data and facilitated the development of a core theory. These methods were chosen as they facilitated 'deep' exploration of the topic of interest, in-line with the research question and thesis

aims, but still allowed scope to investigate potentially important novel themes as they emerged.[67]

The findings of the qualitative study (Chapter 2) were subsequently used to inform the development of a large-scale cross sectional survey of research nurses, data managers/coordinators, trial manages and chief/principle investigators (Chapters 4 and 5). Survey methodology was utilized as an efficient and systematic way to determine whether both the anecdotal reports (Section 1.2) and qualitative data (Chapter 2) were generalizable to the wider population of trial researchers, and to further explore the differing viewpoints of the various professional groups.[75]

In Chapter 6, Qualitative Content Analysis (QCA) was selected as the method of analysis for the review of guidance for front-line data collection staff. QCA was chosen as it provided a systematic method for quantifying and describing qualitative materials.[76] The use of QCA therefore facilitated description of both the amount of published guidance available in the literature and also its content. In addition, QCA methodology facilitated demonstration of the reliability and internal validity of the coding framework, lending credibility to the overall findings.[76,77]

Established systematic review methods were utilized in the review of PRO guidance for trial protocol writers (Chapter 7) and the review of the PRO content of NIHR HTA protocols (Chapter 8). Both reviews were conducted and reported according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA)[78] guidelines (where applicable). Systematic review methodology was

selected as it represents an efficient scientific technique for exploring, summarizing and evaluating large volumes of literature, whilst minimizing bias.[79]

1.5.1 Chronology

The systematic review of 'in-trial' PRO guidance reported in Chapter 6 was the first piece of work to be completed within the thesis (published in PLoS One in April 2013). It is included alongside the two related systematic reviews presented in Chapter 7 and 8, rather than at the start of the thesis, to aid clarity.

The qualitative work outlined in Chapter 2 was the second study completed (published in PLoS One in October 2013) and informed the content and development of the subsequent theoretical viewpoint presented in Chapter 3 (published in JAMA in September 2013) and the survey work described in Chapters 4 and 5.

The two systematic reviews described in Chapters 7 and 8 were completed in May 2014 and submitted to PLoS One in June 2014.

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Chapter 2. PRO data collection in clinical trials: A qualitative study

As described in Chapter 1, anecdotal reports from trial staff suggest: (1) inconsistencies in PRO trial administration; (2) difficulties associated with the management of 'concerning' PRO data; and (3) a lack of PRO-specific protocol content, trial training and guidance available in trials.

This Chapter details a qualitative study exploring the thoughts and experiences of 26 research nurses, data managers, trial coordinators and research facilitators involved in the collection and entry of PRO data in clinical trials.

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Kyte D, Ives J, Draper H, Keeley T, Calvert M (2013) Inconsistencies in Quality of Life Data Collection in Clinical Trials: A Potential Source of Bias? Interviews with Research Nurses and Trialists. PLoS ONE 8(10): e76625. doi:10.1371/journal.pone.0076625.

The work outlined in this Chapter has been disseminated at the following conferences:

- **Kyte D**, Ives J, Draper H, Keeley T, Calvert M (2013) Inconsistencies in Quality of Life Data Collection in Clinical Trials: A Potential Source of Bias? Interviews with Research Nurses and Trialists. NIHR SPCR Research Showcase, Oxford, September 2014. [*Oral*]
- **Kyte D**, Ives J, Draper H, Keeley T, Calvert M (2013) Inconsistencies in Quality of Life Data Collection in Clinical Trials: A Potential Source of Bias? Interviews with Research Nurses and Trialists. The 2nd MRC Clinical Trial Methodology Conference, Edinburgh, November 2013. [*Oral*]

- **Kyte D**, Ives J, Draper H, Keeley T, Calvert M (2013) Inconsistencies in Quality of Life Data Collection in Clinical Trials: A Potential Source of Bias? Interviews with Research Nurses and Trialists. NIHR SPCR Trainees' Annual Event, Oxford, November 2013. [*Poster*]
- **Kyte D**, Ives J, Draper H, Keeley T, Calvert M (2013) Inconsistencies in Quality of Life Data Collection in Clinical Trials: A Potential Source of Bias? Interviews with Research Nurses and Trialists. The International Society for Quality of Life Research, 20th annual conference, Miami, October 2013. [*Poster*]
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- **Kyte D**, Ives J, Draper H, Keeley T, Calvert M (2013) Inconsistencies in Quality of Life Data Collection in Clinical Trials: A Potential Source of Bias? Interviews with Research Nurses and Trialists. University of Birmingham Research Poster Conference, UK, June 2013. [*Poster*]

The work was also presented as part of a two-day symposium held at the University of Birmingham in 2013, hosted by Calvert and Kyte and supported by an Institute for Advanced Studies grant[c]*:*

- Calvert M, **Kyte D**. Best-Practice for Patient Reported Outcomes (PROs) in Randomised Clinical Trials. Institute of Advanced Studies, University of Birmingham, July 2013 [*Oral*]

[c] Calvert M, **Kyte D**. Best-Practice for Patient Reported Outcomes (PROs) in Randomised Clinical Trials. Institute of Advanced Studies, University of Birmingham. £7000

Inconsistencies in Quality of Life Data Collection in Clinical Trials: A Potential Source of Bias? Interviews with Research Nurses and Trialists

Inconsistencies in Quality of Life Data Collection in Clinical Trials: A Potential Source of Bias? Interviews with Research Nurses and Trialists

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Abstract

Background: Patient-reported outcomes (PROs), such as health-related quality of life (HRQL) are increasingly used to evaluate treatment effectiveness in clinical trials, are valued by patients, and may inform important decisions in the clinical setting. It is of concern, therefore, that preliminary evidence, gained from group discussions at UK-wide Medical Research Council (MRC) quality of life training days, suggests there are inconsistent standards of HRQL data collection in trials and appropriate training and education is often lacking. Our objective was to investigate these reports, to determine if they represented isolated experiences, or were indicative of a potentially wider problem.

Methods And Findings: We undertook a qualitative study, conducting 26 semi-structured interviews with research nurses, data managers, trial coordinators and research facilitators involved in the collection and entry of HRQL data in clinical trials, across one primary care NHS trust, two secondary care NHS trusts and two clinical trials units in the UK. We used conventional content analysis to analyze and interpret our data. Our study participants reported (1) inconsistent standards in HRQL measurement, both between, and within, trials, which appeared to risk the introduction of bias; (2), difficulties in dealing with HRQL data that raised concern for the well-being of the trial participant, which in some instances led to the delivery of non-protocol driven co-interventions, (3), a frequent lack of HRQL protocol content and appropriate training and education of trial staff, and (4) that HRQL data collection could be associated with emotional and/or ethical burden.

Conclusions: Our findings suggest there are inconsistencies in the standards of HRQL data collection in some trials resulting from a general lack of HRQL-specific protocol content, training and education. These inconsistencies could lead to biased HRQL trial results. Future research should aim to develop HRQL guidelines and training programmes aimed at supporting researchers to carry out high quality data collection.

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data should be collected using standardised methods [8]. Ideally, the same data collection processes should be applied at all study sites and across all study groups; with the standardised methods that will be employed during the trial clearly outlined in the study protocol, and communicated to research staff through in-house training and supporting trial documentation, for example, standard operating procedures (SOPs) [10].

It is of concern, therefore, that preliminary evidence, gained from UK-wide group discussions at quality of life training days run by the MRC, Midland Hub for Trials Methodology, suggests there are inconsistent standards of HRQL data collection in trials, and related trial protocol content, training and education is often lacking. Furthermore, researchers have reported problems when encountering HRQL data which raises concern for the well-being of the participant in some way (hereafter referred to as 'concerning' data), which may occur on collection of the questionnaire from the patient, or at the point of data entry. When faced with 'concerning' data - typically represented by extreme HRQL scores, or contained within unprompted additional comments recorded on the questionnaire - some researchers reported administering ad-hoc, off-protocol, co-interventions to help improve HRQL: for example, facilitating referral of a patient suffering with depression to a counseling service. Co-interventions, i.e. "any intervention other than the experimental maneuver that alters the frequency of a trial's outcome of interest" [11], may lead to bias if they are administered differently across trial arms. Unless co-interventions in a trial are formally reported and the associated costs captured, under- or over-estimates of clinical efficacy and cost-effectiveness may result.

Any threat to the integrity of PRO trial data should be comprehensively investigated. Therefore, in the absence of existing research, we conducted a qualitative study to explore the experiences and opinions of research nurses and trialists involved in the collection and inputting of PRO data in UK-based clinical trials, with a specific focus on HRQL. Our objective was to investigate reported inconsistencies in HRQL data collection in clinical trials, to determine if they represented isolated experiences, or were indicative of a potentially wider problem.

Methods

Our study employed a qualitative research design; semi-structured interviews were used to gather data from researchers involved in the collection and entry of HRQL data in clinical trials. A favourable ethical review was received from the West Midlands Research Ethics Committee (ref no 12/wm/0068). All participants gave written informed consent prior to taking part in the study. Interview discussions were digitally recorded, professionally transcribed (verbatim) and anonymised prior to analysis. The anonymised transcripts were stored electronically in accordance with the University of Birmingham 'Code of Practice for Research' and will be preserved in an accessible form for ten years prior to being securely deleted. The interviews and primary analysis were conducted by DK, supported by regular meetings with HD, JI and MC, primarily concerned with promoting reflexivity.

Participants and Setting

Researchers were recruited across the following sites: one primary care NHS trust, two secondary care NHS trusts and two clinical trials units. These sites were selected to facilitate recruitment of researchers with a variety of professional backgrounds. All sites were based in the UK. During recruitment, information about the study was cascaded to all research nurses, research facilitators, data managers and trial coordinators at these sites, through their respective research management structures. Individuals were asked to register their interest with DK, who determined eligibility, provided additional information about the study and answered any further questions. Potential participants were deemed eligible if they reported prior experience of involvement in HRQL data collection or data entry within a clinical trial, with direct experience of handling HRQL questionnaires. We sought maximum variation with regard to trial experience (e.g. specialist area, length of experience, primary/secondary care setting) during recruitment, in order to capture viewpoints from a range of researcher roles. Recruitment continued within each distinct staff group until there was data saturation, i.e. no new data was provided by the most-recent batch of interviews from that group.

Interviews

In-depth semi-structured interviews were conducted by DK, following Fielding's guidelines [12]. A topic guide was developed (Interview Topic Guide S1), comprising open-ended questions that maintained a focus on the research aims, but which was sufficiently flexible to allow participants to raise different issues that were important to them. TK piloted questions amongst eight researchers, including three research nurses and five clinical trialists, who held trial management or senior research nurse roles in oncology, osteoarthritis or injury rehabilitation research. The final version of the topic guide included questions on: (1) the experience of the participant regarding HRQL data collection or inputting; (2) the HRQL-specific trial guidelines and/or training that participants had encountered during their research careers; (3) whether 'concerning' data had been encountered, and if so, how it was dealt with; and, (4) the challenges associated with HRQL data-collection and areas in need of improvement. The topic guide evolved alongside data analysis, ensuring that subsequent interviews explored themes arising from ongoing analysis. Therefore, the research remained participant-led and allowed emerging hypotheses to be tested and challenged in subsequent interviews [13]. All interviewees were sent a summary of their interview for checking. One participant suggested minor alterations regarding the way in which an administrative element of their trial had been interpreted. Corrections were made and were subsequently approved by the participant. All other interview summaries were approved without amendment.

Table 1. Characteristics of interviewees.

Analysis

Ongoing and iterative content analysis drew upon principles of grounded theory [14] and utilised both constant comparison [13] and deviant case analysis [15]. Interview transcripts were examined in depth by DK (immersion), prior to first cycle coding. A mixture of in-vivo, process and initial coding methods were utilised during the first cycle [16]. Focused, axial and theoretical coding was employed during subsequent cycles [16]. The aim was to construct a hierarchical network of themes, which captured the essence of the data and facilitated the development of a core theory. All interviews were analysed using the Dedoose (© 2011 SCRC) qualitative data analysis software. HD, JI and MC formally reviewed a subset of 10% of the transcripts to enhance the credibility and trustworthiness of coding and interpretation. Further, regular, meetings were held to discuss the emerging data. Decisions were made about which developing hypotheses needed to be tested in subsequent interviews, and proposed changes to the topic guide were agreed or rejected. Finally, HD, JI, MC and DK met to agree on the final themes and core theory.

Results

Characteristics of Interviewees

26 researchers were interviewed. Interviewees included research nurses, trial coordinators, data managers and research facilitators, and were drawn from all five of the recruitment sites in the study. The characteristics of the interviewees are presented in Table 1. Interviews lasted on average 38 minutes.

without me helping them." [participant 1; research nurse]

"I firmly believe that… the patient is giving up their time to partake in our research, and that I should be available… while they're in there. Because quite a few patients actually panic a bit about, 'I don't understand this question,' or, you know, 'is that right?'…" [participant 4; research nurse]

Missing data. Asking about the interviewees' approach to identifying, and dealing with, missing HRQL data elicited a range of differing responses. Some researchers reported routinely checking completed questionnaires for missing data, some described both checking for missing data and also examining the content of the answers for scoring errors, whilst others did not check the questionnaires at all.

"We do sit there with the patient and just go through it before they leave, just in case [there is] anything they've missed out." [participant 11; research nurse]

"We as research nurses always check the answers to see what they've put." [participant 17; research nurse]

"I was taught, in, in my early years of research… you give that form to a patient in an envelope and they complete it and put it in, and you don't look at it." [participant 15; research nurse]

This variation in approach was also evident when interviewees discussed methods of dealing with missing data. There were not only significant differences between trials, there were examples of differing approaches adopted for different trial outcomes, and even opposing arms, of the same trial, some of which risked the introduction of bias.

"There are specific questions within the [study] questionnaire that we do need to be answered… if they're sort of left off, then we have to try and get in touch with the participants, ring them and ask them those questions over the phone... if they've completed the… necessary questions but then they've left the quality of life [questions] blank, we don't have to chase them for that… I struggle a bit with that… I think you should make as much effort to get the responses to those as you should to get responses to the primary outcome really." [participant 20; trial coordinator]

"If they go into our control group… they're not gonna have any personal contact, then [the questionnaire] will go back out in the post with just a letter, sort of, saying, 'Oh, you accidentally missed out this one,' and, er, and hopefully they'll return it back… if they're put into an exercise, erm, intervention, then they do get seen by [a research facilitator]. I'll ask her to take the questionnaire with her… she'll help them to fill it in." [participant 25; trial coordinator]

Dealing with 'concerning' data

Research nurses (and to a lesser extent data managers) discussed discovering, and subsequently dealing with, 'concerning' HRQL data, i.e. that which raised concerns about a trial participant's well-being. Just over half (n=15, 58%) of our interviewees reported that they had encountered 'concerning' HRQL data at some point during their research careers (participants 2, 5, 6, 8, 10, 16-21 and 23-26). Interviewees were asked whether any particular HRQL information gave rise to concerns. The most common responses were; a significant reduction in quality of life, for example, evidence of low self esteem or depression, or an indicated risk of self-harm or suicide.

"The difficult bit is when you have a comment section at the end… some patients choose that to [describe] something that's happened to them… sometimes about erm depression and if you've read that, then you should act on it." [participant 5; research nurse]

"The sorts of things that I've found concerning have been when people… have done sort of quite long rambling sort of letters, talking about… the struggles that they're going through, and erm that nobody's doing anything and nobody's helping them and what are they supposed to do and does something really bad have to happen… for anything to change… you know 'it's all hopeless, what's the point' sort of thing." [participant 20; trial coordinator]

Recognition and frequency. Interviewees reported that 'concerning' data presented in three ways; (1) most frequently via low domain or aggregate questionnaire scores; (2) via additional information provided by their participants (commonly un-requested comments provided on the back of the questionnaire, or in accompanying letters); and (3) during conversations with the trial participant that were prompted by the act of filling in the questionnaire.

"A couple of times where measurable erm data… that the doctor had done, showed yeah, maybe a bit of a slight wobble but everything is okay. Whereas they're - according to their erm quality of life questionnaire, they will sort of say oh god, it's all awful and it's all really getting worse… that was noted and the patient was called back in early." [participant 17; research nurse]

"People will send their questionnaires back and sometimes they'll attach a letter, or... they'll write little comments on the back… there's been the odd participant erm that's sent

> something back that I've sort of read and been a little bit worried about them." [participant 20; trial coordinator]

> "When we did the questionnaire, she got quite upset… so I spent most of the time talking to her about what help she could, erm, get, and we, I went online and looked up the number of the Alzheimer's Society, and things like that for her." [participant 22; research nurse]

Researchers discussed the frequency with which 'concerning' data was encountered, variously reporting it as 'every other week' (participant 21; trial coordinator), 'two or three percent' (participant 23; data manager) or as approximately 'five percent' (participant 24; research nurse) of the total volume of HRQL data viewed. Some used less precise phrases, for example, 'a couple of times' (participant 17; research nurse), or 'sometimes' (participant 20; trial coordinator): 11 interviewees (42%) reported that they had never come into contact with 'concerning' HRQL data.

Action. The majority of interviewees (n=23, 88%) thought 'concerning' data always warranted some form of response. No consistent way of responding emerged, however, possibly because interviewees also reported that there were generally no instructions available on what to do in such a situation. They therefore reported experience of a range of responses including the following; calling the trial participant back into clinic for a further consultation, altering their medication, offering comfort and, most commonly, referral to their GP and/or to a specialist health professional (generally following prior consultation with the participant).

> "One consultant called me back in because the patient had left [the HRQL questionnaire] with him… and he'd looked at it and was concerned at what he was seeing, and saying, 'That's not the patient that presented to me. We need to call them back in and we need to,' you know, 'talk to them again'." [participant 15; research nurse]

> "The patient came back... [they] were advised over the phone to just change the medication slightly and increase the frequency of drops and then the patient came in earlier and was seen." [participant 17; research nurse]

> "The patient was contacted… The surgery was contacted. And it has been notified to the GP as well that, 'We received this piece of information from your patient X.' So, erm, the GP was aware at that point… that this patient is in, in such a state." [participant 19; research nurse]

No action. One interviewee reported taking no action when encountering data indicating poor HRQL. Another described a strategy that had been implemented in their trial which was aimed at avoiding the issue altogether, namely, removal at the outset of questions that were thought likely to lead to the generation of 'concerning' data.

> "When they say they haven't got a really good quality of life, you think, 'Oh, dear,' you know... not really a lot I can do about that… I'm just recording what the patient has said." [participant 23; data manager]

> "Initially, we did have... one section of questionnaires which was more about, sort of, depression, erm, and it was decided to remove those because we didn't necessarily… like, if someone put particular answers, we'd have to deal with that… so we decided to remove those." [participant 25; trial coordinator]

Reporting of actions. Interviewees were asked if concomitant medicinal interventions, administered as a result of encountering 'concerning' data, would be reported through existing trial mechanisms. Opinion was divided. Some thought this data would be automatically captured.

> "[the co-intervention] would be entered in the, in the database of our trial… So, if, if the other person who's gonna see the patient the next time is looking at the data, they will be collecting that information, they will have that beforehand, and relate it to the, the records in the surgery." [participant 19; research nurse]

Others felt that some trials might find it difficult to fully track such interventions, especially if the period between follow-up clinics was long, or the trial involved postal questionnaires.

> "You don't tend to get any information, erm, coming back from the GP… And I think most patients, you probably won't see them again because some of those questionnaires may be just a one-off… they might be filling the rest of them in and sending through the post. So, if it's not a follow-up thing where you're gonna see the patient again. You might not know… So that's become an issue." [participant 13; research nurse]

Two interviewees talked explicitly about whether non-medicinal interventions, for example referral for clinical psychology or counseling, would be reported/captured: there was uncertainty over whether this would occur.

> "I doubt it whether a… it depends on the system... there may be referral, like, the doctor, the GP may say, 'Referred to the counselor,'… I don't know whether I'll be able to see it. I don't know." [participant 19; research nurse]

Researcher burden

Some interviewees reported feeling emotionally and/or ethically burdened by the task of HRQL data-collection. This sense of burden was usually reported in connection with dealing with HRQL-related participant distress, encountering

'concerning' data, or (predominantly for research nurses) attempting to resolve the tension between the two roles of 'researcher' and 'health-care practitioner'.

Participant distress. Our researchers reported frequently having to deal with patients who were particularly emotional following HRQL measurement. Some therefore felt uncomfortable providing HRQL measures that included questions they knew often distressed patients

> "Some of the patients get quite upset, especially when you ask them about anxiety and depression… I have had occasions where patients just burst into tears… it does tend to be quite an emotional thing for them to, to discuss, really." [participant 22; research nurse]

> "It's almost reinforcing all the problems and some of them have got, you know, 'is this affecting your finances', you know 'are you anxious and worried' and it's like 'well yes I am,'... if they've been unwell, sick… you just sometimes feel like it's the last thing they need to be doing." [participant 5; research nurse]

> "I feel really awful because I'm the one who's handed them this questionnaire... I don't want them to feel, you know, leave feeling depressed or… feeling a bit worried, because that's not what I'm here for." [participant 11; research nurse]

Interviewees also reported that they could be emotionally affected themselves, following such encounters.

> "It looked, to me, as a… completely fed up and frustrated patient, ready to give up life… and I started shaking when I read it." [participant 19; research nurse]

> "Some of the more severe ones, or the more sad ones… you do go home and, and think about them." [participant 21; trial coordinator]

> "I'm reading what's happening to these ladies and gentleman, and it's, it is heartbreaking. And I have cried sometimes." [participant 23; data manager]

Some reported feeling the weight of responsibility when having to decide whether, and how, to handle 'concerning' data. They described the difficulty in deciding whether or not to intervene in these situations, and suggested that they did not always feel prepared or trained to handle such decisions.

> "I remember at a steering group meeting, saying… 'Well, okay, how would you advise I make that decision?' and being told, 'Well, you're not a clinician, you're not supposed to be making that decision,' and me, sort of, saying, 'Okay, but you're asking me to!'… So it's difficult." [participant 21; trial coordinator]

Dual-role tension and duty of care. There were also reports of burden associated with a perceived tension, for some interviewees, between their dual professional roles as health-care practitioners and researchers.

> "We're told constantly… recruit, recruit, recruit... and for commercial trials you have to hit your targets… [but] you build up that very close relationship with people and yeah, it's… they are patients first." [participant 17; research nurse]

> "You do feel that, erm, that contradiction between being a researcher and having to be quite, erm, detached and it's data. And, then, a lot of the patients I know as people, and I've visited them." [participant 21; trial coordinator]

The majority reported resolving this tension in favour of the 'patient' (the trial participant), identifying a perceived duty of care which directed them to consistently place the needs of the patient over and above those of the study. Interviewees tended to justify this position either by appealing to their personal values, or by invoking the obligations associated with their profession: for example, 'make the care of people your first concern', from the Nursing and Midwifery Council Code of Conduct [17].

> "I have been in that position and I have been told that the study comes first [because] that's my role… at the end of the day… that's not how it works… I am [a] registered nurse… I have to act upon that as well." [participant 8; research nurse]

> "You have got this ethical dilemma between the research and the, and the patient, but your patient always comes first, so there shouldn't really be an ethical dilemma."[participant 9; research nurse]

> "You have duty of care to that patient… Let other people worry about the massive numbers and the quality of the data… Your duty of care is there and then to that patient."[participant 24; research nurse]

There was, however, one individual who held the opposite view: that their primary responsibility rested with the trial.

> "I actually think you've got a duty to produce good research data… I know the impact of quality of life data… and I've seen it go through NICE [National Institute for Health and Care Excellence] and I know how important it can be." [participant 15; research nurse]

This interviewee felt that their job was to ensure clean data and that it was the responsibility of those outside of the research study - the participant's GP and regular health care professionals - to monitor and deal with HRQL-related issues, such as anxiety or depression.

> "They're in the system, they're not just seeing a [research] nurse… I think some people feel they're the only person that can pick it up, but if we all work as a team when we're all doing our job, those issues should be picked up as well elsewhere." [participant 15; research nurse]

These statements were discussed with other researchers in subsequent interviews, however, no other individuals supported this point of view.

Deficiencies in HRQL trial management

Interviewees reported perceived deficiencies in trial management relating to HRQL data collection and suggested there were four areas in need of improvement; (1) the provision of adequate data-collection guidelines; (2) the implementation of training; (3) the effective transfer of information between the trial team, the research staff and the trial participants; and, (4) the attitude of trial management groups (TMGs) to HRQL as an outcome.

Guidelines. Interviewees reported they had been given little guidance either in the trial protocol, or in SOPs, on the administration of HRQL measurement, and there were no guidelines on dealing with 'concerning' data.

> "I don't think there's an overall clarity about… using quality of life measures... [if the patient writes] additional information [on their questionnaire], how does that get recorded, how does that get fed back to the team? What happens… if you are concerned about somebody? What's the process? What level should we get involved?...speaking to patients on the phone… what sort of things should we be checking out to make sure that they are actually okay?… these sorts of issues aren't really covered anywhere." [participant 20; trial coordinator]

Interviewees wanted guidelines in these areas, which they felt might be especially useful for inexperienced researchers. There was no consensus, however, on the optimal format for such guidance. The majority supported the reproduction of HRQL guidelines within the trial protocol, but some felt that the protocol was not always written in a language that was readily accessible to them, and instead suggested a role-specific appendix, or a separate SOP or work instruction.

> "All that the nurses have got really is the protocol, which is… it's more for the PI [Principle Investigator], basically, because it's so in-depth… and there's the patient information sheet which is a whittled down version of the protocol. And there's nothing really in between… for the nurses. There's no [specific] guidance for us… So I think something in the middle would be nice." [participant 11; research nurse]

Training. Interviewees expressed discontent at what they felt was a general lack of in-trial HRQL training and wanted improvements in this area.

> "I did not have any quality of life training, had no idea of the importance of quality of life questionnaires, until I went on this [external course]... we should have been aware, because it's such an important part… I really do wish that we'd had this training right at the beginning." [participant 4; research nurse]

Some felt that HRQL training should be delivered as part of existing site inductions, and others that an external study day (or half-day) would better suit their needs. Again, there was a feeling that training would be particularly useful for junior researchers. Interviewees were asked what elements they would like to see included in HRQL training, answers included; the purpose and importance of HRQL measurement, the optimal methods of administration, dealing with difficult situations, counseling distressed participants and dealing with, and reporting, 'concerning' data without introducing bias (participants 1-9, 11-13, 15, 17-20, 22-25).

Education of data collectors and trial participants. Interviewees reported that their trial participants would sometimes decline to answer HRQL questions that they regarded as overly intrusive (e.g. surrounding sexual activity) or struggle to answer sections they regarded as of questionable relevance to their situation (e.g. questions surrounding depression given to participants at low risk of the condition), which might result in missing data.

> "The feedback you get is... 'I can't understand why they're asking me this'…" [participant 4; research nurse]

> "They're a bit, 'Oh, well, what relevance has this got to me having my hip done?'…" [participant 11; research nurse]

> "Usually there's a lot of, around the sexual health... part of the, of the form, they do miss off, especially... They just refuse to answer." [participant 23; data manger]

Research nurses suggested that their participants would be more inclined to answer such questions if they were able to educate them about the relevance of the individual questions, and the purpose and importance of HRQL data generally, to the outcome of the study. Many nurses felt unable to do this, because they were rarely given this information by the TMG in the first place.

> "We could have done with the training on the relevance of quality of life much, much earlier on... I think that would have helped explain the role of quality of life to patients as well, erm, because the feedback you get is… 'I can't understand why they're asking me this,'… so, I think it's very important that you educate the interviewer so that they can explain. [participant 4; research nurse]

Two possible reasons were suggested for this lack information transfer. First, that TMGs may believe the majority of research nurses did not want to be overloaded with information during trial training and those nurses who wanted to find out more about the purpose of HRQL measurement could consult the protocol.

> "The only people that were explained stuff were the GPs... we would tell them what the study's about... 'This is the study.' 'This is what we're trying to find out…' But when it came to the nurses, it wasn't deemed necessary... There was a, a copy of the protocol... to find out more information... you don't want to bog them down... you want to make it seem as easy as possible." [participant 10; trial coordinator]

Second, that TMGs may assume that HRQL measurement was entirely straightforward and therefore did not warrant explanation.

> "Quality of life questions. They're deemed as, 'Well, it's self-explanatory. You just put it through and you ask the questions.' Erm and that, I know, happens."[participant 10; trial coordinator]

Attitude to HRQL measurement. A number of interviewees suggested that HRQL measurement was not taken seriously enough by TMGs, stating that they felt HRQL was often regarded as an 'add-on' rather than a valued outcome. Several stated that improvements in HRQL guidance or training would only be effective if TMGs adopted an earnest attitude toward optimal HRQL assessment.

> "I think you'd need to have the other things in place, that quality of life is taken seriously and is not just thought of as an add-on… and have a good training plan… so that everybody then who was on a trial had that information at the start, they had that training and they had right, this is our role, this is what we do in a situation like this. And this is our duty, I think we'd have to have all of that sorted out before that system would work and be effective." [participant 20; trial coordinator]

Discussion

This study provides insight into the experiences of, and issues faced by, research nurses, trial coordinators, data managers and research facilitators involved in the collection of HRQL data in clinical trials in the UK.

Principal findings

Our results suggest there may be inconsistencies in the quality of HRQL data collection across, and within, clinical trials, which has the potential to adversely affect the reliability and validity of trial results. This variation appears to arise from sub-optimal standards of HRQL-specific trial protocol content, training and education.

Standardisation of data-collection processes is a fundamental aspect of trial design, which is aimed at reducing bias and measurement variability and maximizing data quality [10]. Interviewees in our study reported that both between-site and within-site standardisation was lacking, particularly with regard to logistical aspects surrounding: the timing of HRQL assessment (before/during/after the clinic appointment); the levels of privacy and assistance given to trial participants completing their questionnaires; and approaches to the management of missing data. HRQL assessment should ideally be undertaken at the same pre-specified time points in a trial, normally prior to clinic appointments, which can have an undue influence on PROs such as HRQL [18,19]. Our findings suggest that decisions regarding the timing of HRQL questionnaire completion can be ad-hoc and, in the absence of trial-level instructions, have the potential to vary between trial sites, risking bias. Similarly, our results suggest that the levels of privacy and assistance afforded to trial participants involved in HRQL measurement are also inconsistent across study sites.

Missing data can be a particular problem in trials with a HRQL outcome, and unlike some clinical outcomes, retrospective data capture may not be possible [20]. Methods to minimise missing data should be considered at the design phase of the trial and implemented in a consistent way [21]. Implementation of such methods were not universally reported by our interviewees and there were clear examples of questionable practice. In one trial, it was reported that missing clinical outcomes were actively pursued whereas absent HRQL questionnaires or items were not sought at all (participant 20). This approach may be potentially damaging to the trial as HRQL data is often not missing at random and may, therefore, represent a potential source of bias, especially when levels are high and differ by treatment group [20,22]. In another trial, it was reported by one interviewee (participant 25) that varying methods for retrieving missing HRQL data were employed across opposing arms of the trial, with face-to-face methods being used for the intervention group and postal methods for the control, again, such an approach may risk the introduction of systematic bias.

Our data suggests that inconsistency in HRQL data-collection methods may stem from a general lack of HRQL or PRO-specific protocol content, supporting trial documentation (such as SOP's), and training and education. In the absence of such guidance, some interviewees felt they were left to find their own way of administering PROs, which perhaps explains the variation in methods employed. It is not clear why PRO data collection methods were not routinely included in the protocols of trials where HRQL was a primary, or important secondary, outcome. As far back as 1997, Fayers and colleagues [23] released guidelines for protocol writers, which included specific examples of text aimed at improving HRQL data-collection. Other authors have since produced guidelines that also address aspects of this area, although most are limited by a lack of systematic development or stakeholder involvement [18,19,21,24-33]. More recently, the US Food and

Drug Administration [8] and the Centre for Medical Technology Policy [34] have published guidance documents containing recommendations geared towards the management of missing data and aimed at optimising the implementation of PROs such as HRQL. Moreover, these guidelines specifically promote the training and education of both trial researchers and participants as a key element of clinical trial quality control.

There are, however, some limitations with the current PRO guidance documents. Data-collection is generally not the focus of any paper, meaning that recommendations in this area can be sparse when they appear. In addition, there is no clear consensus in the literature, therefore, differing guidelines are spread across a number of publications [35]. This may, in part, explain why our findings suggest that recommendations are not filtering down to the level of local trial site personnel. Our interviewees also suggested the reason for this lack of information cascade might be that trial management teams did not always feel specific guidance or training was warranted, either because HRQL data-collection was deemed to be self-explanatory, or that the protocol would already provide all necessary information and further guidelines might overload research nurses with additional (and presumably unnecessary) content. Our research nurse interviewees disagreed with these sentiments, appearing to welcome more information on all aspects of HRQL measurement, which they felt was not always straightforward and could present a considerable emotional and/or ethical burden. They also highlighted that the protocols they generally worked with rarely contained HRQL-specific information that was adequate to support their needs, and were not always pitched at a level that was readily accessible to them. Finally, it is of course possible that HRQL-specific information *was* available in at least some trial protocols, but that our interviewees could not accurately recall its content. Evaluation of the quality of HRQL protocol content, and the extent to which relevant guidelines are internalised by trial staff, warrants further research.

Our other main finding surrounds the previously unreported phenomenon of 'concerning' data, which was described as data that raised concerns about the participant's wellbeing. 'Concerning' data, although arising infrequently, was reported to present significant challenges for those who dealt with it, with little or no guidance provided by their TMG on how to manage it. Some research nurses reported feeling a degree of tension between their dual roles as a researcher and practitioner when faced with such data. They acknowledged a professional obligation to make any concern for the trial participant their first priority, but as researchers, they also recognised a duty to maintain the integrity of the trial. This dual-role tension has been discussed elsewhere [36-39]. It can be problematic, as it has been suggested that the need to collect 'clean' data and minimise withdrawals has the potential to disproportionately influence decisions related to the wellbeing of the participant [36]. This view was not supported by our data, with all but one informant reporting that they consistently prioritised the wellbeing of the participant over the needs of the trial. This behavior demonstrates a widespread endorsement by our interviewees of the first principle of 'good clinical practice' as outlined in European Union directive 2005/28/EC: "The rights, safety and well being of the trial subjects shall prevail over the interests of science and society". [40] As our findings suggest, however, this approach was not without its problems. In the presence of 'concerning' data (and in the absence of appropriate guidance), several interviewees reported the provision of non-standardised co-interventions, administered, in good faith, to assist the trial participant in distress. Some interventions, especially those involving onward referral or non-medicinal treatments for example, may not be captured by standard trial reporting systems, which could lead to co-intervention bias [11].

Strengths and limitations of the study

The strength of this study is its use of qualitative methods to provide an insight into the previously unexplored issues surrounding PRO data-collection in UK-based clinical trials, with a specific focus on HRQL. Our use of semi-structured interviews allowed the exploration of several 'core' topics with each of our interviewees, but still allowed scope to investigate novel themes as they emerged. The validation of interview summaries by our study participants, and the triangulation of analysis by four different researchers are further strengths and lend credibility to the data.

A limitation was that the interviewer had prior knowledge of some of the issues that were likely to be discussed, which could have influenced data collection. We attempted to mitigate for this through the use of a topic guide that encouraged the use of non-leading questions and through other credibility enhancing processes, including regular team meetings aimed at facilitating reflexivity, peer review of verbatim interview transcripts and formal triangulation of coding. The recruitment methods meant the participants in this study were self-selected. The results we have presented could be particular to this (UK-based) sample and may not be readily transferred to dissimilar groups and research contexts. The interviewees were, however, recruited from a variety of settings in both primary and secondary care, and were selected to capture a range professional backgrounds and levels of experience.

Conclusions

This is the first study to investigate the views of research nurses, trial coordinators, data managers and research facilitators involved in HRQL data collection. Our findings suggest that there are inconsistencies in the standards of HRQL data collection in some trials, which may affect the reliability and validity of trial data and could lead to biased results. These inconsistencies may stem from a general lack of HRQL-specific protocol content, training and education within trials. We also found that research nurses, and to a lesser extent data managers, are sometimes exposed to HRQL data that cause them to become concerned for the wellbeing of the trial participant. Again, there appears to be a lack of protocol content and training on how to recognise and respond to such data. This lack of guidance risks the provision of co-interventions, which may remain un-reported and have the potential to introduce bias. Further research, using both qualitative and quantitative methods, and undertaken

internationally, is needed to determine the extent of each of the problems highlighted in this study.

Our findings underline the need for improved guidance on PRO data collection in trials and clearer, more detailed, descriptions of how to collect and manage these data in trial protocols and SOPs. Ideally, current guidance documents should be supplanted with internationally endorsed consensus guidelines, specifically tailored to the promotion of best practice in PRO data-collection. In the meantime, trialists should utilise existing PRO and HRQL-specific data-collection recommendations [8,18,19,21,23-34] to inform the trial design process, alongside more general high quality protocol guidelines such as the SPIRIT 2013 statement [10,41]. Trial management teams have a responsibility to provide local site personal with protocol content and supporting trial documentation, alongside trial training and education, which aids optimal collection of both standard and 'concerning' PRO data, whilst minimising the risk of bias.

Supporting Information

Interview Topic Guide S1. (PDF)

Author Contributions

Conceived and designed the experiments: DK JI HD MC. Performed the experiments: DK TK. Analyzed the data: DK JI HD MC. Wrote the manuscript: DK. Critiqued subsequent drafts each adding important intellectual content JI HD TK MC.

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Paper Appendices

Paper Appendix	Thesis Appendix
Interview Topic Guide S1	Appendix 1

Additional Appendices

Appendix 2 – Summary of coding methods and recruitment lessons learned

Chapter 3. PRO alerts

The qualitative data presented in Chapter 2 suggested (in accordance with earlier anecdotal reports) that data collection staff may be intermittently exposed to PRO data that raises concern for the wellbeing of the trial participant. In response, some staff reported administering non-standardised co-interventions, which potentially risked bias and thereby threatened the integrity of PRO trial results. Disseminating information about this previously unreported phenomenon to the research community is important in order to raise awareness and to promote debate regarding the most appropriate management strategy. This Chapter (published in JAMA in 2013) presents a theoretical viewpoint exploring in greater detail issues surrounding the management of 'concerning' PRO data; for the first time introducing the term 'PRO Alert' to describe the exposure of data collection staff to PRO data displaying 'concerning levels of psychological distress or physical symptoms that may require an immediate response'.

This Chapter has been published in JAMA (IF 30) as:

Kyte D, Draper H, Calvert M. Patient-Reported Outcome Alerts: Ethical and Logistical Considerations in Clinical Trials. JAMA. 2013;310(12):1229-1230. doi:10.1001/jama.2013.277222.

The work presented in this Chapter has been accepted for presentation as part of an expert panel discussion at the annual International Society for Quality of Life Research (ISOQOL) conference in October 2014:

- **Kyte D**, Brundage M, Basch E, Velikova G, King M, Calvert M. Monitoring Patient Reported Outcome Alerts in Clinical Trials and Routine Practice: An Expert Panel Discussion of

Current Knowledge and Priority Areas for Research. *Symposium* - ISOQOL 21st Annual Conference in Berlin, Germany, 2014.

The work was also presented as part of a two-day symposium held at the University of Birmingham in 2013:

- Calvert M, **Kyte D**. Best-Practice for Patient Reported Outcomes (PROs) in Randomised Clinical Trials. Institute of Advanced Studies, University of Birmingham, July 2013 [*Oral*]

Patient-Reported Outcome Alerts: Ethical and Logistical Considerations in Clinical Trials

Kyte D, Draper H, Calvert M.

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Chapter 4. PRO data collection in clinical trials: A survey of UK trial staff and management. Part 1 – PRO administration

The findings of Chapter 2 suggest that the anecdotal experiences outlined in Chapter 1 - (1) inconsistencies in PRO administration; (2) difficulties related to the management of 'concerning' PRO data; and (3) a lack of PRO-specific guidance and training in trials - may be shared more broadly by trial staff. The interviews provided significant insight into the nature of the problems and the way they are negotiated by trial staff. The generalizability of the study findings is unclear, however, due to the small sample size and limited recruitment area.

Chapters 4 and 5 present the results of a large-scale cross-sectional survey of UK-based trial staff (research nurses and data managers/coordinators) and trial management (chief/principle investigators and trial managers), the aim of which was to determine the extent to which the qualitative findings presented in Chapter 2, could be generalised to the wider community of trial staff. The decision was taken to present the results of the survey over two papers, as the large volume of data obtained during data collection precluded comprehensive presentation and discussion of all of the findings in one publication. Chapter 4, therefore, presents the results of the survey pertaining to the general aspects surrounding PRO administration in trials. Chapter 5 concentrates on the results of the survey surrounding the management of PRO alerts.

This Chapter is presented in paper format and will be submitted to a peer-reviewed journal as:

Kyte D, Ives J, Draper H, Calvert M. Current Practices in Patient-Reported Outcome (PRO) Data Collection in Trials: A Survey of UK Trial Staff and Management. Part 1 – PRO Administration

Title Page

Title

Current Practices in Patient-Reported Outcome (PRO) Data Collection in Trials: A Survey of UK trial staff and management. Part 1 – PRO administration

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ABSTRACT

Background

Patient-reported outcomes (PROs) are an important measure of effectiveness, increasingly used in clinical trials. PRO questionnaires should be administered in a standardized way across trial sites and routinely screened for avoidable missing data, in order to maximize data quality and minimize risk of bias. Our recent qualitative study, however, has identified concerns about the consistency of PRO administration in trials. The purpose of the current study was to determine the extent to which these qualitative findings could be generalized to the wider community of trial personnel.

Methods and Findings

We conducted an online cross-sectional survey of UK-based research nurses, data managers/coordinators, trial managers and chief/principal investigators involved in clinical trials that use PRO measures (PROMs). Participants were recruited from all 55 UK Clinical Research Collaboration Registered Clinical Trials Units and 19 Comprehensive Local Research Networks. We undertook descriptive analyses of the quantitative data and directed thematic analysis of free-text comments. Factors associated with the management of missing PRO data were explored using logistic regression. 767 respondents completed the survey. The survey data supported the generalizability of our qualitative study findings, suggesting inconsistencies in PROM administration with regard to the level of assistance given to trial participants, the timing of PROM completion in relation to the clinical consultation and the way missing PROM data is managed. Having 10 years or more experience in the research

role was significantly (p=.035) associated with trial personnel managing missing PRO data according to existing recommendations (Odds ratio 2.26 (95% CI 1.06 to 4.82)). There were conflicting reports concerning the current level of PRO-specific guidance provided in trials. There was a consensus, however, that more guidance was needed in future trials and agreement between professional groups about the necessary components.

Conclusions

There are inconsistencies in the way PROMs are administered by trial staff. Such inconsistencies may reduce the quality of PRO data and have the potential to introduce bias. There is a need for improved PRO guidance in future trials that support trial personnel in conducting optimal PRO data collection.

Introduction

Patient-reported outcomes (PROs) are commonly collected in clinical trials in order to measure the effectiveness of new and existing medical interventions from the point of view of patients.[1] PROs are included in trial results to complement clinician-reported outcomes, as evidence suggests that the latter may underestimate the impact of a disease upon the individual.[2] PROs inform the health-care decisions made by patients and their clinicians, support licensing claims for new medicines and influence the development of health policy, including decisions about cost effectiveness.[3-5] In view of their importance, there is a need to ensure rigorous PRO data collection.

PRO trial data is usually collected using validated questionnaires, known as patient-reported outcome measures (PROMs). Trials should be designed to ensure that PROMs are administered in a standardized way across trial sites and, in particular, are routinely screened for avoidable missing data, in order to maximize data quality and reduce the risk of systematic bias.[6-9] Missing PRO data can be a particular problem in trials. In a 2008 review of 285 randomised controlled trials (RCTs), Fielding and colleagues[10] found that, of those trials collecting PROMs, one-third reported ≤ 10% missing PRO data, 18% reported between 11%–20% missing, and 18% reported >20% missing. The prevention of avoidable missing PRO data is therefore a key consideration for researchers, as data is often not missing at random but rather from those participants with the poorest outcomes.[8] As retrospective PRO data capture is frequently not possible, missing data of this type can result in bias.[8,11]

Successful standardization of trial procedures can only be achieved if they are disseminated to all trial staff. PROM administration guidance should, therefore,

appear in the trial protocol and in site start-up training, and may also be included in supporting trial documentation such as standard operating procedures (SOPs).[11-13]

Worryingly, recent qualitative evidence has raised concerns about the conduct of PROM administration in trials.[14] The study, conducted by the authors, consisted of 26 semi-structured interviews with UK-based research nurses, data managers/coordinators and trial managers involved in the collection and entry of PROM data in clinical trials.[14] Three main findings were reported. First, there were inconsistencies in the way in which PROMs were administered in trials, that could adversely affect the quality of PRO trial data and potentially bias results. Reported variability included: (1) the level of assistance given to participants during PROM completion; (2) the timing of PROM completion in relation to the clinical consultation; and (3) the approach of staff to the management of missing PRO data. Second, there was a reported lack of PRO-specific protocol content, training and education available to trial staff. Third, data collection staff reported being intermittently exposed to PRO data that caused them to become concerned for the wellbeing of a trial participant (also known as a 'PRO alert'[15], Box 1) and, in the absence of trial level guidance, reported providing off-protocol co-interventions. Some of these interventions appeared to risk biasing the results of the trial. The aim of this study was to determine the extent to which our qualitative findings could be generalized to the wider community of trial staff using a large-scale cross-sectional survey of UK-based trial personnel. Survey respondents' experiences of PRO alerts and their management are presented in a separate publication.[16d] In this paper, we present the results of the survey specific to PROM administration, with the following objectives:

[d] Chapter 5: PRO data collection in trials: A survey of UK trial staff and management. Part 2 – PRO alerts.

1. To investigate reported inconsistencies in PROM administration in trials.

2. To investigate a reported lack of PRO-specific trial protocol content and training.

3. To determine what PRO-specific trial protocol content and training respondents would like to see in future trials.

Box 1. Definitions.

Patient-Reported Outcome (PRO) – "… any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[5]

PRO Alert – The exposure of data collection staff to PRO data displaying "concerning levels of psychological distress or physical symptoms that may require an immediate response".[15]

Methods

Ethics

A favourable ethical review was received from the West Midlands Research Ethics Committee in April 2012 (ref no 12/wm/ 0068).[e]

Study Design and Sample

An anonymised online cross-sectional survey of UK-based research nurses, data managers/coordinators, trial managers and chief and principal investigators (CPIs) involved in clinical trials with either a primary or secondary PRO was conducted. In 2013, an email containing information about the study, and a link to the online survey, was distributed to all data managers/coordinators, trial managers and CPIs affiliated with the 55 UK Clinical Research Collaboration Registered Clinical Trials Units (CRC-RCTUs). The email was also distributed to all research nurses affiliated with the following National Institute for Health (NIHR) Comprehensive Local Research Networks (CLRNs): Birmingham and the Black Country; County Durham and Tees Valley; Cumbria and Lancashire; Essex and Hertfordshire; Hampshire and Isle of Wight; Kent and Medway; Leicestershire, Northamptonshire and Rutland; Norfolk & Suffolk; North East Yorkshire and Northern Lincolnshire; Northumberland, Tyne and Wear; Peninsula; South Yorkshire; Surrey and Sussex; Thames Valley; Trent; Western; West Anglia; West Midlands North; West Midlands South. Eligible individuals were invited to click on the link and complete the survey. Participants were free to withdraw from the study up to point of survey submission; thereafter withdrawal was not possible as the answers were anonymous.

[e] Appendix 2 of the thesis

Survey Instrument

We designed four online survey instruments (see Appendix I[f]), one for each participant group, the content of which was informed by our qualitative study.[14] The surveys (hosted by www.surveymonkey.com) were developed by DK and revised with input from MC, HD and JI. The survey instruments each contained between fourteen and nineteen questions on the following: (1) demographics; (2) the participant's experience of PROM administration with reference to the most recent trial in which they had been involved, (3) the provision of PRO-specific guidance within the trial, and (4) what PRO guidance/training they would like to see in future trials. Most questions also contained space for free-text comments, to allow respondents to expand upon their answers. The survey instrument was pilot-tested to ensure the content was appropriate and had face validity, and to establish the feasibility of the distribution/collection methods. Additional free-text comment boxes were added to the survey instruments following pilot feedback. No other changes were necessary.

Analysis

Descriptive quantitative analysis was undertaken for each participant group. Frequency distributions were used to describe participant characteristics and survey responses. All analysis was conducted using SPSS© (version 21, IBM©). A pre-specified logistic regression analysis was also undertaken to explore which factors were associated with the appropriate management of missing PRO data by data collection staff, as this can represent an important potential source of bias. Existing literature recommends routine checking of completed PROMs and subsequent

[f] Appendix 4 of the thesis.

'chasing' of missing data.[17] Thus, the dependent variable in the model was the appropriate management of missing data, defined as: 'whether the completed PROM was checked for missing data *and* participants were subsequently asked to complete missing items/questionnaires'. The independent variables were: the role of the data collector (i.e. 'research nurse' or 'data manager'); their length of experience in the research role; whether PRO-specific information was reportedly present in the trial protocol; and whether PRO-specific information was reportedly included in trial training. A minimum of 60 responses were required to satisfy the sample size requirement for this regression analysis (15 per co-variate).[18,19] The regression model was constructed using forced block entry[18,20] and significance was set at $p < 0.05$. DK undertook directed content analysis of the free-text comments responses, using the data from the qualitative study[14] to develop the initial research questions and coding framework.[21] Additional codes were developed as the analysis was conducted and the framework was modified accordingly.[21] JI formally reviewed all coding to enhance trustworthiness, and any disagreements about coding were discussed and resolved.

Results

767 participants responded to the online survey (560 research nurses, 129 trial managers, 41 data managers/coordinators and 37 CPIs). Participant characteristics are summarized in Table 1. As neither the UK CRC-CTUs nor the NIHR CLRNs held data regarding the number of staff involved in trials with a primary or secondary PRO, we were not able to determine a denominator or response rate.

The participants' most recent experience of a trial collecting PROMs was predominantly in the secondary care setting, with trials ranging across clinical specialties (most commonly oncology). The trials appeared to use a number of different PROMs, of which the most common were the five dimension European Quality of Life instrument (EQ-5D), Hospital Anxiety and Depression scale (HADS), the Short-Form Health Survey 12-item (SF-12) and 36-item (SF-36) questionnaires, the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and the Health Assessment Questionnaire (HAQ). The full survey results are presented in Table 2 and summarized below. The qualitative themes generated during analysis of the free-text comments, the proportion of associated comments, and illustrative respondent quotations are also presented.

Table 1. Characteristics of participants

Participant Characteristics	No. (%) Research Nurse Participants[a] (n=560)	No. (%) Data Manager Participants[a] (n=41)	No. (%) Trial Manager Participants[a] (n=129)	No. (%) Chief & Principle Investigator Participants[a] (n=37)
Age, in years				
≤25	4 (0.7)	3 (7.9)	4 (3.1)	0 (0)
26-35	95 (17)	14 (36.8)	51 (39.5)	5 (13.5)
36-45	193 (34.5)	10 (26.3)	43 (33.3)	11 (29.7)
46-55	217 (38.8)	8 (21.1)	23 (17.8)	14 (37.8)
≥56	51 (9.1)	3 (7.9)	8 (6.2)	7 (18.9)
Years in research role				
<1	51 (9.2)	4 (10.5)	12 (9.3)	0 (0)
1-3	208 (37.3)	13 (34.2)	42 (32.6)	11 (29.7)
4-6	147 (26.4)	7 (18.4)	31 (24)	4 (10.8)
7-9	50 (9)	4 (10.5)	12 (9.3)	5 (13.5)
≥10	101 (18.1)	10 (26.3)	32 (24.8)	17 (45.9)
Setting of most recent clinical trial collecting PROMs				
Primary care	112 (20.7)	15 (39.5)	47 (37.9)	16 (44.4)
Secondary care	428 (79.3)	23 (60.5)	77 (62.1)	20 (56.6)
Clinical areas covered by most recent clinical trial collecting PROMs[b]				

Cardiovascular	69 (16.5)	3 (9.4)	10 (10)	0 (0)
Elderly care	17 (4.1)	2 (6.3)	10 (10)	2 (7.4)
General medicine	39 (9.3)	2 (6.3)	7 (7)	0 (0)
General practice	19 (4.5)	3 (9.4)	23 (23)	9 (33.3)
Neurology	51 (12.2)	1 (3.1)	9 (9)	4 (14.8)
Obstetrics & gynaecology	22 (5.3)	3 (9.4)	7 (7)	2 (7.4)
Oncology	119 (28.5)	15 (46.9)	28 (28)	1 (3.7)
Opthalmology	8 (1.9)	1 (3.1)	4 (4)	7 (25.9)
Orthopaedics	35 (8.4)	1 (3.1)	7 (7)	1 (3.7)
Paediatrics	35 (8.4)	2 (6.3)	9 (9)	6 (22.2)
Respiratory	41 (9.8)	5 (15.6)	8 (8)	3 (11.1)
Rheumatology	47 (11.2)	1 (3.1)	6 (6)	5 (18.5)
Measures used in most recent clinical trial collecting PROMs[b]				
EuroQOL EQ-5D	401 (76.1)	25 (67.6)	99 (82.5)	24 (80)
Health Assessment Questionnaire (HAQ)	154 (29.2)	1 (2.7)	4 (3.3)	2 (6.7)
Nottingham Health Profile (NHP)	0 (0)	0 (0)	0 (0)	0 (0)
SF-12® Health Survey or SF-12v2™ Health Survey	36 (6.8)	6 (16.2)	22 (18.3)	7 (23.3)
SF-36® Health Survey or SF-36v2™ Health Survey	104 (19.7)	5 (13.5)	17 (14.2)	6 (20)
Hospital Anxiety and Depression scale (HAD)	115 (21.8)	4 (10.8)	21 (17.5)	11 (36.7)

Arthritis Impact Measurement Scales (AIMS2)	3 (0.6)	0 (0)	0 (0)	2 (6.7)
EORTC QLQ - C30 (Core Questionnaire)	106 (20.1)	9 (24.3)	18 (15)	0 (0)
Minnesota Living with Heart Failure© Questionnaire (MLHF)	9 (1.7)	0 (0)	1 (0.8)	1 (3.3)
Oxford Hip Score (OHS)	9 (1.7)	0 (0)	0 (0)	1 (3.3)
Oxford Knee Score (OKS)	14 (2.7)	1 (2.7)	0 (0)	0 (0)
Roland-Morris Disability Questionnaire (RMDQ)	2 (0.4)	0 (0)	2 (1.7)	4 (13.3)

[a]Columns may not add up to n due to missing values
[b]Participants were able to select multiple categories

Table 2. Questionnaire Responses

Survey Questions and response options	Research Nurse Response Count (%) [n=560][a]	Data Manager Response Count (%) [n=41][a]	Trial Manager Response Count (%) [n=129][a]	Chief and Principal Investigator Response Count (%) [n=37][a]
What assistance did you give to the trial participants during the completion of the questionnaire? [Last Trial]				
"I read the questions out to the participants."	194 (36.9)[b]	-	-	-
"I helped participants to understand the questions."	209 (39.7)[b]	-	-	-
"The participants gave me the answers and I filled in the questionnaire."	121 (23.0)[b]	-	-	-
"I gave no assistance, the participants filled in their questionnaires independently."	348 (66.2)[b]	-	-	-
If the participant had to complete the Quality of Life or other Patient-Reported Outcome Measure questionnaire in clinic, when did they do so? [Last Trial]				
"Always *before* their Consultant/Doctor appointment."	92 (18.2)	-	-	-
"Always *after* their Consultant/Doctor appointment."	47 (9.3)	-	-	-
"Variable, sometimes before and sometimes after their Consultant/Doctor appointment."	242 (47.9)	-	-	-
"Not applicable."	124 (24.6)	-	-	-
Which of the following did you do after trial participants had completed their PROM? [Last Trial]				
"I sent the questionnaire to the data inputting centre without looking at it."	100 (19.6)[b]	-	-	-
"I looked at the completed questionnaire to see if the participant had missed out any questions."	394 (77.3)[b]	-	-	-
"If I discovered missing items, I prompted participants to complete them."	308 (60.4)[b]	-	-	-
"I looked at the completed questionnaire to see if there were any scoring errors (e.g. 2 options selected instead of 1, scoring the wrong way round etc)."	141 (27.6)[b]	-	-	-
"If I suspected a scoring error, I prompted participants to look again at some questions, to ensure they had understood them correctly."	137 (26.9)[b]	-	-	-
Checked for missing PROM data and followed up participant to rectify	277 (49.9)			
Checked for PROM scoring errors and followed up participant to rectify	114 (21.2)			
When the Quality of Life/Patient-Reported Outcome questionnaire data were inputted, which of the following occurred? [Last Trial]				
"The questionnaire was checked to see if the participant had completed all questions."	-	18 (72.0)[b]	-	-
"If items were found to be missing, trial participants were followed up in some way (e.g. by post, by phone or via their research nurse) in order to complete the questionnaire."	-	7 (28.0)[b]	-	-
"The questionnaire was checked for scoring errors (e.g. two answers given instead of one, or reversed scoring)."	-	19 (76.0)[b]	-	-

"If scoring errors were detected, trial participants were followed up in some way (e.g. by post, by phone or via their research nurse) in order to correct them."	-	4 (16.0)[b]	-	-
Checked for missing PROM data and followed up participant to rectify	6 (15.4)			
Checked for PROM scoring errors and followed up participant to rectify	4 (9.8)			
Were the staff involved in data collection given instructions on how to administer the quality of life/patient-reported outcome questionnaire? [Last Trial]				
"Yes."	-	-	90 (70.9)	29 (82.9)
"No."	-	-	37 (29.1)	6 (17.1)
What particular information on Quality of Life/Patient-Reported Outcome measurement was given to the data collection staff? Please read the options below and in each case select either 'Yes, included in trial protocol, training or SOP', or 'No, not included'. [Last Trial]				
"The purpose and/or Importance of Quality of Life/Patient-Reported Outcome data to the trial."	-	-	**Y** 71 (86.6) **N** 11 (13.4)	**Y** 27 (93.1) **N** 2 (6.9)
"Relevance and reasoning behind individual Quality of Life/Patient-Reported Outcome questions."	-	-	**Y** 43 (52.4) **N** 39 (47.6)	**Y** 22 (75.9) **N** 7 (24.1)
"When to administer the questionnaire (time points)."	-	-	**Y** 84 (100) **N** 0 (0)	**Y** 29 (100) **N** 0 (0)
"When to administer the questionnaire during the clinic appointment (before/during/after the consultation)."	-	-	**Y** 53 (67.9) **N** 25 (32.1)	**Y** 22 (78.6) **N** 6 (21.4)
"How much assistance to give the participant during questionnaire completion."	-	-	**Y** 52 (63.4) **N** 30 (36.6)	**Y** 25 (86.2) **N** 4 (13.8)
"How to check for, and deal with, missing Quality of Life/Patient-Reported Outcome data."	-	-	**Y** 48 (58.5) **N** 34 (41.5)	**Y** 24 (82.8) **N** 5 (17.2)
"What to do if participants write additional information on their questionnaires (or attach a letter)."	-	-	**Y** 23 (28.0) **N** 59 (72.0)	**Y** 12 (41.4) **N** 17 (58.6)
Trial protocol and training questions [*Yes (Y); No (N) responses*]				
"The trial protocol included information about Quality of Life/Patient-Reported Outcome measurement."	**Y** 474 (92.2) **N** 40 (7.8)	-	-	-
Reported PRO protocol content present and felt it was adequate for their needs.	415 (87.7)	-	-	-
"I received trial training that included information on Quality of Life/Patient-Reported Outcome measurement."	**Y** 164 (32.7) **N** 338 (67.3)	-	-	-
Reported receiving PRO training and felt it was adequate for their needs.	152 (94.4%)	-	-	-
Trial protocol and training questions [*Yes (Y); No (N) responses*]				
"The trial protocol included information about Quality of Life/Patient-Reported Outcome data inputting."	-	**Y** 13 (50.0) **N** 13 (50.0)	-	-
Reported PRO protocol content present and felt it was adequate for their needs.	-	10 (76.9)	-	-
"I received trial training which included information on Quality of Life/Patient-Reported Outcome data inputting."	-	**Y** 9 (39.1) **N** 14 (60.9)	-	-

Reported receiving PRO training and felt it was adequate for their needs.	-	8 (88.9)	-	-
PRO assessment explanation questions [*Yes (Y); No (N) responses*]				
"It was explained to me why the Quality of Life/Patient-Reported Outcome Measure data was being collected in the trial."	**Y** 314 (60.5) **N** 205 (39.5)	-	-	-
"I was confident I could explain to trial participants why the Quality of Life/Patient-Reported Outcome Measure data was being collected in the trial."	**Y** 456 (87.7) **N** 64 (12.3)	-	-	-
"It was explained to me why each of the questions in the Quality of Life/Patient-Reported Outcome Measure were included, i.e. how each was of relevance to the trial."	**Y** 157 (30.3) **N** 361 (69.7)	-	-	-
"I was confident I could explain to trial participants why each of the questions in the Quality of Life/Patient-Reported Outcome Measure had been included, i.e. how each was of relevance to the trial."	**Y** 312 (59.9) **N** 209 (40.1)	-	-	-
Please read the following statements. In each case, please indicate whether you 'strongly agree', 'agree', have 'no opinion', 'disagree' or 'strongly disagree' with the statement. [Future Trials]				
"There should be more protocol content and trial training covering Quality of Life/Patient-Reported Outcome measurement, in trials employing such outcomes."	**SA** 140 (27.9) **A** 283 (56.5) **NO** 57 (11.4) **D** 20 (4.0) **SD** 1 (0.2)	-	-	-
"There should be more Quality of Life/Patient-Reported Outcome measurement guidance contained within other trial documentation, such as site manuals or standard operating procedures, in trials employing such outcomes."	**SA** 127 (25.4) **A** 302 (60.4) **NO** 52 (10.4) **D** 18 (3.6) **SD** 1 (0.2)	-	-	-
Please read the following statements. In each case, please indicate whether you 'strongly agree', 'agree', have 'no opinion', 'disagree' or 'strongly disagree' with the statement. [Future Trials]				
"There should be more protocol content and trial training for data managers/inputters, covering Quality of Life/Patient-Reported Outcome measurement."	-	**SA** 3 (10.7) **A** 17 (60.7) **NO** 2 (7.1) **D** 6 (21.4) **SD** 0 (0)	-	-
"There should be site manuals or standard operating procedures available to data mangers/inputters that include information on Quality of Life/Patient-Reported Outcome administration in the trial."	-	**SA** 6 (21.4) **A** 18 (64.3) **NO** 3 (10.7) **D** 1 (3.6) **SD** 0 (0)	-	-
Please read the following statements. In each case, please indicate whether you 'strongly agree', 'agree', have 'no opinion', 'disagree' or 'strongly disagree' with the statement. [Future Trials]				
"Data collection staff in trials need more information on Quality of Life/Patient-Reported Outcome measurement - in the trial protocol."	-	-	**SA** 17 (14.8) **A** 33 (28.7) **NO** 23 (20.0)	**SA** 6 (16.7) **A** 12 (33.3) **NO** 12 (33.3)

			D 39 (33.9) **SD** 3 (2.6)	**D** 5 (13.9) **SD** 1 (2.8)
"Data collection staff in trials need more information on Quality of Life/Patient-Reported Outcome measurement - in other trial documentation, such as SOPs."	-	-	**SA** 17 (14.8) **A** 54 (47.0) **NO** 19 (16.5) **D** 22 (19.1) **SD** 3 (2.6)	**SA** 7 (19.4) **A** 16 (44.4) **NO** 8 (22.2) **D** 4 (11.1) **SD** 1 (2.8)
"Data collection staff in trials need more information on Quality of Life/Patient-Reported Outcome measurement - delivered in the form of trial training."	-	-	**SA** 24 (21.1) **A** 55 (48.2) **NO** 17 (14.9) **D** 17 (14.9) **SD** 1 (0.9)	**SA** 6 (16.7) **A** 14 (38.9) **NO** 72 (19.4) **D** 8 (22.2) **SD** 1 (2.8)
"It is important to explain to data collection staff, the purpose and Importance of Quality of Life/Patient-Reported Outcome data to the trial."	-	-	**SA** 41 (36.3) **A** 69 (61.1) **NO** 3 (2.7) **D** 0 (0) **SD** 0 (0)	**SA** 13 (33.3) **A** 20 (55.6) **NO** 2 (5.6) **D** 1 (2.8) **SD** 1 (2.8)
"It is important to explain to data collection staff, the relevance and reasoning behind individual Quality of Life/Patient-Reported Outcome questions."	-	-	**SA** 30 (26.1) **A** 55 (47.8) **NO** 18 (15.7) **D** 12 (10.4) **SD** 0 (0)	**SA** 8 (22.2) **A** 22 (61.1) **NO** 4 (11.1) **D** 0 (0) **SD** 2 (5.6)
Thinking about the future. What particular Quality of Life/Patient-Reported Outcome guidance should be included the trial protocol, what should be included in trial training, and what should be included in a standard operating procedure?				
"Purpose/Importance of Quality of Life/Patient-Reported Outcome data in trial."	**TP** 389 (79.1) **TT** 344 (69.9) **SOP** 131 (26.6)	-	**TP** 77 (67.5) **TT** 89 (78.1) **SOP** 28 (24.6)	**TP** 27 (87.1) **TT** 23 (74.2) **SOP** 15 (48.4)
"How to administer the questionnaire."	**TP** 212 (43.1) **TT** 403 (81.9) **SOP** 275 (55.9)	-	**TP** 43 (38.1) **TT** 101 (89.4) **SOP** 73 (64.6)	**TP** 13 (40.6) **TT** 27 (84.4) **SOP** 23 (71.9)
How to input Quality of Life/Patient-Reported Outcome data into the database[§]	-	**TP** 3 (11.1) **TT** 22 (81.5) **SOP** 18 (66.7)	-	-
"When to administer the questionnaire."	**TP** 359 (73.9) **TT** 328 (67.5) **SOP** 202 (41.6)	-	**TP** 88 (77.2) **TT** 95 (83.3) **SOP** 64 (56.1)	**TP** 23 (71.9) **TT** 28 (87.5) **SOP** 21 (65.6)

"What to do if there is missing data or in the event of scoring errors (e.g. two answers provided instead of one, or reversed scoring)."[§]	-	**TP** 2 (7.3) **TT** 19 (67.3) **SOP** 28 (78.2)	-	-
"What to do if participants write additional information on their questionnaires (or attach a letter)."	**TP** 178 (36.3) **TT** 405 (82.5) **SOP** 232 (47.3)	**TP** 3 (10.7) **TT** 20 (71.4) **SOP** 28 (64.3)	**TP** 14 (12.7) **TT** 83 (75.5) **SOP** 78 (70.9)	**TP** 5 (15.6) **TT** 25 (78.1) **SOP** 22 (68.8)
"Ethical issues associated with Quality of Life/Patient-Reported Outcome use."	**TP** 253 (52.5) **TT** 345 (71.6) **SOP** 180 (37.3)	-	**TP** 57 (56.4) **TT** 68 (67.3) **SOP** 36 (35.6)	**TP** 12 (40.0) **TT** 24 (80.0) **SOP** 16 (53.3)
"How to deal with upset patients (communication/counselling skills)."	**TP** 71 (15.2) **TT** 390 (83.7) **SOP** 204 (43.8)	-	**TP** 6 (6.0) **TT** 91 (91.0) **SOP** 50 (50.0)	**TP** 6 (18.8) **TT** 29 (90.6) **SOP** 17 (53.1)
"Working with non-English language patients."	**TP** 248 (51.8) **TT** 329 (68.7) **SOP** 284 (59.3)	-	**TP** 39 (38.2) **TT** 80 (78.4) **SOP** 66 (64.7)	**TP** 18 (58.1) **TT** 24 (77.4) **SOP** 20 (64.5)
"How to support the participant to answer sensitive questions."	**TP** 76 (15.9) **TT** 429 (89.7) **SOP** 180 (37.7)	-	**TP** 4 (3.7) **TT** 100 (92.6) **SOP** 45 (41.7)	**TP** 8 (27.6) **TT** 27 (93.1) **SOP** 19 (65.5)
"How to collect Quality of Life/Patient-Reported Outcome data without biasing the results."	**TP** 190 (38.7) **TT** 412 (83.9) **SOP** 265 (54.0)	-	**TP** 32 (28.6) **TT** 98 (87.5) **SOP** 63 (56.3)	**TP** 9 (28.1) **TT** 29 (90.6) **SOP** 21 (65.1)
"Collecting Quality of Life/Patient-Reported Outcome data in different patient groups and/or settings."	**TP** 145 (30.3) **TT** 381 (79.9) **SOP** 220 (46.0)	-	**TP** 24 (25.0) **TT** 75 (78.1) **SOP** 42 (43.8)	**TP** 12 (41.4) **TT** 23 (79.3) **SOP** 16 (55.2)
"Relevance and reasoning behind individual Quality of Life/Patient-Reported Outcome questions."	**TP** 269 (55.1) **TT** 371 (76.0) **SOP** 94 (19.3)	-	**TP** 50 (54.3) **TT** 66 (71.7) **SOP** 17 (18.5)	**TP** 12 (42.9) **TT** 23 (82.1) **SOP** 10 (35.7)
"How to deal with difficult situations."	**TP** 71 (15.2) **TT** 391 (83.7) **SOP** 94 (45.6)	-	**TP** 2 (2.0) **TT** 88 (88.9) **SOP** 41 (41.4)	**TP** 5 (16.7) **TT** 27 (90.0) **SOP** 22 (73.3)

Abbreviations: TP, Trial Protocol; TT, Trial Training; SOP, Standard Operating Procedure; Y, Yes; N, No; SA, Strongly Agree; A, Agree; NO, No Opinion; D, Disagree; SD, Strongly Disagree. [a]Columns may not add up to n due to missing values. [b]Participants were able to select multiple categories

Inconsistencies in PROM administration

Participant assistance

66.2% of research nurse respondents reported giving no assistance to the trial participants completing PROMs during their most recent relevant trial. The remainder (44.8%) gave assistance in a variety of different ways. Of these, 37.9% reported helping participants to understand the questions, 36.9% reported reading the PROM questions out to the participants and 23.0% reported being given the answers by participants then filling in the questionnaire on their behalf.

Timing of PROM completion

There were varying responses with regard to the timing of questionnaire completion. 47.9% of nurses reported that the timing with which they administered the PROM varied (i.e. it was 'sometimes before' and 'sometimes after' the clinical consultation) during their most recent trial. 9.3% reported routinely administering the PROM *after* the consultation. Only 18.2% reported routinely administering PROMs *prior* to the participant's clinical consultation, in-line with suggested guidelines.[22,23]

Management of missing PRO data

77.3% of research nurses and 72.0% of data managers reported routinely checking completed PROM questionnaires for missing data in their most recent trial (Figure. 1). However, of the total sample, only 49.9% research nurses and 15.4% of data managers both checked for missing data *and* subsequently attempted to follow-up participants to complete the missing items. 27.6% of research nurses and 76.0% of data mangers reported checking PROM question responses for scoring errors (for example, where two options were selected instead of one), which are often logged as

missing data. Of the total sample, just 21.2% research nurses and 9.8% of data managers reported both checking for scoring errors and subsequently attempting to follow-up participants in order to correct the errors.

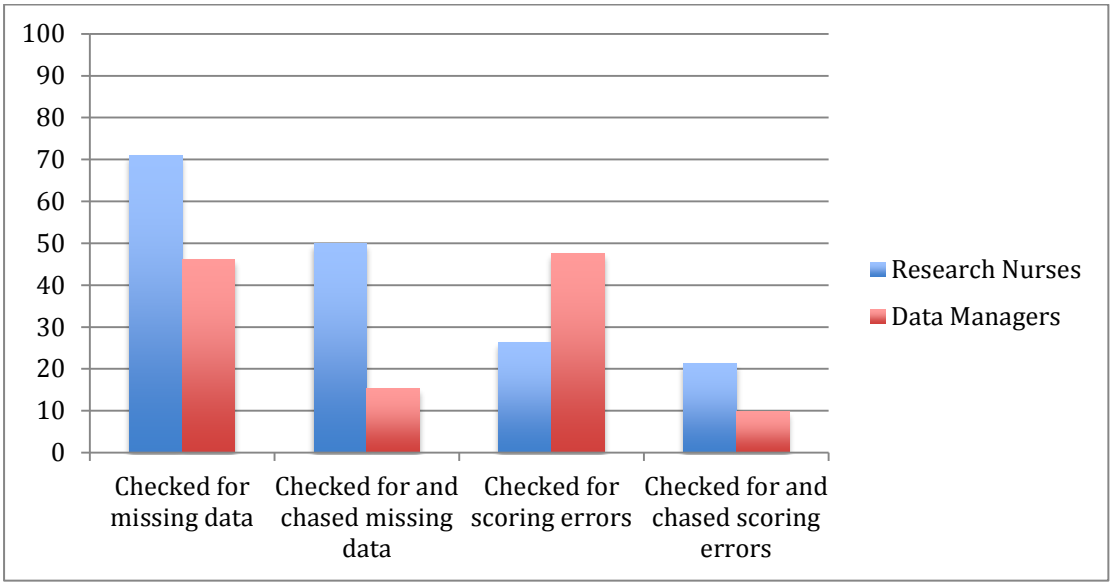

Figure 1. Management of missing data

Determinants of differences in the management of missing data

Table 3 summarizes the findings from an exploratory logistic regression analysis, which investigated predictors of differences in the management of missing data by research nurses and data managers/coordinators. In the final model, only '10 years or more experience in the research role' was significant (P=.035). The odds of individuals with such experience routinely checking *and* chasing missing PROM data were 2.26 (95% CI 1.06 to 4.82) times higher than those with less experience. There were no significant associations between the dependent variable and 'the role of the data collector' (p=.45); 'whether PRO-specific information was reportedly provided in the trial protocol' (p=.94); or 'whether PRO-specific information was reportedly included in trial training' (p=.64).

Table 3. Logistic Regression Results

					95% CI for OR	
	Coefficient	**SE**	**P**	**OR**	**Lower**	**Upper**
Constant	-0.889	0.961				
≥10 years experience as a research nurse	0.814	0.386	0.035	2.258	1.059	4.815

CI, confidence interval; OR, odds ratio, SE, standard error. [Full model presented in Appendix 5 of the thesis]

PRO-Specific Trial Protocol Content and Training: Current Practice

Survey respondents were questioned about the PRO-specific protocol content and training delivered in their most recent trial collecting PROMs. Results are presented first from members of the trial management team (CPIs and trial managers) who are responsible for providing appropriate protocol content and trial-specific training, and then from front-line data collection staff (research nurses and data managers/coordinators) who are the recipients of such training and information.

Protocol content and training provision

82.9% of CPIs and 70.9% of trial managers reported giving instructions to trial staff on how to administer the PROM questionnaire in their most recent relevant trial. Respondents were asked what particular information was provided to data collection staff. 93.1% of CPIs and 86.6% of trial managers reported providing information about the purpose and/or importance of PROM data to the trial and 75.9% and 52.4% respectively reported giving information surrounding the relevance and reasoning behind individual PROM questions. 100% of respondents in both groups reported providing information on when to administer the PROM questionnaire. Over three-quarters of CPIs reported providing information on when to administer the PROM during a clinic (78.6%); how much assistance to give the participant during questionnaire completion (86.2%); and how to check for, and deal with, missing PRO data (82.8%). The proportion of trial managers who reported providing this information was uniformly lower: 67.9%, 63.4% and 58.5% respectively. 41.4% of CPIs and 28.0% of trial managers reported providing information on what action should be taken if participants had written additional information on their PROM, or had attached a letter.

Protocol content and training available to front-line staff

92.2% of research nurses and 50.0% of data managers/coordinators reported that the trial protocol had included some form of PRO-specific information, with 87.7% and 76.9% respectively reporting that the content was adequate for their needs. 32.7% of research nurses and 39.1% of data managers/coordinators reported receiving trial training that incorporated PRO guidance. 94.4% of research nurses and 88.9% of data managers/coordinators who reported receiving PRO training felt it was adequate for their needs. 60.5% of research nurses reported they had received an explanation of why the PROM was being collected in the trial and 87.7% felt confident they could explain this to participants. 30.3% of research nurses reported receiving an explanation regarding the relevance and reasoning behind individual PROM questions and 59.9% felt confident they could explain this to their participants.

Free-text comments relating to trial protocol content and training

There were 40 free-text comments in this section, all provided by research nurses; 10.0% of which appeared to suggest that, whilst nurses felt PRO-specific information was generally present within trial protocols, it could be limited in depth:

> *'Usually there is reference to the fact that the questionnaires are to be completed. No other information is provided or instructions on use, administration etc.'*

40.0% of comments suggested that nursing staff had received little in the way of PRO training:

> *'I was not given any training on PROM basically just been told if patient consent for the study they fill this document.'*

10.0% of comments suggested PROM training was particularly lacking for staff joining the trial at a later stage:

'Our centre was invited to take part in the study quite late on so missed the initial set up that other centres had. Whilst there was some verbal communication regarding how to deliver the questionnaires much of it was down to previous experience/personal communication skills…'

'I took over the study partway through and received minimal instruction relating to the questionnaires. Anything additional I learn en route.'

5.0% reported that PRO trial training was inconsistently delivered across trials:

'I have been taught how to use it many times but not for this study. However, to ensure consistency I believe we should be trained on this for each study.'

A number of comments (37.5%) implied that the impact of a lack of guidance may be minimal. These nurses reported either relying upon either previous experience of PRO assessment in trials, or knowledge gained via attendance at previous training courses, or an independent search for the information they required:

'I have used QOL questionnaires a fair amount so felt confident using the provided tools without needing training.'

'No specific training given by the study centre for this study, but I have completed training on many of the QoL [PROMs] previously.'

'The trial training said that the questionnaires had to be done by the patient, but did not give any reasons why. I did my own reading to find out why this was the case.'

One respondent comment (2.5%) suggested a lack of PROM guidance resulted in an impaired ability to explain aspects surrounding PROM assessment to trial participants:

'I can roughly explain to participants why this information is required, but would prefer to have a better understanding myself to be able to fully explain this to study participants.'

and one respondent comment (2.5%) suggested it led to more queries to the trial team:

'The trial coordinator had to be contacted quite often for clarification as subject asked questions that was not covered in the training session.'

PRO-Specific Trial Protocol Content and Training: Future Practice

Survey respondents were asked two questions in this section: (1) whether they felt more PRO guidance was needed in future trials and (2), after considering a list of possibilities suggested by the findings of our qualitative study, which particular PRO-specific items of information they felt were needed and where should they be provided: in the trial protocol, in trial training, or in supporting trial documentation (e.g. SOPs).

Is more PRO guidance needed?

85.1% of research nurses and 78.6% of data managers/coordinators 'strongly agreed' or 'agreed' there should be more PRO guidance provided in future trials with PRO endpoints (Figure 2). In contrast, 58.2% of trial managers and 56.5% of CPIs 'strongly agreed' or 'agreed' there should be more PRO guidance in trials.

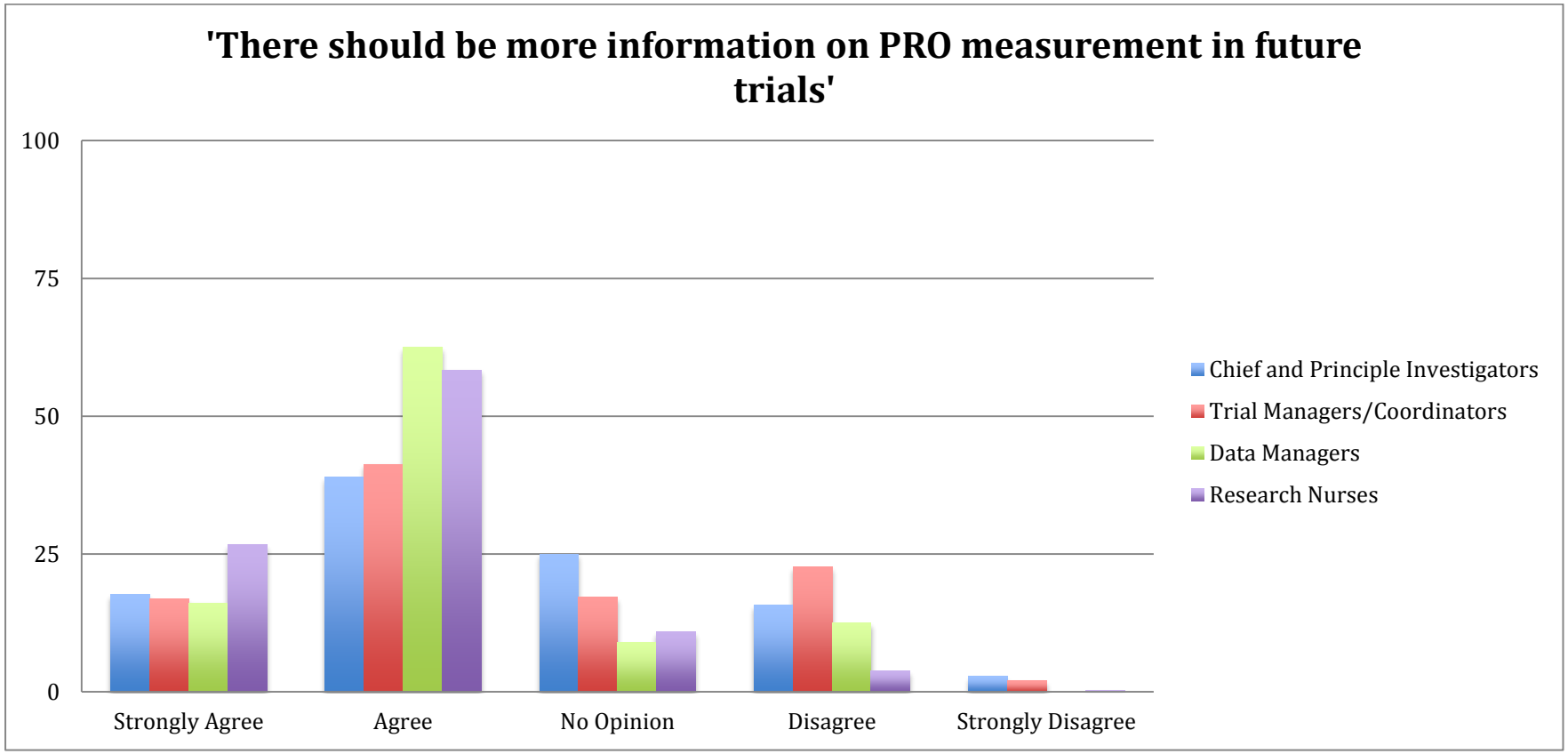

Figure 2. Future PRO guidance provision

What guidance is needed and where should it appear?

In order to highlight where there was agreement on the necessary components of PRO guidance, items that were selected by more than 50% of respondents in a professional group are presented in Table 4 and summarized below.

Table 4. Future PRO guidance provision

	Trial Protocol				Trial Training				SOP			
Suggested PRO-specific items of information[14]	RN	DM	TM	CPI	RN	DM	TM	CPI	RN	DM	TM	CPI
Purpose/Importance of Quality of Life/Patient-Reported Outcome data in trial	*		*	*	*		*	*				
How to administer the questionnaire					*		*	*	*		*	*
How to input Quality of Life/Patient-Reported Outcome data into the database[§]						*				*		
When to administer the questionnaire	*		*	*	*		*	*			*	*
What to do if there is missing data or in the event of scoring errors (e.g. two answers provided instead of one, or reversed scoring)[§]						*				*		
What to do if participants write additional information on their questionnaires (or attach a letter)					*	*	*	*		*	*	*
Ethical issues associated with Quality of Life/Patient-Reported Outcome use	*				*		*	*				
How to deal with upset patients					*		*	*				*
Working with non-English language patients	*			*	*		*	*	*		*	*
How to support the participant to answer sensitive questions					*		*	*				*
How to collect Quality of Life/Patient-Reported Outcome data without biasing the results					*		*	*	*		*	*
Collecting Quality of Life/Patient-Reported Outcome data in different patient groups and/or settings					*		*	*				
Relevance and reasoning behind individual Quality of Life/Patient-Reported Outcome questions	*				*		*	*				
How to deal with difficult situations					*		*	*				*

Abbreviations: RN, research nurses; DM, data managers; TM, trial managers; CPI, chief and principle investigators; '*'= Items selected by >50% of respondents per group.
[§]Exclusively viewed by data manager respondents

Future guidance: front-line staff

More than two-thirds of research nurses selected all of the suggested PRO-specific information for inclusion within trial training, however, only 5 items were selected for inclusion in the trial protocol by >50% of the research nurses surveyed. These were: the 'purpose/importance of PRO data in trial' (79.1%), 'when to administer the questionnaire' (73.9%), the 'relevance and reasoning behind individual PROM questions' (55.1%), 'ethical issues associated with PRO use' (52.5%) and 'working with non-English language patients' (51.8%). Finally, just 2 items were selected by a majority of the research nurse sample for inclusion in SOPs: 'how to administer the questionnaire' (55.9%) and 'how to collect PRO data without biasing the results' (54.0%).

The majority data managers/coordinators selected the following three PRO-specific items of information for inclusion in both training and SOPs; 'how to input PRO data into the database' (trial training, 81.5%; SOPs, 66.7%), 'what to do if there are missing data/scoring errors' (trial training, 67.3%; SOPs, 78.2%) and 'what to do if participants write additional information on their questionnaires (or attach a letter)' (trial training, 71.4%; SOPs, 64.3%).

Future guidance: trial management

More than half of all CPIs and trial managers selected all of the suggested PRO-specific information for inclusion within trial training. Two items were selected by a majority of both CPIs and trial managers for inclusion in the trial protocol: the 'purpose/importance of PRO data in trial' (selected by 84.4% and 67.0% respectively) and 'when to administer the questionnaire; (71.9% and 76.5%). CPI respondents also selected 'working with non-English language patients' (56.3%), whilst trial managers

instead selected the inclusion of ‘ethical issues associated with PRO use’ (50.4%). A majority of both CPIs and trial managers selected 5 items for inclusion in SOPs, including: ‘how to administer the questionnaire’ (71.9% and 64.0%), ‘ when to administer the questionnaire’ (65.6% and 55.7%), ‘what to do if participants write additional information on their questionnaires (or attach a letter)’ (68.8% and 67.8%), ‘working with non-English language patients’ (62.5% and 59.5%), ‘how to collect PRO data without biasing the results’ (65.6% and 54.8%). CPI respondents also selected a further 3 items for inclusion in SOPs, including: ‘how to deal with upset patients’ (53.1%), ‘how to support the participant to answer sensitive questions’ (61.3%) and ‘how to deal with difficult situations’ (68.8%).

Free-text comments regarding future PRO guidance

There were 22 free-text comments in this section. These most commonly suggested that PRO-specific information should be placed within a SOP (27.5%) or included in trial training (22.7%):

> *“I think all… would best placed to be addressed via trial training and in SOP/Data Entry Instructions conventions as oppose[d] to the trial protocol.” [Data manager]*

13.6% of comments suggested trial protocols should predominantly signpost to sources of PRO information, rather than necessarily containing the information themselves:

> *“I think that mention of some things within the Protocol could be quite short e.g. ‘how to deal with difficult situations will be covered in trial training and in SOP xxx date yyy’.” [Research Nurse]*

A number of comments (22.7%) suggested staff felt PRO training should be conducted outside of the trial:

> *‘some of this could be generic to many trials so may be able to train as 'general training' via*

R&D depts rather than trial specific training via CTUs.' [Research Nurse]

Two research nurses each suggested one additional element of PRO guidance, but the optimal location was not specified:

'whether the questionnaire should always be answered by the individual or whether it can be used by family/friends on the patient's behalf.'

'how to answer when a question is ambiguous or the [information] given does not fit in with the suggested answer.'

Finally, one research nurse comment (4.5%) highlighted the importance of including PROM guidance in the participant information:

'… you haven't asked about putting this into the [participant] info sheets which is very important. The patients need to know exactly what is required of them…'

Discussion

Principal Findings

The survey findings support the generalizability of our qualitative evidence[14], suggesting there are inconsistencies in the way PROMs are administered by trial personnel, with regard to: the level of assistance given to participants during PROM completion; the timing with which PROMs are completed in relation to the clinical consultation and the way missing PRO data is monitored and acted upon.

This variability in PRO administration practice is problematic on two fronts. Where it exists between trials it may lessen the confidence with which different PRO trial results may be compared by key stakeholders, including: patients, clinicians, regulatory authorities and policy-makers. Where this variability is present in a single trial, however, it raises a number of concerns. First, marked differences reported in the level of assistance given to trial participants during PRO assessment may result in measurement variability within the study, reducing the quality of the trial data. In addition, increased assistance given to some participants could lead to response bias.[24] Second, the practice of administering PROM questionnaires after a clinical consultation may lead to PRO data contamination, as, if a participant receives bad news or undergoes an invasive procedure, this may colour their questionnaire responses.[22] Our data suggests that the timing of questionnaire delivery may not be consistent between individual trial staff, therefore, it may not be possible to compensate in the analyses for this potential confounder. Third, variation in the management of missing PRO data risks introducing bias as data is more likely to be missing from those participants in a trial with the poorest outcomes[6,8,9,11], who may be

concentrated in a particular arm of the trial, for example, if one intervention in the study results in greater levels of side effects or toxicity.[25] Accordingly, PRO trial design literature widely recommends that data collection staff should check completed questionnaires for missing data and follow-up with the participant (commonly face-to-face in the clinic immediately following completion, or later by phone or post) to complete any omissions where possible.[18] However, over one-fifth of research nurses and data manager respondents reported that they did not check completed PROMs for missing data. In addition, only 50% of those research nurses and 15% of data managers/coordinators checking forms, reported following up with participants to ensure the missing items/questionnaires were completed. It is concerning that a sizable proportion of staff did not routinely check for missing PRO data, however, the low rates of follow-up across all data collection personnel are more worrying: there is little point in monitoring missing data if nothing is done to rectify the situation. These findings suggest that a formal procedure needs to be in place for monitoring *and* responding to missing PRO items/questionnaires in trials. Communicating this procedure to all front-line staff may to help prevent the relatively high rates of missing PRO data seen in some studies.[10] Similarly, both the level of assistance given to participants and the timing of PROM completion should be considered at the trial design phase and appropriate procedures standardised across sites. Failure to standardize PRO assessment methods and minimize avoidable missing data reduces data quality, misuses valuable participant time and research resources, risks the introduction of bias and ultimately devalues these important patient-centred outcomes, undermining their usefulness in informing patient care and resulting in 'research waste'.[8,26]

Our previous qualitative data suggested a lack of PRO-specific guidance in the trial protocol and in the form of trial training.[14] The survey findings revealed mixed opinions in this area. Over two-thirds of trial management respondents reported giving instructions to data collection staff on how to administer the PROM questionnaire. Research nurses concurred that PRO information was commonly present in the protocol, whereas only half of data managers agreed. The research nurse reports are, however, at odds with other available evidence. A recent review of the PRO content of trial protocols[27g] found that instructions on the PRO rationale/hypothesis, data collection methods, training and management were frequently absent from the protocols. Research nurse free text comments in the survey appeared to align with these findings, suggesting that PRO protocol content could often consist of little more than a statement outlining that a PROM would be collected.

There was agreement between staff groups regard levels of PRO training. Less than one-third of research nurses and less than two-fifths of data managers reported receiving trial training that incorporated PRO guidance. Moreover, some staff reported PRO-specific training provision was inconsistent across trials and that training was not always accessible for staff entering a trial once it was underway.

Some research nurses in our survey questioned the usefulness of PRO-specific trial guidance, appearing to rely on their experience and judgment instead. Also, our regression model indicated that staff with greater experience (10 or more years) tended to report dealing more appropriately with missing PRO data, but trial protocol

g Chapter 8: Review of the PRO content of clinical trial protocols

content or training were not significant predictors. It is possible, however, that the protocol content and training received by the respondents did not contain adequate information on the management of missing data. A review of PRO protocol content[28] reported that under half of the protocols detailed plans to minimize levels of avoidable missing PRO data.

When asked about future trials, an overwhelming majority of research nurse and data manager respondents reported that more PRO information should be provided in trials. This contrasted somewhat with earlier answers in the survey indicating satisfaction with PRO protocol content. It would appear that respondents did not feel additional PRO-specific content in protocols was useful and that other mediums of information transfer would be more appropriate. For instance, during the latter survey questions, all groups appeared to agree that in future trials the bulk of PRO information should be provided to staff via trial training, with supporting information appearing in SOPs. Only a minority of respondents advocated additional PRO-specific protocol content and several suggested that PRO information should only be signposted in the trial protocol. Finally, views differed regarding the exact PRO information that should be provided to each professional group, indicating that each had different needs. This should be taken into account during the design of future trials collecting PROMs.

Strengths and Limitations of the Study

This study is the first to survey the opinions of researchers and trial personnel regarding the administration of PROs in trials. We were unable to determine an accurate response rate for the survey owing to the lack of an appropriate denominator.

Nevertheless, our large research nurse sample size should allow reasonably confident generalization of the results in this population. Due to their much smaller sample sizes, caution should be exercised when generalizing the results from the remaining sub-groups. As the survey was anonymised it was not possible to link staff together on a particular study. Thus, further work is needed to definitively establish whether the PRO administration variability seen in this survey may be present in a single trial.

Conclusions

The findings of this large-scale survey of clinical trial staff support the generalizability of qualitative evidence suggesting there are inconsistencies in the way PROMs are administered by trial staff, which may reduce the quality of PRO data and have the potential to introduce bias. There was general agreement amongst respondents that the provision of PRO guidance in future trials should be improved, with the majority of information included in trial training and SOPs, and signposted in the trial protocol.

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Author Contributions

The study was conceived by DK, JI, HD and MC. DK conducted the survey and completed the analysis, with input and supervision from MC, HD and JI. DK prepared the first draft of the manuscript. JI, HD and MC all provided edits and critiqued the manuscript for intellectual content.

Competing Interests

The authors have declared that no competing interests exist.

Abbreviations

PROs, patient-reported outcomes; PROMs, patient-reported outcome measures; SOPs, standard operating procedures; CPIs, chief and principal investigators.

Keywords

Survey; patient-reported outcomes; PROs; patient-reported outcome measures; PROMs; clinical trials; data collection.

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Chapter 5. PRO data collection in clinical trials: A survey of UK trial staff and management. Part 2 – PRO alerts

This Chapter presents the second of two papers outlining the results of a large-scale cross-sectional survey of UK-based trial staff and management, the aim of which was to determine the extent to which the qualitative findings presented in Chapter 2, could be generalised to the wider community of trial staff. The Chapter presents the results of the survey pertaining to the management of PRO alerts.

The following Chapter is presented in paper format and will be submitted to a peer-reviewed journal as:

Kyte D, Ives J, Draper H, Calvert M. Current Practices in Patient-Reported Outcome (PRO) Data Collection in Trials: A Survey of UK trial staff and management. Part 2 – PRO Alerts.

The work presented in this Chapter has been accepted for presentation as part of the following expert panel discussion:

- **Kyte D**, Brundage M, Basch E, Velikova G, King M, Calvert M. Monitoring Patient Reported Outcome Alerts in Clinical Trials and Routine Practice: An Expert Panel Discussion of Current Knowledge and Priority Areas for Research. *Symposium* - ISOQOL 21st Annual Conference in Berlin, Germany, 2014.

Title Page

Title

Current Practices in Patient-Reported Outcome (PRO) Data Collection in Trials: A Survey of UK trial staff and management. Part 2 – PRO Alerts.

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ABSTRACT

Background

Patient-reported outcomes (PROs) are an important endpoint increasingly used in clinical trials. Trial personnel involved in PRO data collection are often asked to check completed PRO questionnaires for missing items to optimize the quality of the data. A recent qualitative study has highlighted that in doing so, staff may be intermittently exposed to PRO alerts: 'concerning levels of psychological distress or physical symptoms that may require an immediate response.' Some staff reported responding to alerts in ways which could introduce bias. The purpose of the current study was to determine whether, and if so to what extent, these qualitative findings could be generalized to the wider community of trial staff.

Methods and Findings

We conducted an online cross-sectional survey of UK-based research nurses, data managers/coordinators, trial managers and chief/principal investigators (CPIs) involved in clinical trials collecting PROs. Participants were recruited from all 55 UK Clinical Research Collaboration Registered Clinical Trials Units and 19 Comprehensive Local Research Networks. We undertook descriptive analyses of the quantitative data and directed thematic analysis of free-text comments. 767 respondents completed the survey. 33.8% of research nurses, 46.7% of data managers/coordinators, 46.2% of trial managers and 50.0% of CPIs reported encountering PRO alerts previously. Of these, 82.9% research nurses and 53.8% data managers/coordinators reported taking action in response to a PRO alert in order to assist the trial participant, but <50.0% were able to record the intervention in the trial

documentation. 84.4% of research nurses, 64.3% of data managers/coordinators, 84.3% of trial managers and 86.1% of CPIs reported that specific PRO alert protocol content was needed in future trials.

Conclusions

Trial staff are intermittently exposed to PRO alerts. They may intervene to aid the trial participant, but may not record the intervention in the trial documentation, potentially risking co-intervention bias. Guidance and training is needed, which supports data collection personnel to manage PRO alerts appropriately, protecting the interests of the trial participant whilst avoiding potential bias.

Introduction

Patient-reported outcomes (PROs) are an important 'patient-centred' endpoint increasingly used in clinical trials.[1] PROs are used by patients, clinicians, drug licensing committees and policy makers to inform significant health-care decisions.[2-4] PRO trial data must therefore be of high quality. One way of maximising the quality of data is to take steps to minimise avoidable missing PRO data, which can be a common problem.[5-8] In some trials front-line research personnel involved in PRO data collection are encouraged to check completed questionnaires for missing items.[9] In so doing, recent qualitative evidence[10] suggests staff may encounter PRO data displaying 'concerning levels of psychological distress or physical symptoms that may require an immediate response', known as a 'PRO alert'.[11] Examples include extreme PROM scores or worrying additional comments recorded on the questionnaire, which were usually read on collection of the completed PROM from the participant or sometimes at the point of data entry.[11] In the absence of trial level guidance, some staff reported providing off-protocol interventions to aid trial participants, which went un-recorded. This could result in co-intervention bias.

The aim of the current study was to determine whether these qualitative findings could be generalised to the wider community of trial staff, to explore how frequently PRO alerts are experienced and by which staff, and to determine how they are currently managed in practice. This is the second of two papers outlining the results of a large-scale cross-sectional survey of UK-based trial staff and management.[12h]

[h] Chapter 4 - Current Practices in Patient-Reported Outcome (PRO) Data Collection in Trials: A Survey of UK trial staff and management. Part 1 – PRO Administration.

Methods

Ethics

A favourable ethical review was received from the West Midlands Research Ethics Committee in April 2012 (ref no 12/wm/0068).

Study Design, Sample and instruments

The study design, sample and instruments are reported in detail in the first survey report.[12] In summary, an anonymised online cross-sectional survey of UK-based research nurses, data managers/coordinators, trial managers and chief and principal investigators (CPIs) involved in clinical trials using either a primary or secondary PRO was undertaken. Recruitment was conducted through all 55 UK Clinical Research Collaboration Registered Clinical Trials Units (CRC-RCTUs) Network and 19 National Institute for Health (NIHR) Comprehensive Local Research Networks (CLRNs). We utilised four online survey instruments (developed by DK and revised with input from MC, HD and JI) hosted by www.surveymonkey.com, which were informed by our qualitative study[10], with one instrument for each participant group. Pilot testing was undertaken and minor alterations were made to the number and location of free-text comments boxes. The results presented here relate to survey questions on the following: (1) whether respondents had encountered 'concerning' PRO trial data in the past; (2) what, if any actions they had taken in response to this PRO alert, (3) whether they had been able to record their actions within the trial documentation, (4) what PRO alert trial training/guidance they had received, (5) what actions they might take in a future trial in response to a PRO alert, and (6) what PRO alert training/guidance they would like to see provided in future trials.

Analysis

Descriptive quantitative analysis was used to examine participant characteristics and survey responses. All analysis was conducted using SPSS© (version 21, IBM©). In addition, DK analysed free-text comments using directed content analysis, where findings from our previous qualitative work[10] were used to develop the initial coding framework.[13] Additional codes were developed as the analysis was conducted and the framework was modified as required.[13] JI formally reviewed all coding to enhance trustworthiness, and any coding disagreements were discussed and resolved.

Results

767 participants responded to the anonymised online survey (560 research nurses, 129 trial managers, 41 data managers/coordinators and 37 CPIs). As neither the UK CRC-CTUs nor the NIHR CLRNs held data regarding the number of staff involved in trials with a primary or secondary PRO, we were not able to determine a denominator or response rate. Participant characteristics are presented in Table 1. The majority of research nurse and CPI respondents were aged between 46 and 55, whilst data managers/coordinators and trial managers taking part in the survey were 26 to 35 years of age. A majority of all respondent groups reported at least 1-3 years of research experience, with CPIs commonly reporting in excess of 10 years experience in a research role. Most participants reported that their last PRO trial had taken place in the primary care setting and incorporated the five dimension European Quality of Life (EQ-5D)[14] instrument. The survey results are presented in Table 2 and the key findings are summarized below. The themes generated during the content analysis of free-text comments are also presented below, alongside the proportion of associated comments and illustrative respondent quotations.

Table 1. Characteristics of participants

Participant Characteristics	No. (%) Research Nurse Participants[a] (n=560)	No. (%) Data Manager Participants[a] (n=41)	No. (%) Trial Manager Participants[a] (n=129)	No. (%) Chief & Principle Investigator Participants[a] (n=37)
Age, years				
≤25	4 (0.7)	3 (7.9)	4 (3.1)	0 (0)
26-35	95 (17)	14 (36.8)	51 (39.5)	5 (13.5)
36-45	193 (34.5)	10 (26.3)	43 (33.3)	11 (29.7)
46-55	217 (38.8)	8 (21.1)	23 (17.8)	14 (37.8)
≥56	51 (9.1)	3 (7.9)	8 (6.2)	7 (18.9)
Years in research role				
<1	51 (9.2)	4 (10.5)	12 (9.3)	0 (0)
1-3	208 (37.3)	13 (34.2)	42 (32.6)	11 (29.7)
4-6	147 (26.4)	7 (18.4)	31 (24)	4 (10.8)
7-9	50 (9)	4 (10.5)	12 (9.3)	5 (13.5)
≥10	101 (18.1)	10 (26.3)	32 (24.8)	17 (45.9)
Setting of most recent clinical trial collecting PROMs[b]				
Primary care	112 (20.7)	15 (39.5)	47 (37.9)	16 (44.4)
Secondary care	428 (79.3)	23 (60.5)	77 (62.1)	20 (56.6)
Clinical areas covered by most recent clinical trial collecting PROMs[b]				

Cardiovascular	69 (16.5)	3 (9.4)	10 (10)	0 (0)
Elderly care	17 (4.1)	2 (6.3)	10 (10)	2 (7.4)
General medicine	39 (9.3)	2 (6.3)	7 (7)	0 (0)
General practice	19 (4.5)	3 (9.4)	23 (23)	9 (33.3)
Neurology	51 (12.2)	1 (3.1)	9 (9)	4 (14.8)
Obstetrics & gynaecology	22 (5.3)	3 (9.4)	7 (7)	2 (7.4)
Oncology	119 (28.5)	15 (46.9)	28 (28)	1 (3.7)
Opthalmology	8 (1.9)	1 (3.1)	4 (4)	7 (25.9)
Orthopaedics	35 (8.4)	1 (3.1)	7 (7)	1 (3.7)
Paediatrics	35 (8.4)	2 (6.3)	9 (9)	6 (22.2)
Respiratory	41 (9.8)	5 (15.6)	8 (8)	3 (11.1)
Rheumatology	47 (11.2)	1 (3.1)	6 (6)	5 (18.5)
PROMs used in most recent clinical trial collecting PROMs[b]				
EuroQol EQ-5D	401 (76.1)	25 (67.6)	99 (82.5)	24 (80)
Health Assessment Questionnaire (HAQ)	154 (29.2)	1 (2.7)	4 (3.3)	2 (6.7)
Nottingham Health Profile (NHP)	0 (0)	0 (0)	0 (0)	0 (0)
SF-12® Health Survey or SF-12v2™ Health Survey	36 (6.8)	6 (16.2)	22 (18.3)	7 (23.3)
SF-36® Health Survey or SF-36v2™ Health Survey	104 (19.7)	5 (13.5)	17 (14.2)	6 (20)
Hospital Anxiety and Depression scale (HAD)	115 (21.8)	4 (10.8)	21 (17.5)	11 (36.7)

Arthritis Impact Measurement Scales (AIMS2)	3 (0.6)	0 (0)	0 (0)	2 (6.7)
EORTC QLQ - C30 (Core Questionnaire)	106 (20.1)	9 (24.3)	18 (15)	0 (0)
Minnesota Living with Heart Failure© Questionnaire (MLHF)	9 (1.7)	0 (0)	1 (0.8)	1 (3.3)
Oxford Hip Score (OHS)	9 (1.7)	0 (0)	0 (0)	1 (3.3)
Oxford Knee Score (OKS)	14 (2.7)	1 (2.7)	0 (0)	0 (0)
Roland-Morris Disability Questionnaire (RMDQ)	2 (0.4)	0 (0)	2 (1.7)	4 (13.3)

[a]Columns may not add up to n due to missing values
[b]Participants could select multiple categories

Table 2. Questionnaire Responses

Survey Question	Research Nurse Response Count (%)[a]	Data Manager Response Count (%)[a]	Trial Manager Response Count (%)[a]	Chief and Principal Investigator Response Count (%)[a]
Some research nurses have reported encountering Quality of Life/Patient-Reported Outcome questionnaires containing answers which raise concern for the wellbeing of the trial participant in some way. This information has been termed: 'concerning' Patient-Reported Outcome information. Have you ever encountered any 'concerning' Patient-Reported Outcome information within a trial?				
"Yes."	176 (33.8)	14 (46.7)	55 (46.2)	18 (50.0)
"No."	318 (61.0)	14 (46.7)	62 (52.1)	18 (50.0)
"Not applicable/Don't know."	27 (5.2%)	2 (6.7)	2 (1.7)	0 (0.0)
Have you ever taken action in response to 'concerning' Patient-Reported Outcome information you have encountered within a trial, in order to assist a trial participant?				
"Yes."	145 (82.9)	7 (53.8)	25 (47.2)	15 (83.3)
"No."	30 (17.1)	6 (46.2)	27 (50.9)	3 (16.7)
Were you able to record all action(s) taken in response to the 'concerning' Patient-Reported Outcome information, in the trial documentation?				
"Yes."	81 (46.0)	4 (30.8)	-	-
"No."	67 (38.1)	4 (30.8)	-	-
"Not applicable."	28 (15.9)	5 (38.5)	-	-
Was there a mechanism in place to record all action(s) taken in response to the 'concerning' Patient-Reported Outcome information, in the trial documentation?				
"Yes."	-	-	25 (47.2)	13 (72.2)

"No."	-	-	27 (50.9)	4 (22.2)
"Not applicable."	-	-	1 (1.9)	1 (5.6)
If your data collection staff were to encounter 'concerning' Patient-Reported Outcome information in a future trial, for example, evidence of anxiety or depression, which of the following would you expect them to do? PLEASE TICK ALL THAT APPLY				
"Not to intervene, it is the responsibility of the trial participant's GP and regular healthcare team to monitor and deal with quality of life related disorders such as anxiety and depression, not the trial staff."	-	-	27 (24.3)[b]	4 (12.1)[b]
"To discuss the findings with their line manager in the trial, or with the PI."	-	-	88 (79.3)[b]	27 (81.8)[b]
"To discuss the findings with a colleague."	-	-	9 (8.1)[b]	7 (21.2)[b]
"To discuss the findings with the participant."	-	-	27 (24.3)[b]	17 (51.5)[b]
"Using their discretion, arrange an appointment with the patient's GP or other appropriate healthcare professional."	-	-	19 (17.1)[b]	10 (30.3)[b]
If you were to encounter 'concerning' Patient-Reported Outcome information in a future trial, for example, evidence of anxiety or depression, which of the following might you consider doing? PLEASE TICK ALL THAT APPLY				
"I would not intervene, it is the responsibility of the trial participant's GP and regular healthcare team to monitor and deal with quality of life related disorders such as anxiety and depression, not the trial staff."	13 (2.6)[b]	11 (42.3)[b]	-	-
"I would not intervene, there is nothing I could do."	-	2 (7.7)[b]	-	-
"I would discuss the findings with my line manager in the trial, or with the PI."	389 (77.5)[b]	14 (53.8)[b]	-	-
"I would discuss the findings with a colleague."	111 (22.1)[b]	1 (3.8)[b]	-	-
"I would discuss the findings with the participants research nurse."	-	11 (42.3)[b]	-	-
"I would discuss the findings with the participant."	335 (66.7)[b]	-	-	-

"Using my discretion, I would arrange an appointment with the patient's GP or other appropriate healthcare professional."	119 (23.7)[b]	-	-	-
What particular information on Quality of Life/Patient-Reported Outcome measurement was given to the data collection staff? Please read the options below and in each case select either 'included in trial protocol, training or SOP', or 'not included'. [LAST TRIAL]				
"How to deal with Quality of Life/Patient-Reported Outcome information that raises concern for the wellbeing of the trial participant (e.g. a questionnaire indicating severe anxiety or depression)."	-	-	**Included** 31 (38.3)	**Included** 22 (75.9)
Please read the following statements. In each case, please answer 'yes', 'no', or 'unsure'				
"There is usually specific guidance on dealing with 'concerning' Patient-Reported Outcome information contained in trial protocols."	**Y** 65 (12.7) **N** 265 (52.0) **UN** 180 (35.3)	**Y** 8 (28.6) **N** 14 (50.0) **UN** 6 (21.4)	-	-
"I have usually had trial training on what to do if I encounter 'concerning' Patient-Reported Outcome information."	**Y** 59 (11.6) **N** 417 (81.9) **UN** 33 (6.5)	**Y** 6 (21.4) **N** 21 (75.0) **UN** 1 (3.6)	-	-
"I feel confident about dealing with 'concerning' Patient-Reported Outcome trial information."	**Y** 279 (54.5) **N** 97 (18.9) **UN** 136 (26.6)	**Y** 11 (39.3) **N** 8 (28.6) **UN** 9 (32.1)	-	-
Please read the following statements. In each case, please indicate whether you 'strongly agree', 'agree', have 'no opinion', 'disagree' or 'strongly disagree' with the statement. [Future Trials]				

"There should be specific protocol content and trial training on how to deal with 'concerning' Patient-Reported Outcome information, in trials employing such outcomes."	**SA** 140 (36.5) **A** 283 (54.1) **NO** 57 (6.4) **D** 20 (2.8) **SD** 1 (0.2)	**SA** 7 (25.0) **A** 11 (39.3) **NO** 5 (17.9) **D** 4 (14.3) **SD** 1 (3.6)	**SA** 27 (47.2) **A** 70 (60.9) **NO** 12 (10.4) **D** 5 (4.3) **SD** 1 (0.9)	**SA** 14 (38.9) **A** 17 (47.2) **NO** 3 (8.3) **D** 2 (5.6) **SD** 0 (0.0)
Thinking about the future. What particular Quality of Life/Patient-Reported Outcome guidance should be included the trial protocol, what should be included in trial training, and what should be included in a standard operating procedure?				
"When/how to deal with 'concerning' Quality of Life/Patient-Reported Outcome information."	**TP** 10 (37.0) **TT** 20 (74.1) **SOP** 13 (48.1)	**TP** 270 (55.3) **TT** 407 (83.4) **SOP** 283 (58.0)	**TP** 49 (43.8) **TT** 95 (84.8) **SOP** 77 (68.8)	**TP** 15 (46.9) **TT** 27 (84.4) **SOP** 28 (87.5)

Abbreviations: TP, Trial Protocol; TT, Trial Training; SOP, Standard Operating Procedure; Y, Yes; N, No; SA, Strongly Agree; A, Agree; NO, No Opinion; D, Disagree; SD, Strongly Disagree. '-', not applicable [a]Columns may not add up to n due to missing values. [b]Participants could select multiple categories

PRO Alerts: Respondent Experiences

Alert encounters and responses

Survey respondents were asked if they had ever encountered 'concerning' PRO data within a trial and, if so, whether they had taken any action in response to it. 33.8% of research nurses, 46.7% of data managers/coordinators, 46.2% of trial managers and 50.0% of CPIs reported encountering such data (Figure 1). Of these, 82.9% research nurses, 53.8% data managers/coordinators, 47.2% trial managers and 83.3% of CPIs reported taking action aimed at assisting the trial participant.

Free-text comments concerning PRO alert discovery and response

There were 144 comments in this section, predominantly provided by research nurses. Comments revealed variation in the factors reported to trigger a PRO alert for different individuals. The majority of comments (28.5%) cited signs of depression and/or suicidal ideation as the initial trigger:

> *'… patient who repeatedly said she was fine in clinic but scored high for depression… consultant and I discussed scores with patient, referred to hospital psychologist… GP prescribed antidepressants.' [Research Nurse]*
>
> *'Patient reported suicidal feelings… reported to co-investigator and PI.' [Research Nurse]*

Some reported responding to signs of 'low mood' or reduced mental-wellbeing (21.8%):

> *'Expression of overwhelming not coping or sadness – use[d] the form completion as an opening to start discussion about the fact there may be an issue and refer to those who can help…' [Research Nurse]*

A number of comments cited specific (extreme) questionnaire scores as a potential alert trigger (11.8%):

> *'If HAD scores were over 11 then we reported them to the GP with the participant's consent. We*

also had a psychologist attached to the cardiac rehab team who would take referrals with the participant's consent.'[Research Nurse]

'…abnormal HADs scores are reported to the participant's GP. Trial nurses/Doctors have also been alerted if something needs following up' [Data Manager]

'a 12 year old scored 30 on a quality of life health questionnaire, I informed her consultant who was also the study PI and her specialist nurse.' [Research Nurse]

Some comments (5.6%) suggested staff also responded to signs of reduced physical wellbeing (e.g. pain, discomfort, vomiting):

'Pain score was severe therefore I reported it to the relevant clinician. I then ensured that this had been acted upon.' [Research Nurse]

Free-text comments outlining the actions taken in response to an alert suggested some variability amongst respondents. Most comments indicated that staff tended to refer to (and/or discuss findings with) a clinically qualified professional external to the trial team (commonly the participant's GP) (48.6%), often with the participant's prior permission (11.8%):

'… patient may express concerns re their analgesia, deteriorating symptoms, need for help with psycho-social issues. I make an entry into the notes and alert the healthcare professional responsible for the participant's care via email.' [Research Nurse]

'During a mental health trial I reported concerns to a GP with the participant's permission due to the nature of answers given.' [Research Nurse]

Other comments (18.1%) suggested staff discussed alert findings directly with the trial participant:

'Discussed the issue with participant to see if any further action… required' [Research Nurse]

Several respondents commented that they usually advised the participant to seek medical advice independently (13.9%):

'Advised them to make an appointment to see their GP' [Research Nurse]

15.3% of free-text comments suggested staff informed members of the trial

management team:

> *'Higher than previously reported depression score. I fed the information back to the PI once I had chatted to the patient to establish that they had answered honestly and accurately' [Research Nurse]*
>
> *'Spoke with the PI immediately in order to ascertain whether an urgent psychological review was required.' [Research Nurse]*

Finally, 6.9% of comments suggested there were formal trial procedures in place to handle PRO alerts:

> *'We wrote it in the trial protocol that we would contact the patients clinician if they scored highly in the HADS questionnaire.' [Trial Manager]*
>
> *'Official process (explained in PIS) for alerting investigators if participants responses on [questionnaire] …suggested suicidal ideation.'[Trial Manager]*

Alert documentation

Respondents involved in trial management (trial managers and CPIs) were asked, with regard to the most recent trial they were involved in, if there was a mechanism in place to record actions taken in response to a PRO alert. 72.2% of CPIs and 47.2% of trial managers reported that such a mechanism was present. Whereas, 46.0% of research nurses and 30.8% of data manager/coordinators reported that they had been able to record their PRO alert actions in the trial documentation.

Free-text comments concerning alert documentation

There were 46 free-text comments in this section, predominantly provided by research nurses and trial managers. There was some disparity between the groups' responses regarding how action taken following a PRO alert was recorded. 51.6% of research nurse comments suggested that actions were recorded in the participant's general medical notes:

'This was not something that the trial documentation was designed for so concerns and actions would have been documented in patient's notes.' [Research Nurse]

However, 53.3% of trial manager comments reported that alert responses were recorded in the trial documentation as a file note and 26.7% reported the use of a specific database entry:

'Comments entered on database, copy of questionnaire kept in file (as usual), and documentation of telephone calls with patient and GP, and copy of fax to GP all retained in file.' [Trial Manager]

A small number of comments from both groups (research nurses, 6.5%; trial managers, 13.3%) suggested action in response to alerts would be detailed in a 'formal risk report', Adverse Event (AE) or Serious Adverse Event (SAE):

'Risk reports always have to be completed and sent to the GP' [Trial Manager]

'…it would be noted as an AE and recorded accordingly' [Research Nurse]

One trial manager comment (2.2%) outlined that responses to alerts had been reported to the NHS trust involved in the research and subsequently at a trial steering group meeting:

'Written evidence that CI and Trial Manager were fully informed. After event, full report provided to the NHS Trust. For trial documentation, detailed anonymised file note and written approval filed from the CI stating they were happy with the way the event was handled and that all procedures were followed appropriately. Event briefly reported (due to confidentiality) at Trial Steering Group.'

PRO Alerts: Future Actions

In this section of the questionnaire, trial management and front-line data collection staff were asked how they would manage PRO alerts in future trials. Figure 2 summarises the responses of each of the professional groups.

Trial Management Staff

CPIs and trial managers were asked how they would expect their data collection staff to manage PRO alerts in future trials. 81.8% of CPIs and 79.3% of trial managers suggested that staff should discuss the findings with their line manager/ principal investigator, or with the trial participant (51.5% and 24.3% respectively). Fewer, 30.3% of CPIs and 17.1% of trial managers, felt it was appropriate for data collection staff to use their discretion and arrange an appointment with the participant's GP or other appropriate healthcare professional. A minority, 12.1% of CPIs and 24.3% of trial managers, felt staff should not intervene, favouring leaving the participant's GP and clinical team to monitor and deal with emerging health issues. Finally, 21.2% of CPIs and 8.1% of trial managers, thought that data collection staff should discuss the alert with a colleague.

Front-line Staff

Research nurses and data managers/coordinators were asked how they would respond to a PRO alert in a future trial. A majority of both groups, 77.5% of research nurses and 53.8% of data managers/coordinators, indicated they would discuss the findings with their line manager or the PI. 66.7% of research nurses said they would discuss findings with the trial participant and 23.7% that they would use their discretion and arrange an appointment with the participant's GP if necessary. A lower proportion, 22.1% of research nurses and 3.8% of data managers/coordinators, reported that they would discuss alert findings with a colleague. Just 2.6% of research nurses indicated that they would not intervene if they encountered a PRO alert. A greater proportion of trial managers/coordinators indicated they would refrain from intervening, either because they felt the participant's GP should manage health issues (42.3%) or because they felt there was nothing they could do to help (7.7%).

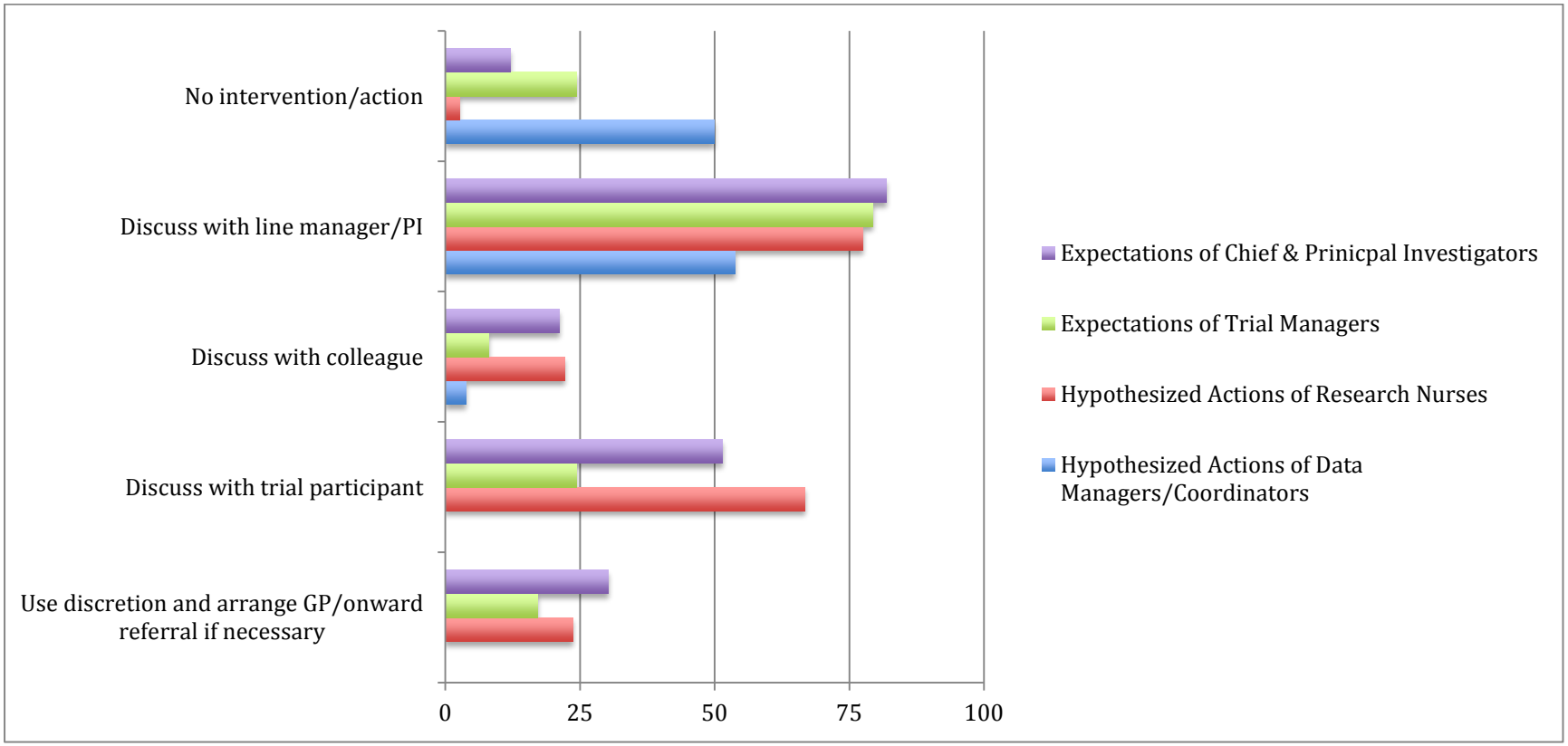

Figure 1. Respondent views on future PRO alert actions

PRO Alerts: Trial Guidance

75.9% of CPIs and 38.3% of trial managers reported that alert guidance was included either in the protocol or in training/SOPs provided during the most recent trial in which they had been involved. In contrast, 12.7% research nurses and 28.6% data managers/coordinators reported the presence of such guidance. Similarly, only 11.6% of research nurses and 21.4% of data managers/coordinators reported receiving trial training incorporating PRO alert guidance.

84.4% of research nurses, 64.3% of data managers/coordinators, 84.3% of trial managers and 86.1% of CPIs agreed or strongly agreed that there should be specific protocol content and trial training on how to deal with 'concerning' PRO information, in trials employing such outcomes. Survey respondents were asked where such information should appear: the trial protocol, in trial training, or in supporting trial documentation (e.g. SOPs). Options selected by a majority (> 50%) of respondents in each group are presented in Table 3 and summarized below.

The majority of all groups selected the option for guidance to be included in trial training (research nurses, 74.1%; data managers/coordinators, 83.4%; trial managers 84.8%; CPIs, 84.4%). A majority of data managers/coordinators, trial managers and CPIs also opted for the inclusion of guidance in SOPs (58.0%, 68.8% and 87.5% respectively). Data managers/coordinators were the only group who selected inclusion of guidance in the trial protocol (55.3%).

Table 3. Future PRO Alert guidance provision

	Trial Protocol				Trial Training				SOP			
PRO-specific information	**RN**	**DM**	**TM**	**CI**	**RN**	**DM**	**TM**	**CI**	**RN**	**DM**	**TM**	**CI**
"When/how to deal with 'concerning' PRO information."		*			*	*	*	*		*	*	*

Abbreviations: RN, research nurses; DM, data managers; TM, trial managers; CPI, chief and principle investigators; '*'= Items supported by >50% of respondents per group

Discussion

The purpose of this study was to determine to what extent our qualitative findings regarding the management of PRO alerts in trials, could be generalised to the wider community of trial staff. In addition, we aimed to explore how broadly PRO alerts are experienced, and to determine how they are currently managed in practice.

Principal findings

Ours is the first quantitative study investigating the phenomenon of PRO alerts in clinical trials. The survey findings support the generalizability of our qualitative evidence[10], suggesting that: a broad range of trial staff intermittently encounter PRO alerts and some intervene to aid the trial participant in question, but do not necessarily record their interventions in the trial documentation. Furthermore, our data suggest there may be a lack of PRO alert guidance for front-line data collection staff, both in trial protocols and training. This may in-part explain the wide variation seen in our sample with regard to the factors that trigger a PRO alert for different individuals, the nature of their subsequent response, and the method with which the response may be recorded in the trial.

A minority of respondents indicated they would not respond to a PRO alert because they felt the participant's regular GP and healthcare team should manage the situation. It is not clear, however, how potential participant distress captured by a trial PROM would be discovered and managed in routine practice. It is not yet common for clinicians to ask their patients to routinely complete PROMs for monitoring purposes or to guide 'real-time' clinical decisions in the UK. Thus, they may not be aware of the deterioration in a patient's wellbeing that is recorded in a trial PROM. Moreover,

unless they are given information to the contrary, trial participants may assume that their PRO responses will followed-up by the trial team and therefore not think it necessary to contact their GP for help. If so, where a research team does not monitor and respond to a PRO alert, the participant may not be offered appropriate care, potentially leading to unnecessary suffering and poorer outcomes. Participants experiencing poor quality of life are more likely to drop out of trials, increasing rates of missing data and potentially affecting the integrity of trial results.[15] More importantly, neglecting to respond to a PRO alert arguably represents an abdication in responsibility by the study team who are ethically and legally bound to place the safety and wellbeing of research participants ahead of the interests of the trial.[16-19]

On the other hand, study personnel who do respond to a PRO alerts may potentially influence the primary outcome of a trial by unwittingly introducing 'co-intervention bias'. This is bias caused by "any intervention other than the experimental manoeuvre that alters the frequency of a trial's outcome of interest."[20] For instance, in some trials, higher levels of toxicity or side effects experienced by participants in one study group may lead to more co-interventions, potentially resulting in an overestimation of the benefits (including cost-effectiveness) of treatment delivered in that arm of the trial.

Unrecorded PRO alert co-interventions are particularly problematic as they go unrecognised by the trial management group and cannot be adjusted for during the analysis. Although a number of CPIs responding to our survey reported that mechanisms were usually in place to record such co-interventions, more than half of trial manager/research nurse respondents and more than two-thirds of data

managers/coordinators disagreed. Moreover, those who were able to record their alert response appeared to do so in different ways. Trial managers detailed actions in the trial documentation, whereas research nurses used participant medical notes, and a small number of trial staff reported alerts as AE's. The potential loss of this data to the trial (if unrecorded or un-retrievable) may affect cost-effectiveness' analyses, leading to underestimated resource use. This variation needs to be addressed and steps should be taken to ensure that all co-interventions are recorded in a consistent manner and appropriately monitored so they are available for analysis where appropriate.

Although CPI respondents felt that adequate PRO alert guidance was provided in trial protocols and training, more than one-half of trial managers, two-thirds of data managers/coordinators and four-fifths of research nurses felt guidance was lacking. The responses of these latter groups are consistent with the results of a recent study evaluating the PRO-specific content of trial protocols[21g], where only 11% of protocols were found to include PRO alert guidance. More than three-fifths of survey respondents wanted specific protocol content and trial training on how to deal with PRO alerts. We suggest that trial management groups should acknowledge both the potential for (and the implications of) PRO alerts in the design phase of the study and should produce appropriate management instructions, made available to all data collection staff, where alerts are a possibility. The exact methods with which PRO alerts are monitored and managed in a trial are open to debate and have been discussed in detail elsewhere.[11] It is likely that each trial will need to carefully consider the risk profile of their study before deciding on the optimal alert management procedures that should be in place.

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g Chapter 8: Review of the patient-reported outcome (PRO) content of clinical trial protocols

Guidance on how to manage PRO alerts is also lacking in the literature.[22] This may explain the absence of agreement between our survey groups regarding the most appropriate way to manage PRO alerts in future trials. There is therefore a need to develop consensus guidelines on PRO alert management in clinical trials, aimed at supporting appropriate PRO trial design and outlining the key considerations for researchers. Furthermore, trial teams should ensure that participants understand how their PRO data will be used in the study, including who will access the data and for what purpose. As a minimum, patient information and consent documentation should include PRO data collection information where appropriate.

Strengths and limitations of the study

Determining an accurate response rate for the survey was difficult owing to the lack of an appropriate denominator. It is therefore possible that our respondents were self-selecting. This group may be more likely to include those with an interest in PROs, whose data could represent that of the most knowledgeable trial personnel. This should be taken into account when interpreting the results of the study. The large research nurse and sample size in this study enhances generalizability of the results in this group. Further research is needed to establish the external validity of the results for the other respondent groups (data managers/coordinators, trial mangers, CPIs) owing to their lower sample sizes. As the survey was anonymised it was not possible to link staff together on a particular study. Further work is needed to establish if the PRO alert management and co-intervention variability seen in this survey may be present in a single trial.

Conclusions

Trial staff intermittently encounter PRO alerts. Some staff intervene to aid participants, but may not be able record the co-intervention in the trial documentation, meaning interventions may not be accounted for in the analysis, potentially leading to co-intervention bias. There is a need for consensus guidelines to assist researchers involved in PRO trial design. Guidelines should aim to encourage trial management groups to have an *a priori* plan in place to deal with PRO alerts, to ensure that participants in need are managed appropriately, whilst also facilitating unbiased PRO data collection and analysis.

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Author Contributions

The study was conceived by DK, JI, HD and MC. DK conducted the survey and completed the analysis, with input and supervision from MC, HD and JI. DK prepared the initial manuscript. JI, HD and MC all provided edits and critiqued the manuscript for intellectual content.

Competing Interests

The authors have declared that no competing interests exist.

Abbreviations

PROs, patient-reported outcomes; PROMs, patient-reported outcome measures; SOPs, standard operating procedures; CPIs, chief and principal investigators.

Keywords

PROs, patient-reported outcomes; PROMs, patient-reported outcome measures; SOPs, standard operating procedures; clinical trials; trial protocol; trial design; PRO alerts

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Chapter 6. PRO guidance for front-line data collection staff in clinical trials

Chapter 2 presented qualitative findings that suggested trial personnel perceive PRO-specific protocol content and training in trials to be inadequate. Chapters 4 and 5 outlined survey findings which, with regard to trial training, presented similar results. This 'triangulation' of data gives greater confidence in the results. The survey also, however, highlighted disagreements between trial staff and management about the adequacy of the PRO-specific content of trial protocols. It therefore remains unclear whether, and if so which, PRO sections in trial protocols may be in need of improvement. In the absence of existing research, it is also unclear what PRO-specific guidance may be available for trial data collection staff in the published literature.

The purpose of the following three Chapters is to examine the PRO-specific guidance available to trial staff and management, both in the literature and in contemporary trial protocols. Chapter 6 presents a systematic review of published PRO guidance for front-line data collection staff involved in the administration of trial PROs. Chapter 7 reviews the published guidance available to protocol developers and Chapter 8 investigates the PRO-specific content of NIHR HTA trial protocols.

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Patient Reported Outcomes (PROs) in Clinical Trials: Is 'In-Trial' Guidance Lacking?

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PLOS ONE

Patient Reported Outcomes (PROs) in Clinical Trials: Is 'In-Trial' Guidance Lacking? A Systematic Review

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Abstract

Background: Patient reported outcomes (PROs) are increasingly assessed in clinical trials, and guidelines are available to inform the design and reporting of such trials. However, researchers involved in PRO data collection report that specific guidance on 'in-trial' activity (recruitment, data collection and data inputting) and the management of 'concerning' PRO data (i.e., data which raises concern for the well-being of the trial participant) appears to be lacking. The purpose of this review was to determine the extent and nature of published guidelines addressing these areas.

Methods and Findings: Systematic review of 1,362 articles identified 18 eligible papers containing 'in-trial' guidelines. Two independent authors undertook a qualitative content analysis of the selected papers. Guidelines presented in each of the articles were coded according to an *a priori* defined coding frame, which demonstrated reliability (pooled Kappa 0.86–0.97), and validity (<2% residual category coding). The majority of guidelines present were concerned with 'pre-trial' activities (72%), for example, outcome measure selection and study design issues, or 'post-trial' activities (16%) such as data analysis, reporting and interpretation. 'In-trial' guidelines represented 9.2% of all guidance across the papers reviewed, with content primarily focused on compliance, quality control, proxy assessment and reporting of data collection. There were no guidelines surrounding the management of concerning PRO data.

Conclusions: The findings highlight there are minimal in-trial guidelines in publication regarding PRO data collection and management in clinical trials. No guidance appears to exist for researchers involved with the handling of concerning PRO data. Guidelines are needed, which support researchers to manage all PRO data appropriately and which facilitate unbiased data collection.

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Introduction

Patient reported outcomes (PROs) such as health-related quality of life (HRQL) are increasingly assessed in clinical trials.[1–3] PROs provide researchers, clinicians and patients with important information regarding the effect of a disease and its treatment: on symptoms (for example, pain or fatigue) and on HRQL or satisfaction with care.[4] In general, patients participating in a trial do not directly benefit from completing a PRO questionnaire. This approach is adopted to ensure trial participants are not tempted to tailor their answers in order to influence the treatment they receive within a study, which is a potential source of bias.[5,6] PRO results are therefore used to inform the care of future patients[6], who, with their clinicians, may use PRO data to inform significant health-care decisions. For example, between interventions offering similar survival or progression-free survival rates, or those that have differing trade-offs between therapeutic benefit and undesirable side-effects.[4] Thus, it is crucial that PROs are administered and processed in an un-biased way.

In order to ensure high quality PRO trial data, consistent and rigorous standardised data collection methods should be used throughout a trial.[7] The use of standardised methods should serve to minimise errors, measurement variability, missing data and systematic bias, thus contributing to the validity of trial results.[8] Local site staff require access to 'in-trial' (i.e. recruitment, data collection and data inputting, see Box S1) guidelines that clearly outline the standardised methods in-use, so that all study personnel may fully incorporate them into practice. Such guidelines should be contained within the trial protocol, supported by standard operating procedures (SOPs) where appropriate.

It is of concern, therefore, that anecdotal evidence - obtained during national quality of life training days run by the MRC Midland Hub for Trials Methodology in the UK - suggests that in-trial PRO guidelines are not routinely included within trial documentation and that, as a result, unstandardised PRO data collection may be common. Researchers also report feeling particularly uncomfortable that they receive no specific guidance on how to manage 'concerning' PRO data, i.e. data that might

raise concern for the wellbeing of the trial participant in some way. Staff encountering such data - commonly represented by markedly low HRQL scores, or unexpected unprompted additional information recorded on the back of questionnaires - were therefore unsure where their responsibility should lie, or whether they should be viewing this information in the first place. In this situation, some described experiencing a 'dual-role' tension between their concurrent responsibilities as a clinician and researcher: the duty to act upon the information to benefit the patient verses that of protecting trial integrity by not intervening. In some instances, reports indicated that off-protocol concomitant interventions had been administered, some of which may not have been captured by standard trial reporting mechanisms. Such interventions have the potential to bias trial results. These anecdotal reports have since been supported by a recently completed qualitative study, in which we used semi-structured interviews to explore the experiences of 26 research nurses, research facilitators, trial coordinators and data managers across three NHS sites and two clinical trials units in the UK[9] (under review). This study confirmed a potential for bias associated with concerning PRO data, during both postal or clinic-based and self-reported or researcher/research nurse-assisted data collection.

These reports suggest a lack of in-trial PRO guidance, with a subsequent absence of systematic monitoring of potentially concerning PRO data and a resulting risk of bias. It is uncertain, however, whether they also reflect a deficiency in the published literature in this area. There are recent publications concerning the design of trials with a PRO outcome[7,10] and, with the development of the CONSORT PRO extension[11], there is now guidance to improve PRO reporting: it remains unclear if the literature provides adequate coverage of in-trial issues.

The purpose of this study was to systematically review the current published in-trial PRO guidance, as no review of this kind had been previously undertaken. The objectives for our review were:

- To investigate the extent and content of the current in-trial PRO guidelines in publication.
- To determine if these guidelines adequately address questions raised by researchers involved in PRO data collection, surrounding the management of concerning PRO data.

Methods

Search strategy

The MEDLINE (Ovid), EMBASE, AMED and CINHAL+ databases were searched from inception to March 2012 (electronic search strategies are presented in full in Appendix S1). We also searched; the US Food and Drug Administration[12], European Medicines Agency[13], General Medical Council[14], Medical Research Council[15] and Royal College of Nursing[16] websites; PROQUEST (Thesis repository); Google; and made use of expert communication in an attempt to find additional potentially eligible papers not returned during the electronic database search. Records were first screened by title/abstract before full-text articles were retrieved for eligibility evaluation. Remaining articles were then subject to a citation search before a final hand-search of all reference lists.

Identification of eligible studies

Papers were deemed eligible if they included any form of in-trial guideline focused on PRO assessment during clinical trials. We defined the term 'in-trial' as relating to recruitment, data collection and data inputting activity, occurring from the first participant recruitment, through to inputting the final participant's data. The reviewers used the Oxford English Dictionary definition of the word 'guideline' during eligibility screening; "a general rule, principle, or piece of advice".[17] Non-English papers were excluded. There were no other restrictions. All citations were downloaded into Endnote® software version 14, and duplicates deleted. DK screened all articles by title/abstract to determine their eligibility and AG reviewed a random sample of 10% in order to evaluate the reliability of the selection process. Agreement was high (Kappa = 0.903) and any discrepancies were resolved through discussion. Full text articles were retrieved following first round exclusions and were also subject to two independent eligibility reviews (DK 100%, AG 10%), this time with perfect agreement.

Data extraction

Data extraction occurred following the final selection of included articles.

DK and CL independently searched each paper to identify all sentences that provided any type of 'guideline statement' (which we defined as 'an expression in words of a general rule, principle, or piece of advice') regarding PRO measurement (in-trial or otherwise). A consensus meeting was then held, to resolve any disagreements and finalise the selection. Each sentence, representing one 'guideline statement', was then extracted, as a text excerpt, into a mixed-method data analysis software package (Dedoose © 2011 SCRC) and tagged with its source data (Article title, Journal, Year of publication).

Data analysis

DK and CL undertook a qualitative content analysis[18] of the excerpts extracted from the included papers. All text excerpts were categorised according to an *a priori* coding frame, which was developed using a concept-driven strategy (i.e. codes were assigned based on the authors' prior knowledge of the literature and the study research questions). DK and CL piloted the coding framework, each independently applying the first draft to a random selection of the included papers[6,7,19] (n = 3 (17%)). Following the pilot, a meeting was held to discuss issues requiring clarification and to reach consensus regarding the data-driven changes that would improve the validity of the framework. Three of the co-authors (MC, HD and JI), who possess expertise in PRO design, implementation, reporting and ethics, checked and approved the face validity of the final coding frame. The definitive coding frame is presented in Figure 1. During the main analysis, DK and CL independently categorised each guideline statement according to the phase of trial activity to which it pertained, using a major dimension within the coding frame. These major dimensions were as follows; 'Pre-Trial', which included all content relating to the trial inception (including training logistics), up to the start of recruitment; 'In-Trial', denoting content directly related to the act of trial recruitment, data collection and inputting; 'Post-Trial', including activity taking place following data collection, for example, data analysis/reporting; 'Future Research', representing statements addressing the future direction of PRO research activity; and 'Other', used to identify guideline statements not captured in the main coding categories. Each individual guideline was also sub-categorised, as appropriate, in order to further identify its role within a given area.

Throughout both the pilot and the main analysis phase, the reviewers met frequently to determine coding reliability for each paper and to seek consensus regarding coding disagreements. The reliability of coding application was determined using Cohen's

Figure 1. Definitive coding frame. Major categories in bold.
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kappa statistic.[20] Specifically, pooled kappa was employed, as it is the preferred method of calculating inter-rater agreement across a large number of coding items.[21] Face validity of the coding frame was further evaluated by determining the proportion of codes applied to the residuals (i.e., the 'Other' major- and sub-categories). A high level of residual coding may indicate that the main categories of the coding frame do not adequately describe the concept under study.[18] Whilst there are no firm guidelines regarding the desirable level of residual coding, we theorised that a figure of less than 5% would support the validity of our coding frame.

A protocol was not published or registered for this study. However, all reviewers followed a protocol detailing *a priori* determined search strategies, data extraction and data analysis methods.

Results

Included studies

The search strategy yielded 1273 citations from MEDLINE, EMBASE, AMED and CINHAL+, 89 citations were returned using other sources (PROQUEST, professional bodies, Google, expert communication) (PRISMA[22] flow diagram, Figure 2). In total, 41 full text articles were retrieved for review. 25 articles were excluded at this stage, as they contained no in-trial guideline statements. An additional 2 papers were included following the reference list and citation searches. A final total of 18 relevant articles were included in the analysis.

Study characteristics

The characteristics of the 18 included papers are summarised in Table 1. The majority of papers were concerned with the incorporation of PRO/HRQL measures into cancer trial design.[5,6,10,23–28] Several considered PRO issues relating to pharmaceutical prescribing/labelling.[1,7,29–32] Two papers presented generalised guidance on using PRO/HRQL measures in clinical trials.[33,34] Finally, one paper presented recommendations for PRO/HRQL assessment in allergy-related clinical trials.[19] The included articles were drawn from 16 different sources and the mean number of excerpts extracted from each paper was 58 (range 16–127).

Data synthesis

Over 1,110 guideline statements were extracted and coded following review of the 18 papers. The coding frame demonstrated reliability, with pooled kappa ranging from 0.86 to 0.97 across articles, and face validity, with overall residual coding at 1.2%. A summary of the final coding breakdown is presented in Table 2.

Major coding categories

'In-trial' guidance, whilst present in all papers, did not represent the major focus of any, accounting for 9.2% of guideline content across the articles reviewed. 'Pre-trial' guidelines were predominant throughout (72.2%), again present in all papers. 'Post-trial' guidance was the next most prevalent category (15.8%), presented across 13 articles.[1,5,7,10,19,23,24,28–33] Statements pertaining to 'future research' represented 1.8% of guidelines (9 papers)[10,19,23,24,26–28,30,31] and the major category 'Other' was attributed to 1% of content (8 papers).[7,10,24,26,27,29–31]

Sub-categories

In-trial. There were no guideline statements addressing the management of concerning PRO data, or related questions

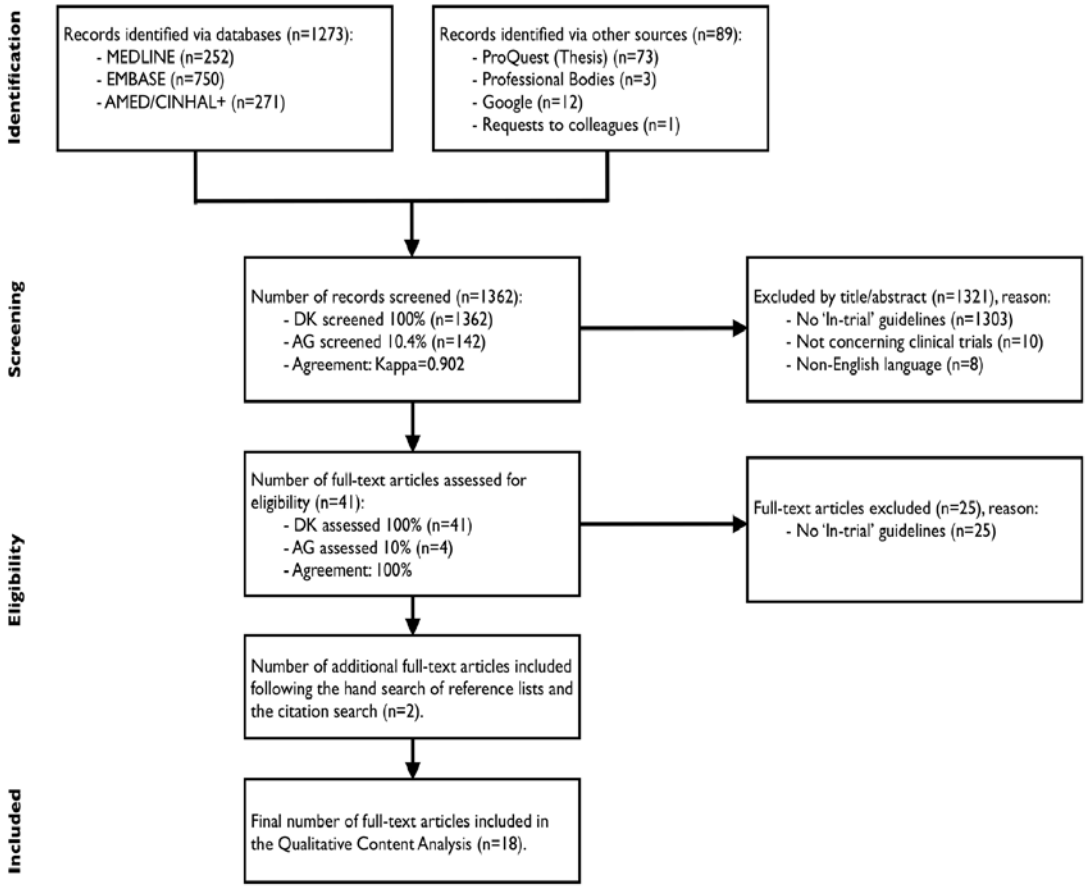

Figure 2. PRISMA flow diagram of study selection process.
doi:10.1371/journal.pone.0060684.g002

Table 1. Study characteristics.

Included Studies	Year of Publication	Source	Excerpts Extracted
Baiardini et al [19]	2010	Allergy	46
Basch et al [10]	2011	Value in Health	120
Calvert & Freemantle [1]	2004	Journal of Clinical Pharmacy and Therapeutics	74
Chassanay et al [29]	2002	Drug Information Journal	127
FDA [30]	2006	Health and Quality of Life Outcomes	86
FDA [7]	2009	FDA Website	116
Fayers [5]	1995	Quality of Life Research	18
Fayers et al [6]	1997	European Journal of cancer	62
Fletcher [23]	1995	British Journal of Clinical Pharmacology	48
Fletcher et al [24]	1992	BMJ	34
Hopwood et al [25]	1997	European Journal of cancer	25
Kiebert et al [26]	1998	Statistics in Medicine	16
Leidy et al [31]	1999	Value in Health	89
Luo & Cappelleri [33]	2008	Clinical Research and Regulatory Affairs	63
Moinpour et al [27]	1989	Journal of the National Cancer Institute	57
Movsas [28]	2003	Seminars in Radiation Oncology	39
Poulter [34]	1997	Good Clinical Practice Journal	19
Revicki et al [32]	2000	Quality of Life Research	80

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Table 2. Coding summary.

Coding Categories	Example Excerpts
'IN-TRIAL' GUIDELINES (9.2%)	
Quality control, compliance & correct use of OM (61.2%)	"In order to maximize compliance when administering the questionnaire investigators should… check the questionnaire for completeness at the time of visit and prompt patients to try and complete any missing items." [1]
Help/proxy assessments (16.5%)	"Interviewers and proxies should be consistent during the trial." [29]
Reporting of data collection/scoring (9.7%)	"The reasons for missing data should be recorded at the time of occurrence and later considered to lend insight into the potential patterns for why data are missing." [33]
Participant information provision & understanding (7.8%)	"The patient must fully understand the purpose of the QOL assessments." [34]
Should PRO data inform management (4.8%)	"Not only, therefore, should the information… not be used to influence treatment, but the patient should be informed clearly that their replies are confidential…" [5]
'PRE-TRIAL' GUIDELINES (9.2%)	
OM evaluation, OM selection, study design & procedure (87%)	"Protocols should include clear justification for the assessment of HRQL, provide details of the instrument and its properties, specify timings of assessments and emphasize the need to maximize compliance." [1]
OM development, validation, modification (12.8%)	"A PROs tool can only be used in a language that differs from the original after translation and back-translation, and a cross-cultural validation is performed." [19]
Other (0.2%)	"Requests for FDA input should be addressed to the review division responsible for the medical product…" [7]
'POST-TRIAL' GUIDELINES (15.8%)	
Data analysis, reporting, presentation (67.7%)	"In settings where there is a large proportion of missing data due to toxicity, morbidity or mortality, sensitivity analysis should be performed to address the possibility that the missing data are non-ignorable or not missing at random." [32]
Data interpretation, labeling & promotional claims (33.3%)	"We suggest that, in general, two well-designed randomized clinical trials with unequivocal results should provide sufficient evidence of an HRQL effect to substantiate a claim in a given population." [31]
'FUTURE RESEARCH' (1.8%)	"A need exists to standardise the terminology used in studies and to define a minimum set of concepts and dimensions of quality of life in order to justify a claim to have measured quality of life." [23]
'OTHER' (1%)	"We encourage instrument developers to make their instruments and related development history available and accessible publicly." [7]

Major coding categories in bold. Abbreviations - OM: Outcome measure, QOL: Quality of Life, HRQL: Health-Related Quality of Life, PRO: Patient-Reported Outcome, FDA: Food & Drug Administration.

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including how additional information recorded on the back of questionnaires should be handled and who should have routine access to PRO data in the first instance. The majority of in-trial guidelines (61.2%) tackled notions surrounding quality control, compliance and the correct use of PROs.[1,5–7,10,19,24–31,33,34] Authors highlighted the importance of minimising missing items during data collection.[6,34] A number of papers presented guidance aimed at improving compliance within a trial in order to maximise data quality: examples included the proposed education of local site staff, training of patients and use of real-time adherence monitoring [1,5,6,10,24,25,27–29,34]. Other guidelines were concerned with piloting[27] and standardisation[28,31] of data collection. Examples of suggested methods of standardisation included the following:

- A named individual, concerned with quality control, serving as a PRO data collection contact at each research site within a trial.[1,6,10]
- The use of standard scripts in interview- or telephone-based questionnaires.[31]
- Ensuring that patients complete questionnaires at the same pre-specified time point, usually selected so as to avoid the undue influence of a preceding event.[31,33]

Where a trial participant is unable to complete their PRO questionnaire, a proxy (commonly a partner or close relative) may be asked to complete the form on their behalf. Discussion surrounding the role of proxies represented 16.5% of in-trial guidelines.[1,5,6,23,29,31,32] Authors mainly highlighted the situations in which proxy assessment was justified.[1,5,6,29,31,32] The use of a proxy was generally promoted as a last resort [1,6,29], however it was acknowledged that proxy data was better than no data at all.[5,29] The ideal identity of the proxy was discussed by two authors, who concluded that, if possible, the same person should be used throughout the trial[29] and they should be close enough to the patient to provide valid data.[32] Guidelines for the reporting of data collection represented 9.7% of in-trial content[5,6,10,26,29,33] and were primarily concerned with the need to document reasons for non-compliance[5,6,10,33] and the need to report whether or not a proxy was used[6,29]. A small number of in-trial guideline statements (7.8%) focused on patient information, endorsing the use of a supplementary leaflet for patients to take home[6], and highlighting the importance of the investigator in ensuring the patient fully understands the role of PRO measurement.[34] Two papers by the same author[5,6] presented guidelines suggesting that PRO data should not be used to influence management during a trial and one paper suggested that trial participants ought to be informed when data would be used for the benefit of future patients only.[10]

Pre-trial. The majority of pre-trial guidelines (87%) were focused on study design, procedural issues (including training logistics) and the evaluation/selection of appropriate PRO measures.[1,5–7,10,19,23–34] Others (12.8%) were concerned with questionnaire development and validation, or with issues arising from questionnaire modification.[1,7,10,19,23,24,28–33]

Post-trial. Most post-trial guidelines (66.7%) concentrated on data analysis, reporting and presentation issues.[1,5,7,10,19,23,24,28–33] The remaining guidance in this area (33.3%) surrounded the interpretation of PRO data and related labeling claims.[5,7,19,23,24,28–33]

Discussion

The purpose of this review was to investigate whether anecdotal claims (subsequently confirmed by data under review), highlighting a lack of in-trial PRO guidance, reflect a deficiency in the published literature in this area. Our main findings suggest there a minimal guidelines in publication focused on in-trial PRO activity and there are a complete lack of guidelines addressing the management of concerning PRO data.

Of the small number of in-trial guidelines that are in circulation, the majority appear to deal with the procedural issues associated with the prevention of missing data. This focus may be understandable given the detrimental effect missing data may have on a trial. Trial reports indicate that PRO questionnaires are commonly returned with incomplete entries and some may not be returned at all.[7] This data may not be missing at random and it represents a serious potential bias when present.[10] Therefore, it is encouraging there is some consensus in the guidelines reviewed. To reduce missing PRO data, authors recommended that:

- The investigator/research nurse should: (1) motivate the patients to complete all questionnaires in-full by ensuring they understand the purpose and importance of the PRO assessment within the trial, (2) check questionnaires for completeness and prompt patients to fill in any missing items, (3) show appreciation for the efforts of the patient in completing the questionnaire.[1,5,6,25,27–29,33,34]
- PRO data is best collected in clinic, in an environment that is private and free from distraction.[1,24,29,34]
- A centrally managed PRO data monitoring system should be in place, coordinated at each site by a named individual, tasked with; evaluating compliance across trial locations, issuing data collection reminders to patients where needed and chasing-up missing items.[1,6,10,25,27,28]

The guidance surrounding missing data is therefore comprehensive. In contrast, no guidelines appear to adequately address aspects surrounding the management of concerning PRO data. This may be a problem given this issue has been identified as key by those involved in PRO data collection, as it can result in dual-role tension and may risk the potential introduction of bias into a trial.

A PRO questionnaire may be the only outcome within a trial capable of identifying 'tolerable' symptoms such as participant anxiety or depression; and the research nurse checking the form may be the only individual to whom participants have disclosed how they feel. Understandably, nurses may feel it is their duty to intervene when faced with PRO data that raises concern for the participant. A problem arises if the intervention is non-medicinal; for example, words of comfort, or advice to visit one's general practitioner, or if the advice results in the participant self-medicating. Direct medicinal interventions are far more easily controlled-for during data analysis. Non-medicinal or self-directed interventions, that are selectively delivered in response to concerning PRO data, may influence patient well-being but remain unrecorded in the trial documentation: this may represent a hitherto unforeseen source of bias.

Research nurses have reported experiencing dual-role tension when handling PRO data. Dual-role tension arises when an individual's values and responsibilities as a researcher conflict with those associated with being a clinical practitioner. Assuming ethical norms have been followed and participant 'risk and burden' does not outweigh the potential benefit of trial participation [35], the nurse *researcher* may justifiably choose not to intervene when concerning PRO data is disclosed, in order to protect trial integrity. This decision may be driven by consequentialist values, geared toward achieving the greatest benefit at the lowest cost, and reasoning that the benefits of producing unbiased trial results outweigh the personal costs experienced by the 'few' participants who continue to (tolerably) suffer. Conversely, nurse *practitioners* are obliged to make the care of their patients their first concern, as outlined in the Nursing and Midwifery Council code of conduct[36], which compels them to take steps to address any evident suffering. This conflict between the two professional duties has been recognized elsewhere[37–39]. However, what sets PRO data collection apart from the management of other trial outcomes is the current lack of published, and trial-based, guidance in this area. In our experience, the trial protocol often contains clear guidelines surrounding the levels at which some clinical outcomes, blood pressure for example, need to reach before the data collector should become concerned.[9] There is usually also a clear system in place to manage participants whose clinical measurements exceed agreed limits. Equivalent guidance is not always provided for PROs. Thus, the researcher collecting/inputting PRO data may be left to determine independently, on a case-by-case basis, whether PRO results signal a risk to the participant that outweighs the benefit of trial involvement. We believe this situation places unreasonable demands upon the researcher and promotes inconsistency, as there is unlikely to be uniformity in decision-making across trial sites; this may adversely affect data quality. Our findings highlight the need to develop and publish specific guidelines that clearly outline how concerning PRO data should be handled, as there are none currently in circulation. PRO in-trial guidelines should be brought in line with those covering traditional clinical outcomes and should define the conditions under which the researcher may take remedial action, and the form this intervention might take.

Limitations

Non-English language papers were excluded from the review, which potentially lessens the generalisability of the results presented. However, this decision was taken as a key element of qualitative content analysis involved determining the implied or latent meaning of the material.[18] We questioned the validity of such analysis using material translated from the original language by a third party, as some latent meaning may be lost during the translation process. Our search strategy dictated that we carefully reviewed papers for their guideline content only if their title/abstract gave an indication that some aspect of in-trial activity might be discussed. It is possible that papers providing 'in-trial' guidance exist, which make no reference to in-trial activity in their title or abstract.

Conclusions

In-trial guidelines aimed at PRO recruitment, data collection and data inputting within clinical trials are lacking. No guidance appears to exist for researchers involved with the handling of concerning PRO data. This is a worry as this activity may be associated with considerable personal and professional anxiety and may risk the introduction of bias when the ethical tension generated, is resolved in favour of responding to the needs of the patient over the expectations of the trial. Further research is needed to produce guidelines aimed at supporting researchers so they can deal effectively with dual-role tensions, manage PRO data appropriately and facilitate unbiased data collection.

Supporting Information

Appendix S1 Search strategies.
(DOCX)

Box S1 Definition of terms.
(DOCX)

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Author Contributions

Conceived and designed the experiments: DK MC HD JI. Performed the experiments: DK AG. Analyzed the data: DK CL. Wrote the paper: DK. Critical revision of manuscript: DK MC HD JI CL AG. Obtained funding: DK MC HD JI.

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Paper Appendices

Paper Appendix	Thesis Appendix
Appendix S1 - Search strategies	Appendix 6

Erratum

Corrections

2 Jan 2014: Kyte DG, Draper H, Ives J, Liles C, Gheorghe A, et al. (2014) Correction: Patient Reported Outcomes (PROs) in Clinical Trials: Is 'In-Trial' Guidance Lacking? A Systematic Review. PLoS ONE 9(1): 10.1371/annotation/e7d2b920-2c2a-425e-b500-982cd72f4d64. doi: 10.1371/annotation/e7d2b920-2c2a-425e-b500-982cd72f4d64 | **View correction**

In Table 2, the first column, seventh row should read "PRE-TRIAL Guidelines (72.2%)".

Citation: Kyte DG, Draper H, Ives J, Liles C, Gheorghe A, et al. (2014) Correction: Patient Reported Outcomes (PROs) in Clinical Trials: Is 'In-Trial' Guidance Lacking? A Systematic Review. PLoS ONE 9(1): 10.1371/annotation/e7d2b920-2c2a-425e-b500-982cd72f4d64. doi:10.1371/annotation/e7d2b920-2c2a-425e-b500-982cd72f4d64

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Chapter 7. PRO guidance for clinical trial protocol developers

The qualitative data presented in Chapter 2 and survey data outlined in Chapters 4 and 5, raised uncertainty over both the presence and usefulness of PRO-specific protocol content in trials. These data prompted the PRO Research Group at the University of Birmingham to apply for funding to investigate the PRO content of trial protocols in the UK. The application was successful and funding was received from the NIHR SPCR in 2013.[i]

We planned to evaluate the completeness of the PRO information contained within a sample of NIHR HTA protocols, however, it became clear that there was no agreed checklist against which we could measure PRO protocol completeness. Therefore, our first step was to conduct a systematic review of the literature detailing the PRO-specific guidance for protocol developers (presented in this Chapter). Through this work, we hoped to determine the available PRO guidance that could be accessed by trial management during the design of trials and, using this information, construct a PRO-protocol checklist of recommended PRO-specific items of information that should be included in a trial protocol.

The following Chapter presents the results of this systematic review, led by Professor Mel Calvert. This paper is presented within the thesis to provide context and aid understanding of the evaluation of HTA PRO protocol content presented in Chapter 8. Under the supervision of Professor Calvert, I played a substantial role in the design of the study, screening of the full text articles, data extraction, analysis and writing the final manuscript.

[i] Calvert M, **Kyte D**, Draper H, Ives J, Gheorghe A, Brundage M, King M, Mercieca-Bebber R. Evaluation of patient reported outcomes in clinical trials: systematic review of trial protocols. NIHR School for Primary Care Research - Funding Round 7. £23,976

This Chapter is presented in paper format and has been submitted to the PLoS One journal for peer review as:

Calvert M, **Kyte D**, Duffy H, Gheorghe A, Mercieca-Bebber R, Ives J, Draper H, Brundage M, Blazeby J, King M. Patient-Reported Outcome (PRO) Assessment in Clinical Trials: A Systematic Review of Guidance for Trial Protocol Writers.

The work presented in this Chapter has been accepted for presentation at the following conference:

- Calvert M, **Kyte D**, Duffy H, Gheorghe A, Mercieca-Bebber R, Ives J, Draper H, Brundage M, Blazeby J, King M. Patient-Reported Outcome (PRO) Assessment in Clinical Trials: A Systematic Review of Guidance for Trial Protocol Writers. NIHR SPCR Research Showcase, September, 2014 [*Poster – Kyte presenting*]

Title Page

Title

Patient-Reported Outcome (PRO) Assessment in Clinical Trials: A Systematic Review of Guidance for Trial Protocol Writers

Authorship

Melanie Calvert[1,2]*, Derek Kyte[1,3], Helen Duffy[1], Adrian Gheorghe[4], Rebecca Mercieca-Bebber[5], Jonathan Ives[6], Heather Draper [2,6], Michael Brundage[7], Jane Blazeby[8], Madeleine King[5]

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ABSTRACT

Background

Evidence suggests there are inconsistencies in patient-reported outcome (PRO) assessment and reporting in some clinical trials, which may limit the use of these data to inform patient care. For trials with a PRO endpoint, routine inclusion of key PRO information in the protocol may help improve both trial conduct and the reporting and appraisal of PRO results; however, it is currently unclear exactly what PRO-specific information should be included. The aim of this review was to summarize the current PRO-specific guidance for clinical trial protocol developers.

Methods and Findings

We searched the MEDLINE, EMBASE, CINHAL and Cochrane Library databases (inception to February 2013) for PRO-specific guidance regarding trial protocol development. Further guidance documents were identified via Google, Google scholar, requests to members of the UK Clinical Research Collaboration registered clinical trials units and international experts in the field. Two independent investigators undertook title/abstract screening, full text review and data extraction, with a third involved in the event of disagreement.

21,175 citations were screened and 54 met the inclusion criteria. Guidance documents were difficult to access: electronic database searches identified just 8 documents, with the remaining 46 sourced elsewhere (5 from citation tracking, 27 from hand searching, 7 from the grey literature review and 7 from experts). 162 separate PRO-specific protocol recommendations were extracted from the included documents. Only 5/162 (3%)

recommendations appeared in more than half of the guidance documents reviewed, indicating a lack of consistency.

Conclusions

PRO-specific protocol guidelines were difficult to access and lacked consistency, therefore, they may be challenging to implement in practice. There is a need to develop readily accessible consensus-driven PRO guidance for protocol developers. Such guidance should be aimed at ensuring key PRO information is routinely included in appropriate trial protocols, in order to facilitate rigorous collection/reporting of PRO data, to effectively inform patient care.

Introduction

Patient-reported outcomes (PROs), including health-related quality of life (HRQL), symptoms such as pain or fatigue, and health utility, are increasingly assessed in clinical trials as a measure of effectiveness.[1,2] PRO trial data may be used to inform clinical care and decision-making, predict long-term outcomes and influence health-policy; but to do so, as with any trial outcome, they must be collected with rigor. Unfortunately, evidence shows that the quality of PRO data can be undermined in some trials by inconsistencies in data collection[3] and, in particular, by high rates of missing data[4]; this adversely affects the integrity and usefulness of such data in clinical practice.

To help ensure optimal PRO data collection, PRO-specific components should be considered during clinical trial design and clearly documented in the trial protocol.[5,6] The trial protocol is the cornerstone of a well-conducted trial, and should provide specific instruction on how to conduct all aspects of the study.[6] The protocol also allows external funding bodies, regulators, research ethics committees, journal editors, health care providers, systematic reviewers and policy makers to evaluate the design and methods.[6] Despite the importance of PROs, recent data suggests that some trial staff feel protocols provide little guidance regarding PRO-specific aspects of the trial, leading to ambiguity and the potential for significant inconsistency in the way PRO data are gathered, analysed, acted upon, and reported.[3,7,8]

The recent publication of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement aims to promote the inclusion of important general methodological components in trial protocols[5,6]; however, it does not provide specific guidance related to PROs. It is currently unclear exactly what PRO-specific information

should be included in trial protocols. The aim of this systematic review was to summarize current PRO-specific guidance for clinical trial protocol developers.

Methods

Ethics

This study received ethical approval from the University of Birmingham ethical review board (ERN_13-0047).

Search Strategy

This review was conducted according to PRISMA guidelines[9] and a protocol is available.[10] The MEDLINE (Ovid), EMBASE, CINHAL and Cochrane Library databases were searched from inception to February 2013 (electronic search strategies are presented in full in Appendix I[j]). Other relevant articles were identified via two Internet search engines (Google and Google Scholar) using the key words 'Patient-Reported Outcomes' or 'Health-Related Quality of Life' in combination with 'Guidance', 'Guidelines' or 'Checklist'. Only the first 30 results (3 pages) of each internet search were reviewed as article relevance diminishes substantially with each page of results.[11] In addition, an international advisory group (MB, AG, JB, RMB and MK) were consulted via email to identify additional 'grey literature' directly relevant to the research question. Finally, PRO guidance/checklists and Standard Operating Procedures (SOPs) were requested from all members of the UK Clinical Research Collaboration registered clinical trials units (CRC-CTU) via email, with one follow up reminder. All citations were downloaded into Endnote® software version X7 and duplicates deleted. Records were then screened by title/abstract before full-text articles/documents were retrieved for eligibility evaluation. Remaining articles were subject to a citation search, before a final hand-search of all reference lists.

Selection Criteria

[j] Appendix 7 of the thesis

Papers and other guidance documents were deemed eligible if they provided guidance, and/or a checklist, concerning the inclusion of PRO-specific information in clinical trial protocols. Non-English papers were screened by language specialists in the School of Health and Population Sciences, University of Birmingham. When more than one edition of a book was available, the latest edition was screened.

Data Extraction and Quality Appraisal

Two reviewers (HDu and AG) independently screened the titles and abstracts of all citations. Full text versions of potentially eligible documents were independently reviewed (HDu and AG) with uncertainties resolved through discussion with a third investigator (MC/DK). Two investigators (MC and DK) independently extracted both the publication details and all PRO-specific protocol recommendations from the final included documents. Both explicit ('stated clearly and in detail, leaving no room for confusion or doubt'[12]) and implicit ('suggested though not directly expressed'[12]) recommendations were extracted.

Data Synthesis

For ease of interpretation, PRO protocol recommendations were extracted and grouped according to eight sections commonly included in trial protocols.[5] Duplicate recommendations within each of these sections were identified by MC and DK, and were merged where necessary following discussion with the international advisory group. Disagreements were resolved in the same manner. The proportion of guidance documents associated with each recommendation was identified. To assess general trends in guidance over time, the proportion of guidance documents per recommendation was analysed retrospectively over 5 year time periods.

Results

Description of Guidance Documents

The literature search yielded 21,175 references. Following application of the inclusion criteria, 54 guidance documents[1,2,13-64] were included in the review (Figure 1). Of these, 8 were identified from the electronic database search, 5 from citation tracking, 27 from hand searching, 7 from the grey literature review and 7 from expert recommendations. Document characteristics are summarised in Table 1. The included materials dated from 1989 to 2013 and included 42 journal articles, 5 books and 7 organizational guideline documents, with the majority focused on HRQL/PRO assessment in cancer trials (n= 35, 64.8 %) and written from a non-regulatory perspective (n=44, 81.5%).

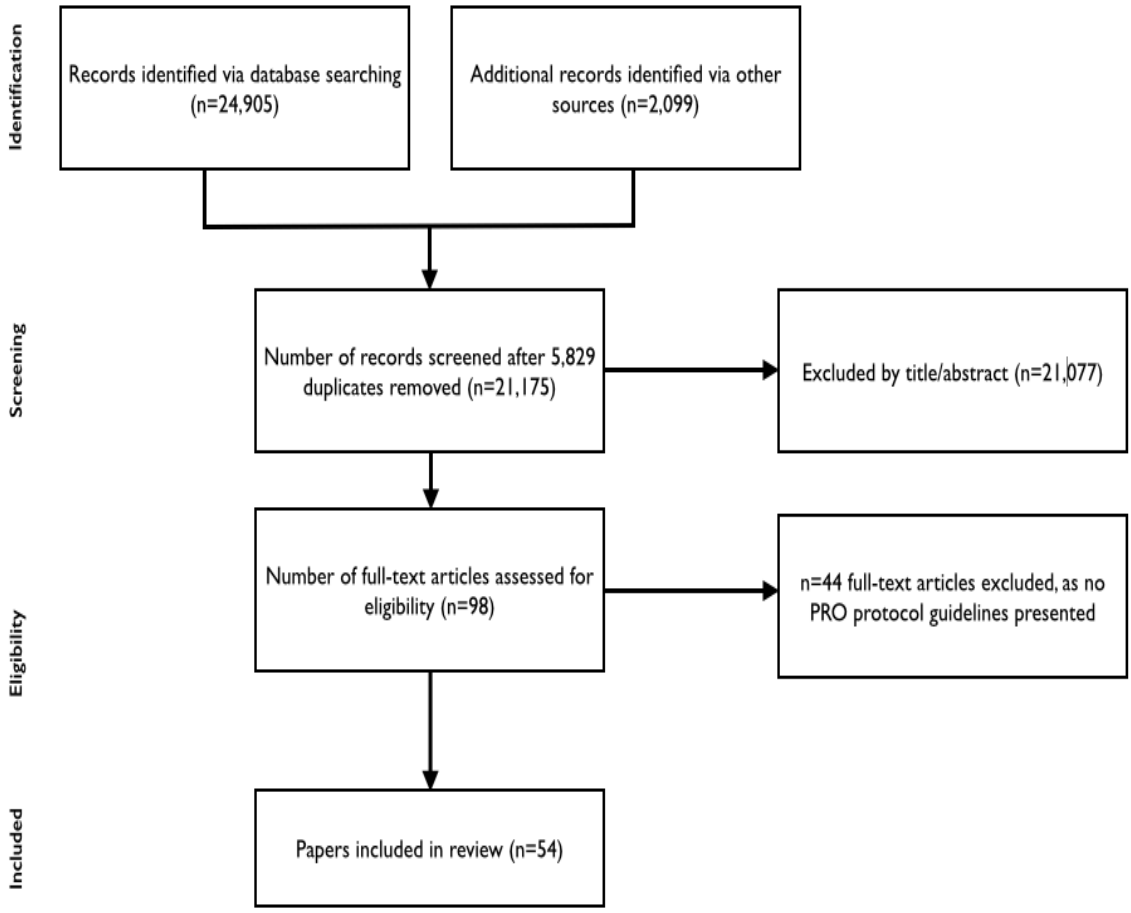

Figure 1. PRISMA flow diagram

Table 1. Guidance Document Characteristics

Authors	Year	Clinical area	PRO Protocol Checklist provided	Regulatory Focus	Source
Moinpour et al.[43]	1989	Oncology			Journal of the National Cancer Institute
Schron & Schumaker[58]	1992	Cardiovascular			Progress in cardiovascular Nursing
Gotay et al.[31]	1992a	Oncology			Journal of the National cancer Institute
Osoba[50]	1992	Oncology	Yes		Quality of Life Research
Gotay et al.[30]	1992b	Oncology			Oncology
Nayfield et al.[47]	1992	Oncology			Quality of Life Research
Sadura et al.[56]	1992	Oncology			Journal of the National Cancer Institute
Hayden et al. [34]	1993	Oncology			Oncology Nursing Forum
Cella et al. [20]	1993	General			Quality of Life research
Spilker[61]	1996	General			Book (Chapters 45 and 72)
Molin & Arrigo[45]	1995	Oncology	Yes		European Journal of Cancer
Fayers et al.[27]	1997	Oncology	Yes		European Journal Cancer
Kiebert[36]	1997	Oncology	Yes		European Journal of Cancer
Bernhard et al.[14]	1998a	Oncology			Statistics in medicine
Bernhard et al.[15]	1998b	Oncology			Statistics in medicine
Osoba[52]	1998	Oncology			Statistics in Medicine
Simes et al.[59]	1998	Oncology			Statistics in medicine
Moinpour & Lovato[44]	1998	Oncology			Statistics in Medicine
Brooks et al.[17]	1998	Cardiovascular			Medical Care
Leidy et al.[40]	1999	General		Yes	Value in Health
Osoba[51]	1999	Oncology			European Journal of Cancer
de Haes et al.[22]	2000	Oncology			European Journal Cancer
Revicki et al.[55]	2000	General		Yes	Quality of life Research
Bottomley[16]	2001	Oncology			Applied Clinical Trials
Hakamies-Blomqvist et al.[32]	2001	Oncology			Journal of Advanced Nursing
Santanello et al.[57]	2002	General		Yes	Value in Health
Chassany et al.[21]	2002	General	Yes	Yes	Drug Information Journal
EORTC QLG[64]	2002	Oncology			Guidance document
Movsas[46]	2003	Oncology			Seminars in Radiation Oncology
Calvert & Freemantle[19]	2004	General	Yes		Journal of Clinical Pharmacy and Therapeutics
Wiklund[63]	2004	General	Yes	Yes	Fundamental & Clinical Pharmacology
Buchanan et al.[18]	2005	Oncology			Journal of Clinical Oncology
Fayers & Hays[26]	2005	General			Book (Chapter 3.2)
Lipscomb[41]	2005	Oncology			Book (Fairclough Chapter)
Avery & Blazeby[13]	2006	Oncology			World Journal of Surgery
TRoG[62]	2007	Oncology			Policy document
Ganz & Gotay[29]	2007	Oncology			Journal of Clinical Oncology
Lipscomb et al.[2]	2007	Oncology			Journal of Clinical Oncology
Land et al.[39]	2007	Oncology			Journal of Clinical Oncology
Patrick et al.[53]	2007	General		Yes	Value in Health
Sloan et al.[60]	2007	General		Yes	Value in Health

Revicki et al.[54]	2007	General		Yes	Value in Health
Fayers & Machin[26]	2007	General	Yes		Book
FDA[28]	2009	General		Yes	Guidance document
Fairclough[24]	2010	General	Yes		Book
Hao[33]	2010	Oncology		Yes	Expert Reviews
NCIC CTG[48]	2010	Oncology	Yes		Guidance document
Basch et al.[1]	2011	Oncology			Guidance document
King[37]	2011	Oncology	Yes		Web-based guidance document
Efficace & Taphoorn[23]	2012	Oncology			Journal of Neurooncology
Jensen et al.[35]	2012	Oncology			Clinical Investigation
Novik et al.[49]	2012	Haematology			Guidance document
Macefield et al.[42]	2013	Oncology			British Journal of Surgery
Kyte et al.[38]	2013	General			JAMA

PRO Protocol Guidance

The included guidance documents contained 162 separate recommendations regarding PRO information that should be included in trial protocols. Of these, 134 recommendations were explicit (e.g. 'All analyses should be clearly defined a priori in the research protocol'[21]), and 28 were implicit (e.g. '…investigators need to provide a rationale for the selection of a particular HRQL instrument'[18]). Protocol recommendations are summarised below and are presented in full in Appendix II[k]. An additional 10 PRO recommendations were discovered that related to other supporting trial documentation, these are presented in Appendix III[l], but are not discussed further in this paper.

Administrative information

There were n=4 recommendations regarding trial administration. These centred around identifying the roles and responsibilities of PRO personnel and ranged from advocating involvement of the research nurse in PRO protocol development, to providing the contact details of the Quality of Life (QOL) sub-study coordinator.

Introduction: Background, rationale, and objectives/hypotheses

There were n=11 separate recommendations related to the inclusion of PROs in the introductory sections of the protocol. n=2 focused on aspects surrounding PRO-specific background information, for instance, the need to describe the PRO population of interest. n=5 recommendations concerned specification of the PRO rationale, for example, justifying the relevance of PRO assessment in the disease and population under investigation. n=4 were concerned with outlining the PRO hypothesis and objectives.

[k] Appendix 8 of the thesis

[l] Appendix 9 of the thesis

Methods: Participants, interventions and outcomes

There were n=25 different recommendations within this section, focused on a number of areas, including: the PRO study setting (n=1), the PRO-specific eligibility criteria (n=3), the need to specify the PRO as an endpoint (n=5), the PRO-specific sample size (n=2) and blinding considerations (n=2). n=12 different recommendations related to timing of the PRO assessment, ranging from: including PRO assessment timings in the main protocol assessment schedule and specifying time windows, to justifying timings according to the study research questions, length of recall of the questionnaire, the natural history of the disease under study, and any planned analysis.

Methods: assignment of interventions

There were no PRO-specific recommendations identified under this heading.

Methods: Data Collection, management and analysis

n=94 recommendations related to PRO-specific protocol guidance for data collection, management and analysis. n=4 were focused the identification/description of the PRO instrument, for example, the need to outline the questionnaire domains and number of items. n=13 were concerned with justifying the choice of instrument, for example, the importance of referencing the validity, reliability and responsiveness of the tool. n=10 concentrated on detailing the data collection plan and n=16 focused on describing the data collection/training guidelines. n=19 concerned plans to minimise missing data, for example, specifying who would check questionnaires for missing items. There were n=7 recommendations regarding PRO specific quality assurance, ranging from the inclusion of guidance for data entry coding decisions regarding missing or ambiguous responses, to specifying procedures for a central PRO data monitoring system aimed at identifying and rectifying potential data collection

problems. n=25 recommendations focused on PRO analysis, including n=13 on the PRO-specific components of the statistical analysis plan, for instance, the need to include an a priori estimation of expected change in PRO score. n=2 focused on plans to address multiple hypothesis testing, such as pre-specification of sequence of testing. n=6 were concerned with defining clinical significance, for example, describing and justifying the minimal clinically important difference/change. Finally, there were n=4 recommendations focused on specifying methods to deal with missing PRO data, for instance, defining proposed sensitivity analyses for imputation methods.

Methods: Monitoring

There were n=4 recommendations regarding PRO specific trial monitoring, ranging from the need to define the role of the Data Monitoring Committee in relation to PROs, to the inclusion of a plan to manage PRO Alerts.

Ethics and Dissemination

There were n=3 recommendations focused on PRO-specific consent information and n=2 recommendations addressed PRO specific confidentiality issues, such as the need to specify whether QOL data would be used to influence patient management. n=2 recommendations focused on the need to include PRO-specific dissemination plans, through both peer-reviewed scientific publication and direct participant contact.

Appendices

n=14 recommendations focused on the inclusion of relevant PRO documents as protocol appendices, including: a copy of the PRO questionnaire(s), sample patient information and consent materials containing PRO information and a PRO-specific administration flow chart/checklist.

Other Trial Documentation

n=10 recommendations focused on PRO information that should be included in protocol-related trial documents such as Standard Operating Procedures (SOPs), Case Report Forms (CRFs) or training manuals.

Time trends and Common Recommendations

The availability of PRO-specific guidance over time is shown in Figure 2. The data suggest that there has been consistent publication of PRO protocol guidance, across all areas, over the last 25 years (Table 2). In addition, over 75% of recommendations extracted for this study have been available for at least 10 years.

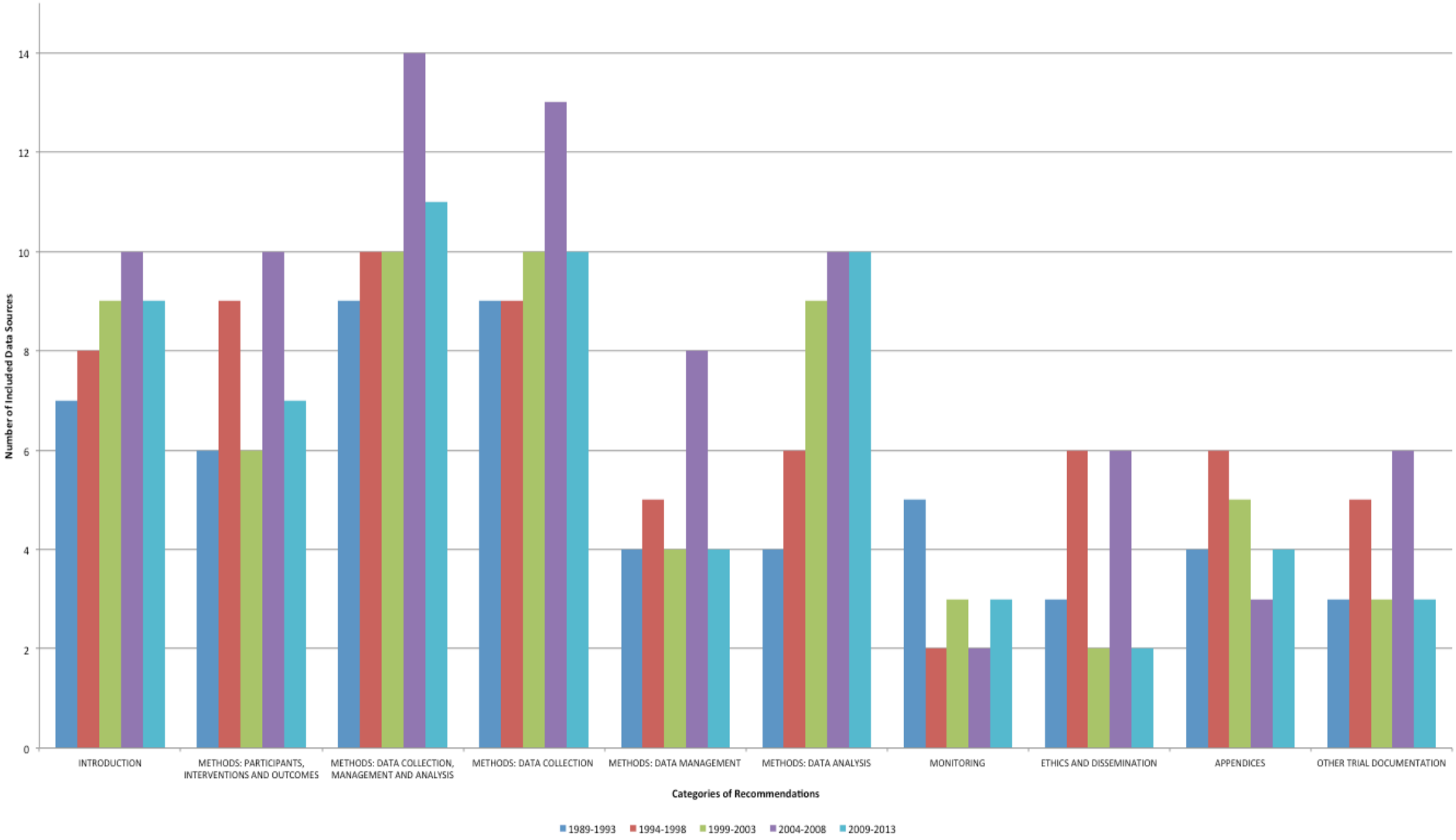

Figure 2. PRO protocol guidance trends over time

Table 2. New PRO protocol guidance over time (total, n=162)

Time Period	N (%) of new PRO Protocol Recommendations
1989-1993	70 (43.21)
1994-1999	30 (18.52)
1999-2003	23 (14.20)
2004-2008	9 (5.56)
2009-2013	30 (18.52)

A summary of the most commonly cited PRO protocol recommendations is shown in Table 3. Only 3% (n=5) of recommendations appeared in more than half of the documents included in the study, highlighting a lack of consistency in the PRO guidance literature reviewed. In order of frequency, these were: the need to specify the timing of QOL assessment, the provision of PRO data collection guidelines and/or a training plan, specification (and justification) for the chosen PRO questionnaire, routine inclusion of *a priori* defined PRO analysis plans and specifying a named person within the trial with responsibility for overseeing QOL assessment.

Table 3. Recommendations appearing in more than 25% of guidance documents

Recommendation	Number (%) of Guidance Documents: total, n=162
Specify the timing of QOL assessments and link to hypotheses.	37 (68.52)
Provide guidelines and/or training plan for PRO data collection.	36 (66.67)
Specify which QOL questionnaires will be used and link to clinical justifications and hypotheses via specific domains/questions.	32 (59.26)
All analyses should be clearly defined a priori in the protocol.	29 (53.70)
Specify that a named person at each centre (and/or centrally) be nominated to take responsibility for administration, collection and checking of QOL forms and specify whether this is or is not the treating clinician.	27 (50.00)
Provide a rationale for measuring QOL e.g. superior intervention/negative impact of intervention/equivalence.	26 (48.15)
State the QOL hypothesis (and corresponding null hypothesis) and to which outcome the hypothesis relates.	23 (42.59)
Describe methods for handling missing data.	22 (40.74)
Specify how QOL will be assessed e.g. pencil and paper, online, etc.	22 (40.74)
State the sample size and power requirements in relation to the rationale/objectives/hypothesis.	22 (40.74)
Identify QOL as an objective/state research objective of HRQL component in relation to dimensions, population and timeframe.	22 (40.74)
Specify procedures for checking questionnaires/prevention of avoidable missing data e.g. who will check form, and how will they deal with missing questionnaire(s) or items.	21 (38.89)
Provide instructions on how the patient should complete the form (e.g. without conferring with friends/relatives, all questions should be answered even if the patient feels them to be irrelevant).	21 (38.89)

Emphasise importance of good compliance/describe procedures to maximise compliance/minimise missing data.	20 (37.04)
Plan for multiplicity/controlling type 1 error - summary measures/adjustments.	19 (35.19)
Describe the questionnaire(s) (including, number of items/domains, instrument scaling/scoring, reliability, content and construct validity, responsiveness, sensitivity, respondent burden, cultural adaptation/validity, recall period) +/- validation plan if appropriate.	19 (35.19)
Specify if baseline assessment is pre-randomisation.	19 (35.19)
Specify if QOL completion is a pre-randomisation eligibility condition.	18 (33.33)
PRO endpoints should be fully integrated in trial protocol/data collection.	18 (33.33)
Include a pre-specified data collection plan.	17 (31.48)
Specify the HRQL domains the study intervention is expected to effect.	17 (31.48)
Specify standardised timing of questionnaire delivery (e.g. before/whilst/after seeing clinician).	16 (29.63)
Specify acceptable time windows for each assessment.	16 (29.63)
Explain the QOL assessment procedure within the PIS/consent and, if appropriate, identify if consent to QOL assessment is required for entry into the trial.	14 (25.93)
Specify if help and or proxy assessments are permitted (and what level of assistance allowed).	14 (25.93)
Reference the validity, reliability and responsiveness of the instrument (may be more succinct with refs if PROM widely used).	14 (25.93)
Specify the timeframe of interest/primary time-point for analysis and the rationale for this.	14 (25.93)

Define the role of the PRO endpoint (primary, important secondary, exploratory).	14 (25.93)

Discussion

Summary of Findings

Our review is the first to summarise the current PRO-specific guidance for clinical trial protocol developers. In total, we identified 54 guidance documents[1,2,13-64], which provided 162 separate recommendations regarding PRO-specific information that should be included in protocols containing a PRO endpoint.

Unfortunately, although some PRO protocol guidance has been in existence for over 25 years, our findings suggest it may struggle to effectively influence practice. First, with the exception of 8 publications[21,23,32-35,57,58] sourced via electronic database searches, the guidance literature was particularly difficult to access. The remaining 46 documents, which provided more than half (56.7%) of all PRO protocol recommendations, were obtained via time-consuming citation tracking, hand-searching, grey literature review and expert contact. It is unlikely that protocol developers would have had the time or resources to carry out such a comprehensive search. As such, developers may currently be reliant on the 8 documents outlined above that are available via easily accessible scientific databases. This is problematic, as these publications provide less than half of the current PRO protocol recommendations in circulation. Given that recommendations are spread over a wide variety of sources, over reliance on a small number of guidance documents may mean important PRO design considerations are overlooked. Even the two publications that provided most recommendations, Chassanay[21] and Fairclough[24] (42 recommendations each, 24 shared), provided just 37.04% of the total in circulation.

Second, although developers can now more easily access PRO guidance through this review, they still face the challenge of trying to incorporate a large number of recommendations into what is usually a rather limited amount of space within the protocol. For instance, we identified 94 unique recommendations regarding data collection, management and analysis, of which 19 addressed minimising missing data. Tackling missing PRO data is clearly an important design consideration since it helps reduce bias and preserves statistical power[65], however, it may be difficult for protocol developers to incorporate all 19 recommendations within a study protocol. Consolidated, easily accessible and internationally endorsed consensus guidelines on the essential PRO protocol content are required to help preserve trial integrity and to provide guidance that is useful in practice.

Our review provides a useful starting point as it presents a comprehensive list of the PRO protocol guidance currently available. It remains unclear at this stage, however, exactly which of the recommendations identified in this study should be incorporated into more user-friendly consolidated guidelines. A number of recommendations are supported by multiple sources and appear to be underpinned by a clear theoretical justification (for example, the need to provide a rationale for PRO measurement (recommended in 48.15% of guidance documents)), and may be promising candidates for inclusion. There were, however, a number of other recommendations that were less frequently cited, but still may have important implications for trial conduct, reporting and the quality of PRO results. For example, referencing the PRO instrument validity and reliability in the protocol (recommended in 25.93% of guidance documents) will help ensure that the psychometric properties of the PRO have been duly considered during the trial design and will help facilitate later

reporting in accordance with the CONSORT-PRO extension.[66] In addition, only four publications provided recommendations regarding the handling of PRO Alerts in trials, that is: 'concerning levels of psychological distress or physical symptoms that may require an immediate response'.[8] However, evidence suggests that without clear, pre-specified, plans for the management of PRO Alerts, contained either in the trial protocol or supporting documentation/training, variation may occur in their management risking co-intervention bias and suboptimal patient care.[3]

Consolidated PRO guidance for protocol developers should therefore be developed using robust consensus methodology to ensure that the merits of all individual recommendations outlined in this review are carefully considered prior to selection/rejection. The definitive guidelines should aim to improve the quality of PRO trial design and reporting, resulting in more robust PRO trial data that will exert a greater influence on clinical practice and will provide an improved information base for future patients. Researchers should be supported in implementing the guidance through training and online resources. Furthermore, endorsement by funding bodies and Institutional Review Boards/Ethical Committees, who review the content of protocols, and journal editors, who are responsible for their publication, is important to ensure widespread adoption.

Strengths and Limitations

Our review has for the first time collated and summarised the existing PRO guidance available for protocol developers using systematic methods and multiple reviewers. An unavoidable limitation of our approach is that the PRO item categorisation and indexing employed during our analysis is influenced by reviewer interpretation. Also,

publications included in the study had to provide guidance on PRO-protocol content; however such guidance was not always the main focus or aim of some of the included articles. Again, the interpretation of the reviewer may subtly alter the original meaning of the text drawn from such material. The use of independent dual data extraction by 2 investigators (with a third to mediate) sought to reduce these effects, however, they remain a legitimate concern. Relevant PRO guidance literature was difficult to source and appeared to be particularly poorly indexed. Whilst we employed a number of resources to comprehensively search the literature (including electronic databases, citation tracking and hand searching, internet search engines and expert contact) it is possible that further PRO guidance exists that was not included in our study.

Conclusion

PRO-specific protocol guidance is difficult to access, lacks consistency and is unwieldy; with over 160 recommendations spread across 54 different publications. It is therefore extremely challenging to implement in practice. There is a need to develop easily accessible consolidated, and consensus-driven, PRO protocol guidelines. Guidance should aim to ensure key PRO information is routinely included in trial protocols with a PRO endpoint, in order to facilitate the rigorous collection and reporting of PRO data, thus maximising its capacity to effectively inform patient care.

Financial Disclosure

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Author Contributions

All authors contributed to the design of the study and obtained funding. AG and HDu searched the literature and screened titles, abstracts and full text articles with input from a third reviewer (MC/DK) where necessary. HDu and RMB searched the grey literature. MC and DK extracted data from included publications. MB, JB, MK and RMB formed an expert advisory panel that identified additional grey literature relevant to the research question. MC wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the final version for publication.

Competing Interests

The authors have declared that no competing interests exist.

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Keywords

Patient-reported outcomes; PROs; patient-reported outcome measures; PROMs; clinical trials; trial protocol; protocol writing; protocol development.

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Chapter 8. Review of the PRO content of clinical trial protocols

The following Chapter presents the first systematic review of the PRO-specific content of clinical trial protocols (conducted on a sample of UK NIHR HTA protocols and funded by the NIHR SPCR).

This Chapter also outlines the development of a novel checklist used to evaluate the completeness of PRO protocol information, constructed using existing PRO protocol guidelines identified during the systematic review reported in Chapter 7. It is important to acknowledge that this checklist represents a first step. In the time afforded by the funding stream it was not possible to conduct a full-scale consensus process to determine which of the 162 recommendations presented in the guidance review, should be included in a definitive checklist outlining essential PRO protocol elements. Thus, the current version of the checklist was constructed so as to retain all recommendations at this stage, until a consensus project could be undertaken. The PRO Research Group at the University of Birmingham, in partnership with national and international collaborators[m], have applied to the Medical Research Council (MRC) Methodology Research Panel for funds to support such a project:

- Calvert M, **Kyte D**, Altman D, Blazeby J, Brown J, Brundage M, Coast J, Draper H, Ives J, Roberts L, von Hildebrand M, King M. **Im**proving **Pa**tient-**R**eported Outcome Content in **T**rial Protocols (**IMPART**). MRC - Methodology Research Panel. £458,751.70

[m] Project Partners include: SPIRIT developers: Profs David Moher and An-Wen Chan**;** the Patient and Public Involvement NIHR Central Commissioning Facility; the NIHR Evaluation, Trials and Studies Coordinating Centre; the UKCRC Registered CTU Network; the International Society for Quality of Life Research (ISOQOL); the MRC Hubs for Trials Methodology Research; the Health Research Authority; the Birmingham Health Partners and Institute for Translational Medicine.

The following Chapter is presented in paper format and has been submitted to the PLoS One journal for peer review as:

Kyte D, Duffy H, Fletcher B, Gheorghe A, Mercieca-Bebber R, King M, Draper H, Ives J, Brundage M, Blazeby J, Calvert M. Systematic review of the patient-reported outcome (PRO) content of clinical trial protocols.

The work in this Chapter has been accepted for presentation at the following conferences:

- **Kyte D**, Duffy H, Fletcher B, Gheorghe A, Mercieca-Bebber R, King M, Draper H, Ives J, Brundage M, Blazeby J, Calvert M. Evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. North American Primary Care Research Group (NAPCRG) Annual Meeting, November, New York 2014 [*Oral*]
- **Kyte D**, Duffy H, Fletcher B, Gheorghe A, Mercieca-Bebber R, King M, Draper H, Ives J, Brundage M, Blazeby J, Calvert M. Evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. NIHR SPCR Research Showcase, September, 2014 [*Oral*]
- **Kyte D**, Duffy H, Fletcher B, Gheorghe A, Mercieca-Bebber R, King M, Draper H, Ives J, Brundage M, Blazeby J, Calvert M. Evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. NIHR SPCR Trainees Event, September, 2014 [*Poster*]

Title Page

Title

Systematic Review of the patient-reported outcome (PRO) content of clinical trial protocols.

Authorship

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ABSTRACT

Background

Qualitative evidence suggests that patient-reported outcome (PRO) information is frequently absent from clinical trial protocols, potentially leading to inconsistent PRO data collection and risking bias. Direct evidence regarding the extent of PRO trial protocol content is lacking. The aim of this study was to systematically review the PRO-specific content of UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme clinical trial protocols.

Methods and Findings

We conducted an electronic search of the NIHR HTA programme database (inception to August 2013) for protocols describing a randomized controlled trial including a primary/secondary PRO (judged by agreement between two independent investigators). Two investigators independently reviewed the content of each protocol, using a specially constructed PRO-specific protocol checklist, alongside the 'Standard Protocol Items: Recommendations for Interventional Trials' (SPIRIT) Checklist. Disagreements were resolved through discussion with a third investigator. 75 trial protocols were included in the analysis. Protocols included a mean of 63% SPIRIT items (n=32, range 4-18, SD 3.56) and 33% PRO checklist items (n=11, range 16-41, SD 5.62). Protocols containing a primary PRO generally included slightly more PRO checklist items (mean 43%). PRO protocol content was not associated with general protocol completeness; thus, protocols judged as relatively

‘complete’ using SPIRIT were still likely to have omitted a large proportion of PRO information.

Conclusions

The PRO components of HTA clinical trial protocols require improvement. Information on the PRO rationale/hypothesis, data collection methods, training and management was often absent. The study findings also suggest there are a number of PRO protocol checklist items that are not fully addressed by the current SPIRIT statement. We therefore advocate the development of consensus-based supplementary PRO guidelines, aimed at improving the completeness and quality of PRO content in clinical trial protocols.

Introduction

The value of assessing patient-reported outcomes (PROs) in clinical trials has been emphasized by major international health-policy and regulatory authorities, and by patients.[1-3] PROs provide the patient's perspective on the degree and impact of disease symptoms and the physical, functional and psychological consequences of treatment. If captured in a scientifically rigorous way, PRO results may aid clinical decision-making[4], support labeling claims[5] and influence healthcare policy.[6] It is important, therefore, that details regarding PRO assessment are included in the trial protocol, to ensure that PRO data is collected and managed appropriately.

The trial protocol is a key document, which should provide sufficient detail to facilitate understanding of the study design and administration, and enable appraisal of the trial's scientific, methodological and ethical rigor by funders and ethics commitees.[7,8] However, important information relating to study design, implementation and dissemination is often omitted from trial protocols.[9-11] This has led to the development of international guidance for protocol developers and reviewers, in the form of the SPIRIT 2013 statement (Standard Protocol Items: Recommendations for Interventional Trials), which is aimed at enhancing general study design, conduct, reporting and external review.[7,8] PRO-specific information within trial protocols has received little scrutiny to-date. Recent qualitative evidence, however, suggests that trial personnel perceive it to be sub-optimal.[12] Poor PRO protocol content could lead to variation in PRO measurement across trial sites, potentially reducing data quality and biasing trial results.[12] Our objective was to systematically review randomised controlled trial (RCT) protocols including either a primary or secondary PRO outcome, evaluating the completeness of their PRO-

specific content using a specially developed PRO protocol checklist. We also used the SPIRIT tool to measure how complete the protocols were in broad terms, to investigate whether levels of PRO content were associated with general protocol completeness.

Methods

Ethics

The University of Birmingham ethical review board approved this study (ERN_13-0047).

Protocol Selection

We reviewed protocols submitted to the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, on assumption that they would provide a representative snapshot of such documentation within the domain of health-care research. The NIHR-HTA programme is the largest such funding stream in the UK (comparable to the National Institutes of Health in the US and the Australian New Zealand Clinical Trials Registry in Australasia) and as a public interest funder, promotes the inclusion of patient-centred outcomes in its research.[13] Two investigators (BF, HDu) independently reviewed the NIHR-HTA database (inception to August 2013, http://www.hta.ac.uk/research/index.shtml) for RCTs with a primary or secondary PRO endpoint. Disagreements regarding trial eligibility were resolved through discussion with a third reviewer (DK/MC). The most up-to-date trial protocols were retrieved for review, either from the HTA database, the trial website, or via the named trial representative (contacted by email, followed by one email reminder after 2 weeks).

Data Extraction

Two investigators (DK, HDu) independently extracted the following data from each protocol using a predesigned data extraction form: year of protocol publication, the

name(s) of the PRO(s) used in the trial, whether the PRO was a primary or secondary outcome, the trial setting (primary or secondary care) and the clinical specialty.

Protocol Checklists

The completeness of the PRO-specific content of trial protocols was assessed using a PRO protocol checklist (Table 1), generated from 162 recommendations identified in our systematic review of PRO-specific guidance for trial protocol writers.[14n] To construct the checklist, recommendations were grouped into major categories comprising 33 PRO-specific items for inclusion in a trial protocol. The individual recommendations were retained under each item as subcategories (illustrated in Figure 1). MC and DK constructed the initial framework of the PRO protocol checklist, which was then reviewed by HDr and JI, before being amended and approved by an international expert external advisory group (MB, JB, RMB, MK) (see Appendix I[o] for the full checklist).

[n] Chapter 7: Patient-Reported Outcome (PRO) Assessment in Clinical Trials: A Systematic Review of Guidance for Trial Protocol Writers

[o] Appendix 10 of the thesis

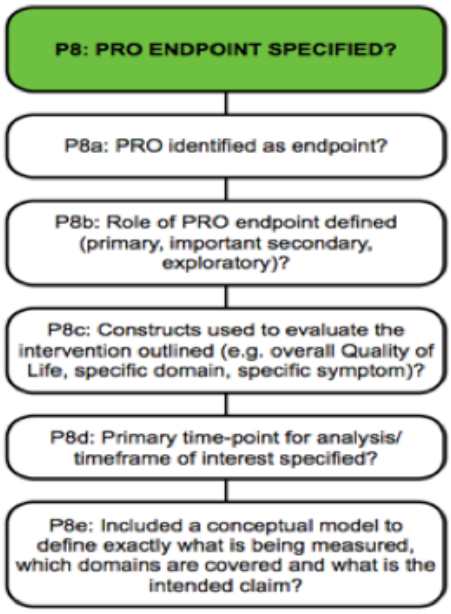

Figure 1. PRO protocol checklist item P8 (green) and associated sub-categories (white)

The completeness of general sections within each protocol was assessed using SPIRIT, as a proxy measure of the overall strength of the protocol.[7,8] The SPIRIT resources include a checklist[7] containing 51 individual recommended protocol items, spread over 33 categories and an accompanying explanatory paper[8] and website (www.spirit-statement.org).

Table 1. PRO-specific protocol checklist

SPIRIT Section	PRO Checklist Item Number	PRO Checklist Item Description
Administrative information		
	P1	Roles & Responsibilities of PRO Personnel Identified?
Introduction		
	P2	Background PRO-specific information provided?
	P3	PRO-specific rationale provided?
	P4	PRO-specific hypothesis provided?
	P5	PRO-specific objectives stated (in relation to dimensions, population and timeframe)?
Methods: Participants, interventions and outcomes		
	P6	Details & rationale of PRO study sample/setting provided?
	P7	PRO considerations discussed in the eligibility criteria?
	P8	PRO endpoint specified?
	P9	Timing of PRO assessments specified?
	P10	Timing of PRO assessment justified?
	P11	PRO sample size discussed & justified?
Methods: Assignment of interventions (for controlled trials)		
	P12	PROs discussed in relation to blinding?

Methods: Data collection, management and analysis		
	P13	PROM identified & described?
	P14	Choice of PROM justified in relation to study hypothesis?
	P15	Choice of PROM justified in relation to measurement properties?
	P16	Choice of PROM justified in relation to acceptability & patient burden?
	P17	PRO data collection plan included?
	P18	PRO data collection guidelines/training information provided for trial personnel?
	P19	Plans to avoid/minimise missing data provided?
	P20	PRO-specific Quality Assurance (QA) described?
	P21	PRO Statistical Analysis Plan Provided?
	P22	Plans to address multiplicity of PRO data provided?
	P23	PRO clinical significance defined?
	P24	Statistical methods to deal with missing PRO data defined?
Monitoring		
	P25	PRO data monitoring defined?
	P26	Plan for the identification and management of PRO Alerts included?
Ethics and dissemination		
	P27	PRO-specific consent information provided?
	P28	PRO-specific confidentiality procedures described?
	P29	PRO dissemination policy outlined?
Appendices		

	P30	PRO information included in consent materials?
	P31	PRO assessment checklist and/or flowsheet provided in appendix?
	P32	Exact version of PROM provided in CRF/appendix (with translated versions if appropriate)?
	P33	PROM completion instructions provided in CRF/appendix?

Abbreviations: PRO, patient-reported outcome; PROM, patient-reported outcome measure; CRF, case-report form.

Protocol Review

Two investigators (DK, HDu) independently assessed the content of the included protocols using the PRO and SPIRIT checklists. For each trial protocol assessed, items on each checklist were either described as 'present' or 'absent'. One point was assigned for each item 'present', giving a total score (maximum achievable, 51 for SPIRIT and 33 for the PRO checklist). In addition, for the PRO protocol checklist, the investigators also determined whether all sub-categories were satisfied for each item categorized as 'present'. Therefore, PRO items that were marked as 'present', but that failed to satisfy all of the appropriate sub-categories, were additionally tagged as 'incomplete'. Levels of investigator agreement were determined for both checklists. Disagreements were resolved through discussion with a third investigator (MC) if required.

Data Analysis

Analyses were performed using SAS V9.2 (SAS Institute, Cary NC). Descriptive analyses were conducted on the number of PRO-specific and SPIRIT checklist items present in the included protocols. To explore factors associated with the inclusion of PRO-specific protocol items, we performed a pre-specified multiple regression analysis in which the dependent variable was the PRO-specific protocol checklist score and the independent variables were: whether the PRO was named as a primary or secondary outcome, the trial setting, the clinical specialty and the SPIRIT checklist score. 75 protocols were required to satisfy the sample size requirement for this regression analysis (15 per co-variate[15]). The relationship between the PRO-specific protocol checklist score and the candidate explanatory variables was assessed using a backward stepwise selection process with α = 0.05 as criteria for model inclusion.

Results

At the time of the review (August 2013) 459 studies were listed on the HTA database, of which 284 fulfilled the inclusion criteria. As our sample size requirement was 75, we restricted our review to the 75 most recent trial protocols to provide an up-to-date picture of the PRO-specific content in such documentation. Levels of investigator agreement for both checklists were high (86%) and all disagreements were resolved through discussion. Characteristics of the included protocols are presented in Table 2. A PRO was the primary outcome in 41%; 38% were conducted in a primary care setting, 51% were conducted in secondary care and 11% were conducted in both. In total, 251 different PRO measures were used across the included trials (Appendix II[p]), the most common being the five dimension European Quality of Life instrument (EQ-5D), the Short-Form Health Survey 12-item (SF-12) and 36-item (SF-36) questionnaires and the Hospital Anxiety and Depression Scale (HADS).

[p] Appendix 11 of the thesis

Table 2. Characteristics of included protocols (N=75)

Characteristic	Protocols, No. (%)
Year	
2012	29 (39)
2013	46 (61)
Study PRO endpoint & setting	
PRO 1^{o} Outcome	31 (41)
Primary care setting	29 (38)
Secondary care setting	38 (51)
Both primary & secondary care	8 (11)
Clinical Research Area	
Mental Health	15 (20)
Neurology	8 (11)
Orthopaedics; Paediatric; Vascular	5 (7)
Obstetrics & Gynaecology; Oncology; Respiratory;	4 (5)
Cardiology; Physical Activity; Smoking Cessation	3 (4)
Falls Prevention; Gastroenterology; Weight Loss	2 (3)
Aids; Colorectal; Dermatology; Diabetes; Elderly Care; Emergency Services; General Practice; Hepatology; Nephrology; Urology	1 (1)
PROMS[#]	
EQ5D	56 (75)
SF36	13 (17)
SF12	12 (16)
Hospital Anxiety and Depression Scale (HADS)	9 (12)
Patient Health Questionnaire 9 (PHQ-9)	6 (8)
Pediatric Quality of Life Inventory (PEDSQL);	5 (7)
Epworth Sleepiness Scale (ESS); Beck Depression Inventory (BDI); Generalised Anxiety Disorder (GAD-7); Calgary Sleep Apnoea Quality of Life Index (SAQLI); Carer/Proxy/Parent Completion EQ-5D	3 (4)

Client Services Receipt Inventory (CSRI); WHOQOL-BREF Secondary; The Lubben Social Network Scale (LSNS); Resource Use questionnaire; Morisky Medication Adherence Scale; International Physical Activity Questionnaire (IPAQ); Clinical Outcomes in Routine Evaluation Outcome Measure (CORE-OM); Falls Efficacy Scale; Nottingham Activities of Daily Living (NEADL); Olerud & Molander Ankle Score (OMAS)	2 (3)

[#]PROMS listed used in >1 protocol. Total Number of PROMS used n=251. A full list appears in Appendix II [Appendix 10 of the thesis]

Adherence to SPIRIT and PRO Checklists

Protocols included a mean of 63% SPIRIT recommendations (n=32 of 51, range 4-18, SD 3.56) and 33% PRO-specific items (n=11 of 33, range 16-41, SD 5.62). Protocol adherence to individual SPIRIT and PRO checklist items is presented in Figures 2 and 3, summarized in Table 3, and discussed below.

Fig. 2 Protocol adherence to individual SPIRIT checklist items. *Denominator adjusted as n=46 blinded trials included in sample.

Fig. 3 Protocol adherence to individual PRO checklist items. *Denominator adjusted as n=46 blinded trials included in sample.

Table 3. Protocol adherence to individual SPIRIT and PRO checklist items (Sample, n=75)

SPIRIT CHECKLIST	TOTAL	PRO CHECKLIST	COMPLETE	INCOMPLETE	TOTAL
Administrative Information					
ITEM 1: Title	**97.33%**				
ITEM 2A: Trial identifier and registry name	**57.33%**				
ITEM 2B: WHO Trial Registration Data Set	**0.00%**				
ITEM 3: Protocol version	**98.67%**				
ITEM 4: Funding	**64.00%**				
ITEM 5A: Protocol contributors	**8.00%**				
ITEM 5B: Trial sponsor information	**88.00%**				
ITEM 5C: Role of sponsor and funders in study	**1.33%**				
ITEM 5D: roles of coordinating centre/steering committee etc.	**84.00%**				
		ITEM 1: Roles & Responsibilities of PRO Personnel Identified?	**0.00%**	**6.67%**	**6.67%**
INTRODUCTION					
ITEM 6A: Description of research question and justification for undertaking the trial	**98.67%**				
ITEM 6B: Explanation for choice of comparators	**64.00%**				
		ITEM 2: Background PRO-specific information provided?	**24.00%**	**25.33%**	**49.33%**
		ITEM 3: PRO-specific rationale provided?	**0.00%**	**8.00%**	**8.00%**
ITEM 7: Objectives	**97.33%**				
		ITEM 4: PRO-specific hypothesis provided?	**17.33%**	**1.33%**	**18.67%**
		ITEM 5: PRO-specific objectives stated (in relation to dimensions, population and timeframe)?	**38.67%**	**38.67%**	**77.33%**
ITEM 8: Description of trial design	**96.00%**				
Methods: Participants, Interventions and Outcomes					

ITEM 9: Study setting	**68.00%**				
		ITEM 6: Details & rationale of PRO study sample/setting provided?	**0.00%**	**0.00%**	**0.00%**
ITEM 10: Eligibility criteria	**100.00%**				
		ITEM 7: PRO considerations discussed in the eligibility criteria?	**12.00%**	**33.33%**	**45.33%**
INTERVENTION					
ITEM 11A: Interventions for each group	**97.33%**				
ITEM 11B: Criteria for discontinuing or modifying allocated interventions	**50.67%**				
ITEM 11C: Strategies to improve adherence to intervention protocols	**50.67%**				
ITEM 11D: Relevant concomitant care and interventions	**29.33%**				
ITEM 12: Outcomes	**82.67%**				
		ITEM 8: PRO endpoint specified?	**62.67%**	**34.67%**	**97.33%**
ITEM 13: Participant timeline	**50.67%**				
		ITEM 9: Timing of PRO assessments specified?	**0.00%**	**97.33%**	**97.33%**
		ITEM 10: Timings of PRO assessment justified?	**4.00%**	**2.67%**	**6.67%**
ITEM 14: Sample size	**97.33%**				
		ITEM 11: PRO sample size discussed & justified?	**30.67%**	**20.00%**	**50.67%**
ITEM 15: Recruitment	**86.67%**				
Methods: Assignment of interventions (for controlled trials)					
ITEM 16A: Allocation Sequence generation	**86.67%**				
ITEM 16B: Allocation concealment	**81.33%**				

ITEM 16C: Allocation Implementation	**34.67%**				
BLINDING					
ITEM 17A: Who will be blinded after assignment to interventions*	**96.23%**				
ITEM 17B: circumstances under which unblinding is permissible*	**28.30%**				
		ITEM 12: PROs discussed in relation to blinding?*	**3.77%**	**0.00%**	**3.77%**
Methods: Data Collection, Management and Analysis					
ITEM 18A: Plans for assessment and collection of outcomes	**96.00%**				
		ITEM 13: PROM identified & described?	**1.33%**	**98.67%**	**100.00%**
		ITEM 14: Choice of PROM justified in relation to study hypothesis?	**9.33%**	**32.00%**	**41.33%**
		ITEM 15: Choice of PROM justified in relation to measurement properties?	**5.33%**	**32.00%**	**37.33%**
		ITEM 16: Choice of PROM justified in relation to acceptability & patient burden?	**2.67%**	**12.00%**	**14.67%**
		ITEM 17: PRO data collection plan included?	**1.33%**	**82.67%**	**84.00%**
		ITEM 18: PRO data collection guidelines/training information provided for trial personnel?	**0.00%**	**8.00%**	**8.00%**
		ITEM 19: Plans to avoid/minimise missing data provided?	**34.67%**	**12.00%**	**46.67%**
ITEM 18B: Plans to promote participant retention	**80.00%**				
ITEM 19: Data management	**86.67%**				

		ITEM 20: PRO-specific Quality Assurance (QA) described?	**0.00%**	**60.00%**	**60.00%**
ITEM 20A: Statistical methods for analysing primary and secondary outcomes	**98.67%**				
		ITEM 21: PRO Statistical Analysis Plan Provided?	**77.33%**	**18.67%**	**96.00%**
		ITEM 22: Plans to address multiplicity of PRO data provided?	**1.33%**	**0.00%**	**1.33%**
		ITEM 23: PRO clinical significance defined?	**0.00%**	**1.33%**	**1.33%**
		ITEM 24: Statistical methods to deal with missing PRO data defined?	**21.33%**	**24.00%**	**45.33%**
ITEM 20B: Methods for any additional analyses (e.g., subgroup and adjusted analyses)	**70.67%**				
ITEM 20C: analysis population relating to protocol nonadherence	**72.00%**				
MONITORING					
ITEM 21A: Composition of DMC etc.	**85.33%**				
ITEM 21B: Description of any interim analyses and stopping guidelines	**66.67%**				
		ITEM 25: PRO data monitoring defined?	**1.33%**	**0.00%**	**1.33%**
ITEM 22: Harms	**85.33%**				
		ITEM 26: Plan for the identification and management of PRO alerts included?	**8.00%**	**2.67%**	**10.67%**
ITEM 23: auditing	**54.67%**				
Ethics and Dissemination					
ITEM 24: research ethics approval	**88.00%**				

ITEM 25: protocol amendments	**16.00%**				
ITEM 26A: consent or assent	**89.33%**				
ITEM 26B: consent or assent (BIO SPECIMENS)	**8.00%**				
		ITEM 27: PRO-specific consent information provided?	**1.33%**	**0.00%**	**1.33%**
ITEM 27: CONFIDENTIALITY	**62.67%**				
		ITEM 28: PRO-specific confidentiality procedures described?	**4.00%**	**0.00%**	**4.00%**
ITEM 28: DECLARATION OF INTERESTS	**0.00%**				
ITEM 29: ACCESS TO DATA	**2.67%**				
ITEM 30: ANCILLARY AND POST-TRIAL CARE	**62.67%**				
ITEM 31A: Dissemination policy	**74.67%**				
ITEM 31B: Authorship eligibility guidelines	**36.00%**				
		ITEM 29: PROs dissemination policy outlined?	**33.33%**	**0.00%**	**33.33%**
ITEM 31C: Plans, if any, for granting public access to the full protocol	**0.00%**				
APPENDICES					

ITEM 32: INFORMED CONSENT MATERIALS	**68.00%**				
		ITEM 30: PRO information included in consent materials?	**25.33%**	**33.33%**	**58.67%**
ITEM 33: BIOLOGICAL SPECIMENS	**18.67%**				
		ITEM 31: PRO assessment checklist and/or flowsheet provided in appendix?	**0.00%**	**0.00%**	**0.00%**
		ITEM 32: Exact version of PROM provided in CRF/appendix (with translated versions if appropriate)?	**10.67%**	**0.00%**	**10.67%**
		ITEM 33: PROM completion instructions provided in CRF/appendix?	**0.00%**	**0.00%**	**0.00%**

*Note: n=46 blinded trials included in final sample, denominator adjusted accordingly. Abbreviations: PRO, patient-reported outcome; PROM, patient-reported outcome measure; CRF, case-report form.

Administrative information

SPIRIT

Protocols routinely included general administrative information including: the project title (97%), protocol version (99%), trial sponsor (88%) and coordinating centre/steering committee details (84%). Just under two-thirds presented information regarding trial registration (57%) or sources of funding (64%). Few (8%) made it clear who had contributed to the production of the protocol.

PRO-specific

Five (7%) protocols included administrative information regarding the roles and responsibilities of trial personnel involved in the design and collection of PRO data.

Introduction

SPIRIT

Almost all protocols (99%) included general background information in the introduction and outlined the trial rationale or included specific trial objectives or hypotheses (97%).

PRO-specific

Just under half of the protocols (49%) provided background details regarding the relevant existing PRO research (or lack of) in the area of interest, but very few (8%) included a rationale for the collection of PRO data within the trial. Over two-thirds also included PRO-specific objectives (77%), however, over one-third of these (39%) were incomplete. For example, details regarding the PRO dimensions under

investigation or the timeframe of interest were often missing. In addition, less than one-third of protocols (19%) provided a PRO-specific hypothesis.

Methods: Participants, Interventions and Outcomes

SPIRIT

Just over two-thirds of protocols (68%) included a description of the study setting(s), whilst 100% included general eligibility criteria. Protocols routinely included information on trial recruitment methods (87%), interventions (97%), outcomes (83%) and sample size requirements (97%). Half of the protocols (50%) presented criteria for discontinuing or modifying interventions, strategies to improve adherence to intervention protocols and included a participant time schedule. Less than one-third (29%) discussed relevant concomitant care and interventions.

PRO-specific

Just under half of the included protocols (45%) discussed PRO-specific eligibility considerations. None provided a description/rationale addressing which trial participants were eligible for PRO analysis. There was routine reporting of the timing of PRO assessments (97%), but justification for PRO timings was rarely provided (7%). PRO endpoints were described in nearly all protocols (97%), however, in more than one-third (35%) the information provided was incomplete. For example, the primary time-point for analysis, or an outline of the constructs used to evaluate the intervention (e.g. overall quality of life, or a specific domain/symptom) were frequently absent. Similarly, whilst PRO sample size requirements were provided in

approximately half of the included protocols (51%), 20% of these failed to justify the assumptions underpinning PRO analyses.

Methods: Assignment of Interventions (for controlled trials)

SPIRIT

All of the included trials were controlled and 61% employed some form of blinding. Most protocols detailed methods of allocation sequence generation and concealment (87% and 81% respectively), but few outlined who would assign participants to interventions (35%). Almost all protocols (96%) identified who would be blinded to the trial interventions, but less than one-third (28%) discussed the circumstances under which un-blinding was permissible.

PRO-specific

3% of protocols discussed PROs in relation to blinding.

Methods: Data Collection

SPIRIT

Most protocols (96%) provided general plans for the assessment and collection of trial outcomes and over two-thirds (80%) described proposed strategies for the promotion of participant retention.

PRO-specific

PROMs were always named (100%), but details regarding the measures were frequently missing, for example, the number of items/domains, methods for

instrument scaling/scoring and estimated average completion time. The choice of PROM was rarely justified, whether in relation to the study hypothesis (justified in 41%), measurement properties (justified in 37%), or in relation to participant acceptability/burden (justified in 15%). Where some justification (of any type) was present (n=33 protocols, 44%), it was commonly incomplete, for example, often information was not provided regarding the evidence-base (or lack of) for all measurement properties for a given tool, or for all tools used within a trial, and references were regularly absent. Brief information surrounding the plans for PRO data collection was included in 84% of protocols, but again elements were often absent, for example, there was a lack of information on who should administer the PROM and the level of assistance allowed during assessment, whether proxy assessment was permissible and where PRO assessment would take place. Just under half of the protocols (47%) detailed plans to minimize levels of avoidable missing PRO data. Finally, only 8% of protocols provided information surrounding PRO data collection guidelines and/or training for trial personnel.

Methods: Management and Analysis

SPIRIT

Data management issues were discussed in 87% of protocols. Statistical methods for analysing (non-PRO) primary and secondary outcomes were routinely included in almost all (99%) protocols and over two-thirds discussed methods of additional analysis (71%) (e.g. subgroup analysis) and the handling of protocol non-adherence (72%).

PRO-specific

PRO-specific quality assurance issues were discussed in 60% of protocols. A PRO statistical analysis plan was provided in 96% of protocols, however, very few (1%) provided plans to address multiplicity of PRO data or were explicit about PRO clinical significance levels; and less than half (45%) detailed statistical methods to deal with missing PRO data.

Monitoring

SPIRIT

Information regarding the Data Monitoring Committee, interim analysis, stopping guidelines and trial auditing arrangements was included in 85%, 67% and 55% of protocols respectively. Plans for monitoring and managing adverse events/harms were included in 85% of protocols.

PRO-specific

PRO-specific data monitoring issues were discussed in 1% of protocols. Plans for the identification and management of 'PRO Alerts' - where trial personnel encounter 'concerning' individual participant PRO data that may require a prompt response[16] - were included in 11% of protocols.

Ethics and Dissemination

SPIRIT

Inclusion of ethics approval information (88%), informed consent/assent procedures (89%) and a dissemination policy (75%) was common. Just under two-thirds of

protocols discussed confidentiality (63%) and ancillary and post-trial care (63%). Less commonly mentioned was authorship eligibility (36%), access to trial data (3%) or declaration of interests (0%).

PRO-specific

A third of protocols discussed PRO-specific dissemination (33%), but few tackled PRO consent (1%) or confidentiality (4%) issues.

Appendices

SPIRIT

Fifty-one (68%) of the included protocols included patient information and consent materials in an appendix.

PRO-specific

PRO-specific information was included in 59% of patient information sheets. An exact version of the PROM(s) employed by the study was included in 11% of appendices; none included a PRO assessment checklist/flowchart.

Determinants of Differences in PRO-specific Protocol Content

Table 4 summarizes the findings from our exploratory multiple regression analysis, which investigated predictors of differences in the PRO-specific checklist score between protocols. In the final model, only the nature of the PRO endpoint (primary versus secondary) was significant (P<.001), suggesting that protocols describing trials with a primary PRO include on average 5.14 (95% CI 3.92 to 6.36) additional recommended PRO-specific items compared to those employing a secondary PRO

endpoint. There were no significant associations between the PRO checklist score and the year of protocol publication (P=.18), the trial setting (P=.08), the clinical specialty (P=.14) or the SPIRIT checklist score (P=.17).

Table 4. Regression model investigating predictors of PRO-specific checklist score[a]

Independent Variable	**β (95% CI)**	***P* Value**	**R^2**
PRO listed as the primary outcome	5.00 (3.79 to 6.21)[b]	<0.001	0.47[c]

Abbreviations: CI, confidence interval
[a]Model with PRO protocol checklist score (max 33) the dependent variable (n=75 included protocols)
[b]Intercept: 14.07 (95% CI 13.12 to 15.02)
[c]Reflects the proportion of variability in the PRO-specific checklist score explained by the statistical model
[The full (first) model is presented in Appendix 12 of the thesis]

Discussion

Summary of Findings

To our knowledge, this is the first study attempting to evaluate the PRO-specific content of trial protocols. We found that routine inclusion of PRO information was poor (33%) and that over half (61%) of included PRO items were incomplete. Trials with a primary PRO endpoint tended to routinely include slightly more PRO information in their protocols (mean 43%). The level of PRO protocol content was not associated with general protocol completeness; thus, protocols judged as relatively 'complete' using SPIRIT were still likely not to have included a large proportion of the items on the PRO checklist.

Our findings are concordant with the prevailing empirical evidence that important general methodological details are often missing from protocols.[9-11,17,18] On average, the reviewed protocols failed to include over one-third (37%) of the recommended protocol items outlined in SPIRIT[7] and over two-thirds (67%) of PRO checklist items. Our results also concur with qualitative data drawn from UK-based trial personnel, revealing a perception that PRO-specific information in clinical trial protocols is lacking.[12]

Omission of recommended PRO content in trial protocols could lead to inconsistent assessment of important 'patient-centred' outcomes[12], risking biased and unreliable trial results, and lessening the impact of PROs on routine clinical care. This practice may mislead clinical or health policy decision-making, reduce the value of patient

participation in trials and waste limited healthcare and research resources: this is unethical.[19]

The particularly low PRO checklist adherence we observed in our study is somewhat unsurprising, as evidence suggests existing PRO guidance for protocol writers is difficult to access and lacks consistency.[14q] Until such time as this guidance improves, it may be difficult for researchers to effectively incorporate PRO information into their protocols. Unfortunately, our findings here also suggest that PRO-specific protocol items are either not addressed by the current SPIRIT checklist (for example, the management of 'PRO Alerts'[16]); or are addressed only partially, such that fuller explanation is warranted to provide meaningful guidance to protocol developers who may not be familiar with PRO methodology (for example, approaches to minimise avoidable missing PRO data). The scope and number of additional PRO items, and the current lack of coherence in the guidance literature, justifies the need for supplementary PRO-specific guidelines. The PRO protocol checklist developed for this study could be incorporated into such guidelines. It is important to note, however, in designing the PRO checklist we deliberately sought to retain all PRO protocol guidance extracted in our review[14q], without making a judgment on which items might be essential and which may be optional, or if the essential versus optional items might differ depending on whether a PRO was a primary or secondary outcome. The checklist therefore provides the research community with a comprehensive starting point, as opposed to a definitive tool; and does not amount to an international consensus, but rather represents an approximation of it for illustrative purposes. The next step would be for the PRO protocol checklist be subjected to a formal

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[q] Chapter 7: Patient-Reported Outcome (PRO) Assessment in Clinical Trials: A Systematic Review of Guidance for Trial Protocol Writers

international consensus process to ensure that it provides appropriate and consistent guidance to protocol developers and focuses on only those PRO-specific protocol items that are deemed most important by the scientific community and other relevant stakeholders, including patients. Following this process, the checklist may prove a valuable addition to formal PRO protocol guidelines, aimed at improving the completeness and quality of PRO content in clinical trial protocols.

Strengths and Weaknesses

The major strength of this study is its use of systematic methods and multiple reviewers at all stages. The SPIRIT 2013 statement was developed with comprehensive stakeholder involvement using rigorous and systematic methodology.[20,21] The PRO-specific checklist used in this study was developed by experts in the field, is supported by a systematic review of existing guidance[14] and demonstrated high levels of inter-rater agreement. However, it is yet to undergo a formal consensus process or validation. Both the PRO and SPIRIT checklists are still very recent and would not have been available to the developers of many of the included protocols, therefore validation of our findings in a contemporary sample of protocols is required. Our protocol sample is relatively small, and all describe trials that are UK-led (within a single funding stream), potentially restricting generalizability. Nevertheless, the sample includes studies focusing on a range of clinical specialties, conducted in a variety of healthcare settings and employing a broad spectrum of PROs, thus enhancing external validity. Finally, it is possible that the trial protocols from other funding bodies are more advanced, in PRO terms, than those included in our review, although this is unlikely given the stature and nature of the HTA programme, further work would be needed to test this hypothesis.

Conclusions

The PRO components of HTA clinical trial protocols require improvement. Detailed instructions on the PRO rationale/hypothesis, data collection methods, training and management were often absent from protocols, and even where such information appeared it was frequently incomplete. This is unsurprising, however, as existing PRO guidance for protocol writers lacks consistency and PRO-specific protocol items are not fully addressed by the current SPIRIT statement. There is a need for consensus-based supplementary guidelines outlining recommended standard PRO content for inclusion within trial protocols.

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Author Contributions

All authors contributed to the design of the study. MC, DK, AG, HDr, JI, MB, JB, RMB and MK obtained funding. BF and HDu searched for eligible trial HTA protocols, with input from a third reviewer (DK/MC) when necessary. DK and HDu extracted data from included protocols. DK and HDu evaluated the content of included protocols using the SPIRIT and PRO-specific checklists, with assistance from MC where necessary. MC and DK produced the PRO-specific checklist with input from the international advisory panel (MB, JB, MK and RMB) and all approved the final version. DK conducted the main analysis. DK wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the final version for publication.

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Keywords

Patient-reported outcomes; PROs; patient-reported outcome measures; PROMs; clinical trials; trial protocols; protocol writing; protocol development; checklist; SPIRIT

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Chapter 9. Discussion and conclusions

This chapter summarises and synthesizes the principal findings presented in the thesis. The aim was to investigate anecdotal reports from trial staff detailing: (1) inconsistencies in PRO trial administration; (2) difficulties related to the management of 'concerning' PRO data; and (3) a lack of PRO-specific guidance and training in trials; in order to:

- Establish whether the reports were generalizable to the wider community of trial staff.
- Explore the methodological issues associated with PRO measurement in clinical trials and identify ethical issues requiring considered debate.
- Examine current PRO-specific trial guidance and determine whether, and if so which, areas may be in need of improvement.

A series of novel studies were undertaken to address these aims, the results of which represent an original contribution to the field of PROs research. Initially, a qualitative study of trial researchers involved in PRO data collection was conducted in order to gain a greater understanding of the nature and demands of PRO assessment in trials, and to explore, in greater depth, the issues that had been raised by trial staff (Chapter 2; published in PLoS One, 2013[1]; to-date 1,368 views, 2 citations).

Aspects emerging from this qualitative work regarding the previously unreported phenomenon of 'concerning' PRO data in trials, were further examined in a viewpoint paper published in JAMA in 2013[2], in which the term 'PRO alert' - the exposure of staff to 'concerning' PRO information - was coined.

A large-scale survey of trial staff and management involved in PRO assessment was subsequently conducted (Chapters 4 and 5), in order to determine if the anecdotal reports and qualitative data outlined above were generalizable to the wider population of trial staff, and to further explore the differing viewpoints of the various professional groups.

A systematic review exploring the 'in-trial' PRO guidance literature available to front-line trial staff was presented in Chapter 6 (published in PLoS One, 2013[3]; to-date 1,992 views, 4 citations). A large-scale systematic review investigating the PRO-specific guidance literature available to trial protocol developers was presented in Chapter 7 (led by Calvert, Kyte second author). Finally, using a novel PRO protocol checklist, the PRO components of NIHR HTA trial protocols were subjected to systematic evaluation to determine the directly accessible PRO-specific information available to researchers involved in trials (Chapter 8).

9.1 Summary of principal findings

9.1.1 Inconsistencies in PRO data collection

The qualitative findings presented in Chapter 2 revealed a perception amongst trial staff that there are inconsistencies in the administration and management of PROs in some UK trials.[1] It was argued that such inconsistencies had the potential to undermine the quality of PRO data and introduce bias. Specifically, standardization of PRO data collection processes appeared to be lacking with regard to the timing of PRO assessment, levels of privacy and assistance provided to participants completing questionnaires, and approaches to the management of missing PRO data.

A cross-sectional survey of 767 UK-based research nurses, data managers/coordinators, trial managers and CPIs (Chapter 4) demonstrated these qualitative findings could be generalized to the wider community of trial staff. The data also provided further evidence of a wide variation in the approach of staff to PRO assessment in trials. It was argued that, if this variation was to occur in a single trial (as suggested by qualitative findings presented in Chapter 2), it had the potential to introduce bias.

9.1.2 PRO alerts in clinical trials

Qualitative data[1] (Chapter 2), supported by quantitative survey findings (Chapter 5), confirmed the presence of the previously unreported phenomenon of 'concerning' PRO data in trials. Data suggested trial staff may be intermittently exposed to 'PRO alerts': participant PRO data indicating 'concerning levels of psychological distress or physical symptoms that may require an immediate response.'[2] Some staff responding to alerts reported intervening to aid the trial participant, but did not always record the intervention in the trial documentation, potentially risking co-intervention bias. There was also reported variation in factors that triggered a PRO alert for different individuals, the nature of their subsequent response and the method with which the response was recorded in the trial (where this was a possibility). It was therefore argued (Chapter 3) that trial management groups should standardize PRO alert management across trial sites using *a priori* developed procedures, which should be included in trial training and SOPs, and signposted in the trial protocol.[2] The advantages and disadvantages of four potential alert management options were presented.

9.1.3 PRO trial guidance

The findings of the systematic review presented in Chapter 6 suggested there is a lack of published 'in-trial' PRO guidance for front-line data collection staff addressing general PRO assessment and the management of 'concerning' PRO data. Qualitative (Chapter 2) and Quantitative (Chapters 4 and 5) findings also highlighted a perception amongst staff that PRO-specific training in trials is lacking. Evidence presented in Chapter 7 suggested PRO guidance for protocol developers lacks consensus and is difficult to access. A review of NIHR HTA trial protocols (Chapter 8) evaluated the PRO-specific guidance directly available to front-line trial staff. This found that PRO protocol information (regarding both administration and alert management) was frequently absent, even where the PRO was a primary outcome. In addition, protocols judged as relatively 'complete' in general terms, as measured by SPIRIT, were still likely to include very little PRO information.

9.2 Interpretation and implications of findings

9.2.1 Variation in PRO administration and sub-optimal guidance

Ensuring adequate standardisation of data collection processes across study sites is a key consideration during the design phase of a trial.[4-9] Ideally, identical procedures for collecting and recording data should be used by all trial staff in order to minimise errors/missing data, thereby maximising data quality and reducing the risk of bias.[5] Data collection procedures should ideally be outlined in the trial protocol, and reinforced during trial training, so that all trial personnel are properly acquainted with them[5,10]; these recommendations apply equally to all trial outcomes, including PROs. Unfortunately, as outlined in Chapters 2, 4, 5 and 8 of the thesis, in relation to PRO data collection, both protocol content and trial training can vary in

quality. As guidance also appears to be lacking in the literature[3] (Chapter 6), it is unsurprising that qualitative[1] (Chapter 2) and quantitative (Chapter 4) findings suggest PROMs can be administered inconsistently by trial staff. This thesis highlights three specific problem areas: differing levels of assistance given to participants completing PROs may lead to response bias; variation in the timing of PRO completion in relation to the clinical consultation may lead to data contamination; and differences in the management of missing PRO items/questionnaires may reduce the quality of PRO trial data and could introduce attrition bias. The presence of such inconsistency in a trial compromises the reliability and validity of PRO trial results, at best, weakening the confidence with which PRO findings may be used to inform patients, clinicians, labelling committees and policy makers; and at worst misleading clinical or health policy decision-making, reducing the value of patient trial participation and wasting research resources.[11]

9.2.2 Logistical and ethical considerations of PRO alerts

The findings presented in this thesis suggest that the previously unreported presence of PRO alerts in trials may be problematic, especially where they are inconsistently managed (Chapters 2, 3 and 5). Unfortunately evidence suggests there are no clear guidelines in the literature addressing the management of PRO alerts in trials[3] (Chapter 6). In addition, both protocol content and trial training covering PRO alerts is lacking, even though trial staff appear to desire it (Chapters 2, 5 and 8). As argued in Chapter 3, consensus is required on how best to manage PRO alerts prior to the development of appropriate trial guidance. A consensus will need to take into account and accommodate the potential implications of the two different PRO alert

management approaches discussed by trial staff surveyed/interviewed during this doctoral research.

Approach 1: non-intervention

A minority of trial staff appeared to support not responding to 'concerning' PRO data where it was encountered. The main argument provided for this approach was that the management of the participant's progress and treatment was felt to be the responsibility of clinicians external to the trial (Chapters 2 and 5). For example, the survey of UK trial staff presented in Chapter 4 reported that 12% of CPIs, 24% of trial managers and 42% of data managers/coordinators felt data collectors should not intervene in the event of a PRO alert, but instead allow the trial participant's GP and regular healthcare team to monitor and deal with any issues. There is, however, an assumption here that clinicians outside of the research team are routinely and regularly monitoring patients using the same PROM tools as researchers and would therefore be aware of any deterioration in the patient's quality of life. This is unlikely to be the case. In the UK, PROMs are not yet administered in all areas as part of routine clinical care. Where PROMs are collected, they tend to be aggregated as a measure of the effectiveness for an entire NHS healthcare provider or for purpose of service evaluation and commissioning: as, for example, in the NHS PROMs initiative.[12] There are signs that this may change in the future[12-18], but this is not yet the norm. Thus, health care teams may not be aware of deterioration in a patient's wellbeing, which may have been identified in a trial PROM. If the research team ignore PRO alerts in their trial, the trial participant will not necessarily receive appropriate care, and so the belief that they will is misguided. Whilst it may be the

case that the trial participant's care team has the primary responsibility for managing their healthcare, this does not mean that the trial team has no such responsibility.

UK researchers have an ethical and legal duty of care to trial participants that is outlined in several sources including the Declaration of Helsinki[19], the Department of Health Research Governance Framework for Health and Social Care[20] and the European Union Directives 2001/20/EC[21] and 2005/28/EC[22]. These guidelines mandate that the protection of the trial participants' safety and well-being should remain the priority in clinical trials. To this end, trial management groups are required to undertake a thorough assessment of the predictable risks to participants during the design phase of a trial and to outline the procedures which will be implemented to minimise such risk.[19] The findings presented in this thesis suggest there is a risk that trial PROs may uncover deterioration in a participant's well being that is not known to clinicians outside of the study: researchers therefore have an obligation to recognize this 'predictable risk' at the design stage of a trial and should have a management plan in place to address it.[19-22] By choosing to avoid action in the face of a PRO alert, researchers may be failing to discharge their duty of care towards the participants in the trial.

Where PROs *are* collected and monitored for alerts in routine clinical practice, the situation is less clear-cut. The PRO assessment method/schedule employed by the trial may be different to that used in clinical practice, and a PRO alert raised by trial data monitoring may not yet have been picked up by the clinical team. Ignoring the alert may again lead to delayed intervention potentially compromising the wellbeing of the participant. This situation may be avoided, however, if it were possible for a

clinical team to share its routinely collected PROM data with the trial team. For example, the use of a shared electronic PRO (e-PRO) assessment platform, would allow trial staff to extract the PRO data they require for the study, whilst the system could automatically flag PRO alerts to the clinical team, protecting the interests of the patients. Such systems are in development[14,16,18,23-28], but are not yet commonly employed in the UK (this is further discussed in section 9.3.3). Thus, where shared e-PRO systems are not viable, and given that the welfare of the trial participant is always paramount, researchers have an obligation to act on PRO alerts.[19-22] This responsibility could simply be discharged by passing on information to the clinical team; who would then have responsibility for determining the most appropriate clinical response.

Approach 2: monitoring and intervention

The majority of trial personnel interviewed (Chapter 2) and surveyed (Chapter 5) advocated intervening in response to a PRO alert, appearing to consistently prioritise the wellbeing of the participant over the needs of the trial. Whilst this approach adheres to the legal and ethical frameworks governing such research[19-22], it was not without its problems.

The evidence presented in this thesis suggests trial staff may deliver ad-hoc co-interventions to participants in response to PRO alerts and that such interventions may not be recorded in the trial documentation (Chapters 2 and 5).[1] In doing so, trial personnel may unwittingly introduce co-intervention bias if PRO alerts are not evenly distributed across trial groups.[29] This could be the case, for example, in trials where drug toxicity is more prevalent in a particular arm of the study. Non-reporting of PRO

alert co-interventions means the data may not be available to trial statisticians, therefore, it may not be possible to control for this potential confounder. This could lead to overall under- or over-estimates of effectiveness, harming the integrity of the trial results.

Implications

A clear legal and ethical case can be made that PRO alerts should not be ignored by trial staff. However, it is also apparent that ad-hoc alert interventions, although potentially beneficial for the trial participant, may pose significant problems for the trial results. Alerts should, therefore, be managed in a way that prioritizes the wellbeing of the trial participant, but also promotes high quality data collection, whilst allowing the collection of co-intervention information to inform the study analysis. Further research, in concert with considered ethical debate, is required to determine the most appropriate way to manage PRO alerts in trials and to facilitate the development of appropriate guidance.

9.3 Recommendations for future research

Based on the work presented in this thesis, there remains much research to be completed surrounding the implementation of PROs in trials and the improvement of methodological rigour. Whilst several research initiatives have focused on PROs in the past decade, most have concentrated on either the generation or selection of PROs for trials, or the reporting of PRO trial results, rather than on the implementation of PRO assessment. For instance, the PROMIS (Patient Reported Outcomes Measurement Information System) cooperative group have worked to develop reliable

and precise PROMs for trial use.[30] The COSMIN (**CO**nsensus-based **S**tandards for the selection of health **M**easurement **In**struments) group have focused on PRO instrument selection, developing the COSMIN tool for researchers wishing to evaluate the measurement properties of existing PROMs.[31,32] The COMET (Core Outcome Measures in Effectiveness Trials) initiative has sought to agree standardized sets of outcomes (including both PROs and clinician-reported outcomes) for trials addressing cognate research areas, providing further assistance for researchers involved in PRO trial design.[33,34] There has also been recent attention on the reporting of PRO trial results with the publication of the CONSORT (Consolidated Standards of Reporting Trials) PRO extension.[35,36] The extension provides 5 additional PRO-specific items and 9 'elaborations' to the 25-item CONSORT checklist, published in 2010, which aimed to improve the completeness of RCT reports.[37] Areas surrounding PRO protocol development and PRO trial conduct, however, require further research and are discussed below.

9.3.1 PRO protocol development

The systematic review presented in Chapter 8 found that PRO-specific content was often absent from trial protocols. The evidence presented in this thesis, coupled with the experiences of the PRO Research Group at the University of Birmingham, suggest three key factors may be responsible:

i. There is a lack of easily accessible, highly visible, consolidated and internationally endorsed guidelines for protocol developers, which contain recommendations on standard PRO-specific protocol items.
ii. There is a lack of PRO-specific education/training available for researchers involved in production of the protocol.

iii. Research funders and RECs do not require, and may not consider, minimum requirements for the PRO content of protocols during their review processes, meaning there is little incentive for researchers to improve such items.

A template for the development of future PRO protocol guidelines is presented in the work conducted by the SPIRIT group, who recently provided the research community with general resources geared towards improving the completeness of trial protocols.[4,5,38,39] Rigorous Delphi and consensus methods were used to develop a checklist[4] containing recommended items for inclusion in a trial protocol and an accompanying explanatory paper[5] and website (www.spirit-statement.org). Evidence presented in this thesis (Chapter 8) suggests SPIRIT may not effectively address PRO-specific protocol content. However, the methods used to construct the SPIRIT resources could readily be used for the development of a PRO-specific 'SPIRIT PRO Extension' checklist, explanatory paper and web-based training resource. The aim would be to promote the use of the SPIRIT PRO Extension resources by trial researchers, funders and journal editors to:

- Improve the completeness and quality of the PRO content in clinical trial protocols.
- Promote optimal PRO data collection, management, analysis and reporting so that PRO data are of sufficient quality to effectively inform patient choice and care.

The University of Birmingham PRO Research Group, in partnership with national and international collaborators – including members of the SPIRIT group – have therefore submitted a funding application to the MRC Methodology Research Panel to support

development of a SPIRIT PRO extension.[r] Within the bid, a separate work-package is tasked with identifying PRO-specific protocol items that are of specific relevance to research ethics evaluation, to inform the development of guidance for ethics committees that consider project applications with a PRO component.

9.3.2 PRO trial conduct

The systematic review presented in Chapter 6 highlighted a lack of published 'in-trial' PRO guidance for front-line staff.[3] Both qualitative (Chapter 2) and quantitative (Chapters 4, 5, 8) data suggest user-friendly PRO guidance may also be lacking in trial protocols, trial training and SOPs. Researchers in Australia are attempting to rectify this. Doctoral research, conducted by Mercieca-Bebber, and supervised by King, Calvert and Stockler (Kyte: external advisor), is currently focusing on the development of a checklist detailing the optimal PRO components of site manuals (equivalent to SOPs in the UK).[40s] Results presented in Chapter 2 to 4 of the thesis, which highlight that trial staff would welcome PRO information included in documentation other than the trial protocol, suggests this approach may be successful in improving accessibility and engagement with PRO guidance and will hopefully lead to improvements in PRO trial conduct. Further research is also required to improve the provision and content of PRO trial training. Results presented in the thesis (Chapters 3 and 4) highlight potential topics for inclusion in such training. Using this information, one potential first step may be to develop a 'GCP-type' PRO training package, incorporating end-user input, which could be evaluated

[r] Calvert M, **Kyte D**, Altman D, Blazeby J, Brown J, Brundage M, Coast J, Draper H, Ives J, Roberts L, von Hildebrand M, King M. **Im**proving **Pa**tient-**R**eported Outcome Content in **T**rial Protocols (**IMPART**). MRC - Methodology Research Panel. £458,751.70

[s] Improving Patient-Reported Outcome research practices and Documentation (The ImPROveD Study) Mercieca-Bebber R, Calvert M, Stockler M, **Kyte D**, Rutherford C, King M

in a RCT. The impact of such training on important outcomes including the consistency with which PROs are administered in the trial and the rates of missing PRO data should be investigated. If proven to be effective, the use of free-to-access training of this type may represent a practical way to increase PRO understanding amongst trial researchers, without increasing the burden on trials with finite resources.

9.3.3 PRO alerts

Evidence presented in this thesis suggests PRO alert guidance is lacking, both in the literature and within trial documentation (Chapters 2, 3 and 5). In the absence of published research concerning PRO alerts, examples drawn from related 'incidental findings' literature may be useful in directing future work in this area. An incidental finding (IF) is defined as:

> "…a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study."(pg. 1)[41]

With modern advances in genetic testing and imaging, IFs have become more common in research, however, up until relatively recently, there was little guidance for researchers on how to handle them and a lack of consensus regarding the optimal approach.[41] There are parallels between IFs and PRO alerts in trials. In both instances, additional information pertinent to the well-being of the participant is uncovered during the trial, which may not be available to the participant's regular health care team. In attempting to formulate a consensus approach regarding the management of IFs, Lawrenz and Sobotka[42] conducted a comprehensive review of publically available guidance and consent forms in the US, including: federal authority websites, professional societies and the top 100 National Institutes of Health funded

universities. Following on from this work, and a further review of key ethics sources, Wolf and colleagues[41] proffered several IF management recommendations. The group concluded that researchers were obligated to address the potential for IFs in trials, establish procedures for their management and communicate these plans via the trial protocol and participant information resources.

These recommendations cannot necessary be directly applied to PRO alerts, however. Research findings must meet three criteria to be classed as an IF: (1) an observation during the course of a research study; (2) with potential health/reproductive importance; (3) that is outside of the study aims.[41] Whilst PRO alerts may fulfil the first two criteria, they will often not meet the last, as the PRO will have commonly been selected as either a primary or secondary endpoint in the trial. Thus, there are issues unique to PRO alerts that require exploration. For instance, it remains unclear how the management of alerts might tie in with existing adverse event (AE) reporting in trials. Therefore, focused consideration of the pertinent ethical issues surrounding PRO alerts in trials is required before appropriate guidance can be produced. To facilitate this process, it is important that work with patient groups, as well as the potential users of alert guidance, is undertaken. In addition, it is recommended that a review of current PRO alert management, patient information and consent in trials – from an ethical perspective - should be conducted. Ethical debate is then required to address the questions surrounding researcher PRO alert obligations that have been raised by the work presented in this thesis, including:

- Are trial staff obliged to monitor their PRO data for alerts? What are researcher's responsibilities if they encounter a PRO alert, whether by design, or inadvertently – and what factors are these responsibilities reliant on?

- If alerts are to be monitored and responded to, how do we ensure the process does not become overly paternalistic, or simply an unwelcome invasion of privacy?
- What should trial participants be told, both prior to their involvement in a trial (i.e. in information sheets and consent forms), and if their PRO data gives rise to an alert once the study is underway?
- What PRO alert details should be included in trial protocols, trial training and SOPs?

It is important that trial teams' acknowledge the potential implications of PRO alerts, as their mismanagement may leave participants at risk of harm and may compromise the integrity of the study. Practical alert guidelines are clearly needed. These may be informed by current developments in the field of e-PRO trial measurement. There are a number of initiatives that are starting to investigate the feasibility of using e-PROs to report alerts in trials. In the US, the PRO-CTCAE (Common Terminology Criteria for Adverse Events) project is currently testing an electronic-based system for patient self-reported AE's in patients with cancer.[25,26,43] The REPORT-UK project is currently evaluating the feasibility of a similar system in the UK, which it is hoped will allow participants to report AE's as well as other PROs.[14] The results of these projects will be influential in future discussions surrounding the optimal management of PRO alerts in trials. In addition, with the advancing, and increasingly accessible, technology provided via personal computers, laptops, tablets and mobile devices, there is also likely to be an increase in the use of e-PRO data capture in routine clinical care.[24] Evidence suggests e-PRO use is increasing in the US, mainly in cancer care.[24,28] For example, Andikyan and colleagues[23] demonstrated the feasibility and

acceptability of a web-based e-PRO system in patients with cancer recovering from gynecologic surgery. The system appeared to be successful in monitoring for alerts and in triggering early intervention where required.[23] Some UK systems have also been described in the literature. The advanced symptom management system (ASyMS©) described by McCann and colleagues[18] is a mobile-phone-based platform used to capture PRO information provided by patients with breast, lung and colorectal cancer. The system was used effectively for the identification of chemotherapy related toxicity symptoms and appeared to facilitate prompt therapeutic intervention where required.[18] In addition, a novel web-based platform, the eRAPID (**E**lectronic patient self-**R**eporting of **A**dverse-events: **P**atient **I**nformation and a**D**vice) system, is currently undergoing development and testing, and has been proven acceptable in a sample of patients with a range of common cancers.[16] The presence of such systems in routine clinical practice will undoubtedly have implications for the way PRO alerts are managed in trials in the future and such innovations should be considered during the development of any PRO alert guidance.

9.3.4 PRO trial assessment: patient perspectives

A number of research questions emerged during the development of this project, which could only be answered by trial participants themselves, for example:

- What are participant's perceptions/understanding of how their PRO data will be used in a trial?
- Do participants feel fully informed about the purpose of PRO data and how much do they wish to be told?
- Do potential participants want to be involved in the selection of trial PROMs, and/or the mode of delivery?

- Do participants want their PRO data to be monitored for alerts and would they want researchers to intervene in response to an alert?
- How exactly do participants want researchers to manage PRO data and PRO alerts in trials?
- Where participants provide additional data on PRO questionnaires, what would they like researchers to do with this information?

Investigating trial participants' perspectives surrounding the management of PRO assessment in trials will be an important step in producing future guidance. Initially, this doctoral work also included plans to conduct a qualitative study (involving current and former trial participants with direct experience of PRO trial assessment), which focused on the research questions identified above. Recruitment was attempted at the same five sites detailed in the qualitative study of trial staff presented in Chapter 2. These sites acted as participant identification centres (PICs), with local collaborators (lead research nurses) at each site tasked with identifying potentially eligible patients and providing them with information about our study. Interested individuals were asked to contact the lead researcher (Kyte) to discuss the study and, if they wished to proceed, arrange a suitable time and venue for the interview. Unfortunately, the study under-recruited, completing just 4 interviews. As data saturation had not been reached on any of the topics covered during the interviews, the results have not been analyzed for presentation in this thesis. Instead, we plan to seek ethical approval and additional funding to continue this part of the project beyond the end of the SPCR-funded studentship, using alternative recruitment methods to reach data saturation (Appendix 2).

We are also currently conducting two studies investigating participant information provision and understanding. The first involves analysis of the PRO-specific content of patient information and consent documentation within NIHR HTA trials collecting a primary or secondary PRO.[t] This study will help determine exactly what PRO information is currently provided to the potential participants of trials. The second is a MRC hub-funded study which will use mixed-methods to examine what potential research participants understand about PRO measurement and management after reading actual trial participant information sheets.[u]

Finally, it is recommended that trial participant/patient stakeholders be involved, as research partners, in the co-development of: (1) the PRO alert trial guidelines, (2) the PRO protocol guidelines, and (3) the PRO trial training guidelines recommended in this thesis. This will help ensure that such material incorporates the views of those who provide PRO data, in addition to those who conduct and manage PRO assessment in trials. This is important: evidence suggests patient and public involvement in general health-related research is widely valued[44,45] as it may lead to improvements in study design[44,46]; maximise the relevance, validity and representativeness of research findings[47]; and enhance the quality and acceptability of guideline documents.[48]

[t] **Kyte D**, Fletcher B, Ives J, Draper H, Duffy H, Calvert M. Evaluation of the patient-reported outcome (PRO) content of patient information in clinical trials. (*In preparation*).

[u] Ives J, Draper H, Calvert M, **Kyte D**. What do potential research participants understand about patient reported outcome measurement and management? An investigation of trial information provision. MRC Midland Hub for Trials Methodology Research. £29,051

9.4 Strengths and limitations

There has been little previous research investigating the administration of PROs in trials and less still addressing PRO alerts. Thus, the qualitative study (Chapter 2), PRO alert viewpoint (Chapter 3), researcher surveys (Chapters 4 and 5), systematic review of 'in-trial' guidance (Chapter 6), systematic review of PRO protocol guidance (Chapter 7) and evaluation of PRO protocol content (Chapter 8) presented in this thesis are all novel and represent original contributions to the field of PRO research. The research highlights hitherto unforeseen difficulties concerning the conduct and management of PRO assessment in clinical trials. The findings have been disseminated in the following ways:

- Six publications in high impact peer-reviewed scientific journals such as JAMA and PLoS One (including Chapters 2, 3 and 6 of the thesis).[1,49-53] With two papers under review (Chapters 7 and 8).
- One symposia[54]; one workshop[55]; six oral presentations[56-61] and eight poster presentations at prestigious national and international scientific conferences, including:
    - The International Society for Quality of Life Research (ISOQOL) annual conference, Budapest 2012, Miami 2013 and Berlin 2014.
    - The North American Primary Care Research Group (NAPCRG) annual meeting, New York 2014.
    - The 2nd MRC Clinical Trial Methodology Conference, Edinburgh 2013.
- A two-day symposium hosted by Calvert and Kyte at the University of Birmingham, July 2013.[62]

In addition, the work has informed the development of four successful research funding applications totaling over £140,000[63-66], and three that are currently under review[67-69] totaling over £950,000. It is hoped that, through continued dissemination and grant support, the work presented in this thesis will facilitate the evidence-based improvement of PRO protocol content and PRO assessment in clinical trials.

In the absence of prior research, a qualitative study was conducted to investigate reported inconsistencies in PRO trial measurement (Chapter 2). Limitations of the study include the risk of researcher bias and the low sample size and restricted (geographic) recruitment area, which could restrict the generalizability of the findings. However, the risk of the researcher unduly influencing qualitative data collection and analysis was mitigated through use of an interview topic guide, participant review of interview transcripts and triangulation of data analysis.[1] Moreover, the generalizability of the study findings was upheld in a large-scale survey of UK-based trial staff and management (Chapters 4 and 5).

In the PRO alert viewpoint (Chapter 3), several potential alert management options were proposed. One limitation here is that the basis for these options primarily relied on the anecdotal experiences of the authors, and their additional contributors, as no previous related research has been reported. Although both the authors and contributors had extensive first-hand experience of clinical trials to draw upon, and the subsequent survey findings presented in Chapter 5 provide some external support for the proposed options; additional empirical evidence evaluating these, and other, PRO alert management options is required to definitively determine their acceptability and appropriateness.

The strengths of the cross-sectional survey (Chapters 4 and 5) are its wide recruitment area and large sample sizes of research nurse (n=560) and trial manager (n=129) respondents. It is, however, limited by much smaller sample sizes for the data manager/coordinator (n=41) and CPI (n=37) respondent groups. As such, generalization of the findings particular to these cohorts is not advised until such time as they are validated in an external study. Validation of the survey findings suggesting inconsistencies in PRO data collection should also be investigated in non-UK settings, to determine if the results are generalizable to the international research environment. Determining an accurate response rate for the survey was difficult owing to the lack of an appropriate denominator. It is therefore possible that our respondents were self-selecting. If so, this group is more likely to include those with an interest in PROs, therefore their data could represent the most knowledgeable trial personnel: this should be taken into account when interpreting the findings of the survey.

Selection of the QCA method[70] for the systematic review of 'in-trial' guidance (Chapter 6), meant that non-English language papers were excluded. This decision was taken because determining the latent meaning of translated material during the QCA process would have relied heavily on the interpretation of the translator(s), potentially impacting on the reliability and validity of the findings. Exclusion of such papers may, however, have affected the results, as potentially influential articles could have been overlooked: this may have lessened the generalizability of the results. However, the QCA method was purposefully chosen as it enabled a comprehensive analysis of both explicit and implicit 'in-trial' guidelines present in the literature[70]: an important first-step in evaluating the PRO-specific guidance available to trial

personnel. The use of QCA methodology also allowed examination of the reliability and validity of the coding framework, strengthening the study design and lending credibility to the findings.[70]

The review of PRO protocol guidance (Chapter 7) was strengthened by its use of systematic methods and multiple reviewers, which conformed with PRISMA guidelines.[71] The main limitation is that poor indexing of the PRO protocol guidance literature meant that, although the search strategy was comprehensive, it is possible that further guidance exists that was not included in the study.

The strengths of the protocol review (Chapter 8) are again its systematic methods and use of multiple investigators at each stage, and also the high agreement between raters using the SPIRIT and PRO-specific checklists. However, it is limited by the lack of validation of the PRO protocol checklist. In addition, the generalizability of the findings to other trial protocols or funders is somewhat restricted by the moderate sample size and limited sample setting. Validation of the findings in multiple settings is therefore required. The PRO checklist incorporated all 162 recommendations extracted in the systematic review of PRO protocol guidance (Chapter 7) and therefore represents a comprehensive starting point only, utilised for illustrative purposes. Funding is being sought to support a formal consensus process to determine which items are essential and which may be optional in the definitive checklist and whether the make-up of items may differ if the PRO is a primary or secondary endpoint in a trial.[v] Thus, as things currently stand, the evaluation of PRO protocol content presented in Chapter 8 highlights the *potential* deficiencies of such

[v] Calvert M, **Kyte D**, Altman D, Blazeby J, Brown J, Brundage M, Coast J, Draper H, Ives J, Roberts L, von Hildebrand M, King M. **Im**proving **Pa**tient-**R**eported Outcome Content in **T**rial Protocols (**IMPART**). MRC - Methodology Research Panel. £458,751.70

documentation, rather than providing a conclusive answer. Repetition of this study once consensus has been reached over the definitive PRO protocol checklist, in a larger sample size and across differing funders, is therefore warranted.

Finally, as previously discussed (section 9.3.4), the patient viewpoint on both the methodological and ethical issues faced during PRO data collection in trials was underexplored in this thesis, secondary to a failure to recruit sufficient numbers of patients during the study. It is therefore important in future planned work in this area, that the design and implementation of recruitment is conducted with the full involvement of patient partners – with appropriate targeting of third sector recruitment centres and coordinated follow-up of research sites – to ensure optimal study recruitment (Appendix 2).[44-46,72]

9.6 Conclusions

'We must do all that we can to make patient reported outcome assessment feasible and credible. If we fail in our task we will have left out the heart of all health-care research: the patient.'[73]

This research presents three principal findings. First, there is a perception amongst trial staff that there are inconsistencies in the administration and management of PROs in some UK trials. Such inconsistencies have the potential to undermine PRO data quality and introduce bias. Second, trial staff intermittently encounter PRO alerts: 'concerning levels of psychological distress or physical symptoms that may require an immediate response.'[2] Some staff intervene to aid the trial participant, but may not record the intervention in the trial documentation, potentially risking co-intervention bias. Third, PRO trial guidance appears sub-optimal. There is a lack of published PRO guidelines for front-line data collection staff, addressing both general 'in-trial' PRO assessment and the management of PRO alerts. There is also a perception amongst trial staff that PRO-specific training in trials is lacking. In addition, empirical evidence suggests PRO guidance for protocol developers is inconsistent and difficult to access; and that PRO information is commonly absent from trial protocols, even where a PRO is the primary outcome.

There is a need for comprehensive consensus-based PRO guidelines addressing protocol development, training and the management of PRO alerts in trials. Guidelines should aim to facilitate improvements in PRO protocol content and PRO assessment, whilst protecting the interests of trial participants, to enhance the

credibility of PROs as an important trial outcome and optimise their ability to inform patient care and policy.

9.7 References

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Appendices

Appendix 1

Chapter 2 – Interview topic guide S1

The **M**ethodological and **E**thical Issues Associated with Health-Related **Q**uality **o**f **L**ife Measurement in Clinical Trials (**ME-QOL**).

Researcher Interview Topic Guide

Guidance notes to the interviewer

Note: *If the participant becomes distressed or unwell, the interviewer will adopt the following approaches, dependent upon the participant's wishes:*

1) If the participant wishes, the interviewer will suspend or terminate the interview, and will stay with the participant until they are feeling better.

2) If the participant has another person to provide care, at the request of the participant, the interviewer will either suspend the interview and leave the room, or will terminate the interview completely.

3) If the interviewer feels it is warranted, and if the participant agrees, he will provide the contact details of appropriate support agencies.

4) If the interviewer feels that there is reason to be concerned for the physical/mental health of a participant, he will inform the participant of his intention to take the appropriate action, e.g. call the GP.

Points to discuss with the participant prior to signing the consent form

- Recap on key information in the PIS
  - I will be recording this interview, so I have something to help me remember accurately what we talk about today, the only people who will hear the recording are myself and my supervisor, is this ok?
  - If there is anything you find you do not wish to talk about please let me know. I will aim to follow your lead in terms of what we discuss, but if we do stray on to a topic that you are not keen to talk about, tell me straight away and we can discuss something else.
  - We can stop the interview whenever you like. If you would like to take a break, or feel upset or unwell, please let me know and we will suspend or stop the interview entirely.

Participant and researcher sign consent form if participant still wishes to take part.

Introduction to Interview

Thank you for agreeing to take part in this interview. The aim of this interview is to discuss your ideas and experiences surrounding the way in which research trials measure a patient's quality of life. There are no 'right' or 'wrong' answers, we are interested in *your* views based on your experience of administering quality of life questionnaires as part of your research role. I am now going to start the recording.

Begin Interview

Main body of Interview

1) How much experience do you have of viewing quality of life information?

Prompts
- Roughly how often do you view participant quality of life data during a trial?
- For what purpose(s) might you view quality of life data during a trial?

2) As a nurse/data manager under what circumstances can you imagine acting (or feeling tempted to act) on the quality of life data viewed during a trial?

Prompts
- What kinds of actions might you take in these circumstances?
- What factors do you think might influence the decision of a researcher tempted to act on the quality of life data they may have viewed during a trial?

3) What mechanisms were available within the trials you have been involved in, for reporting any intervention undertaken in response to viewing a participant's quality of life data?

Prompts
- EITHER: So how would you have known what to do under circumstances like those we have just been discussing? OR: How did you know about these mechanisms? What did you think about their general usefulness?

4) In your opinion, what are the challenges of administering quality of life questionnaires in trials?

Prompts
- What professional tensions might arise when administering quality of life questionnaire in trials?
- How do those designing research need to respond to these tensions?

5) Some participants complete the quality of life questionnaire, but then write extra (unrequested) information either on the bottom, or on the back of the form. Why do you think they do this?

Prompts
- What kind of information do you think they might add?
- Have you witnessed this in practice?
- What are your thoughts on what should be done with this extra information?

6) In your opinion, what are the key training needs for researchers involved in handling/ administering quality of life data?

Prompts
- To what extent have any of the things we've discussed today suggested areas where you feel more training may be required?

- Where do you think people in your role/doing you job turn to for support when they face tensions for which they do not feel adequately trained or briefed?

Post Interview – Debrief

- I have no more questions, but I'd like to give you the opportunity to say anything else about quality of life questionnaires, your experience of completing them, or anything else we've discussed today?

- *Outline what will happen next:* (1) the recording will be typed up and annonymised, then analysed alongside all the other interviews, (2) we will send you a summary of this analysis (unless you would prefer that we didn't) and will invite your comments. You do not have to comment on these results if you do not wish to.

- Finally, if you decide that you do not want what you have said today to be included in my research, you will need to tell me this within 2 working days – so by [*insert an actual day, according to timing of interview*]. After this it will be too late to withdraw as I will not be able to untangle what you have told me from what other people have told me.

- Thank you for taking part in the interview today.

Appendix 2

Chapter 2 - Summary of coding methods and recruitment lessons learned

Summary of Coding Methods

Coding of the qualitative data was conducted in two main iterations or 'cycles'. The objective of first cycle coding was to deconstruct as much of the data into small coding 'chunks' as possible (also referred as 'initial' coding), to ensure the analysis captured all possible emerging themes. A mixture of coding methods were used in this phase, as described by Saldana[1]. These included:

- In-vivo coding – i.e. wherever possible using the participants' own words to code the data, e.g. 'Luxury' – *Discussion surrounding the viewpoint that QoL/PRO training may be seen as a 'luxury' by some staff*
- Process coding – i.e. the use of 'gerunds' (verbs ending in '–ing') to denote action, e.g. 'Checking' Questionnaire
- Initial coding – i.e. "…breaking down qualitative data into discrete parts…"[1].

In the second cycle of coding, the objective was to start to develop the major themes arising from the data. In this phase of the analysis the following coding methods were utilised:

- Focused – i.e. searching for the most frequent/significant initial codes for the purpose of developing major categories/themes from the study data.
- Axial – i.e. combining related initial codes identified in the first cycle to develop major categories/themes.

- Theoretical – i.e. development of core themes arising from the data.

Throughout the analysis phase, regular investigator meetings were held to discuss both individual coding decisions and the subsequent development of study themes. In addition, the interview topic guide was reviewed to ascertain whether any additions or changes were necessary in order to further explore new or emerging themes, or to test existing hypotheses, in the next round of interviews. An example of how this process worked in practice appears in Box 1.

- All research nurse interviewees prior to participant 15 had indicated that, when faced with concerning PRO data in a trial, they would usually place the needs of the participant over those of the trial and act to aid the trial participant in question. This became our working hypothesis: that research nurses felt their duty of care rested with the participants of the study.
- Participant 15 (also a research nurse), however, held the opposite view: that securing high quality data for a trial - the results of which may be of benefit to many future patients - was more important than responding to the needs of an individual trial participant.
- Within an investigator meeting, a decision was made to raise this contrasting viewpoint with subsequent interviewees to determine if it was an isolated view or was supported by other study participants. This is known as ‘deviant case analysis’[2], i.e. deliberately seeking out and testing a viewpoint that is in opposition to the working hypothesis to determine the strength of the hypothesis in question.

- In this instance the viewpoint of participant 15 was not supported by any of the subsequent interviewees. This was highlighted in the final study publication.

Box 1. Example of theme exploration

Once data collection was complete, an investigator meeting was held to discuss the final themes, combining them into major categories where appropriate; e.g. the themes 'Logistical issues' and 'Missing data' were combined within the major category 'Inconsistency in HRQL data collection'. The individual themes and major categories where further discussed and a core theory developed, as reported in the final publication (Chapter 2).

Incomplete Recruitment to the Patient Qualitative Study - Lessons Learned

Initially, this doctoral work included plans to conduct a qualitative study involving current and former trial participants with direct experience of PRO trial assessment. This study was to focus on research questions including:

- What are participant's perceptions/understanding of how their PRO data will be used in a trial?
- Do participants feel fully informed about the purpose of PRO data and how much do they wish to be told?
- Do potential participants want to be involved in the selection of trial PROMs, and/or the mode of delivery?
- Do participants want their PRO data to be monitored for alerts and would they want researchers to intervene in response to an alert?

- How exactly do participants want researchers to manage PRO data and PRO alerts in trials?
- Where participants provide additional data on PRO questionnaires, what would they like researchers to do with this information?

Recruitment was attempted at the same five sites detailed in the qualitative study of trial staff presented in Chapter 2. These sites acted as participant identification centres, with local collaborators (lead research nurses) at each site tasked with identifying potentially eligible patients and providing them with information about our study. Interested individuals were asked to contact the lead researcher (Kyte) to discuss the study and, if they wished to proceed, arrange a suitable time and venue for the interview. Unfortunately, the study under-recruited, completing just 4 interviews. As data saturation had not been reached on any of the topics covered during the interviews, the results were not analyzed for presentation in the thesis.

Having reflected on the failed recruitment for this aspect of the thesis I feel I can draw experience from a number of mistakes that were made during the study design phase, and it's subsequent implementation, which should improve the design of future intended studies in this area.

First, I believe, with hindsight, that patient partnership input during the design phase of the thesis was underutilised. Our patient partner (PP) provided invaluable advice regarding the participant information and consent forms, and also the patient interview topic guides, however, looking back I realise I failed to involve the PP in discussions regarding recruitment and other important areas of the project. This was a

missed opportunity: in their 2012 systematic review, Brett and colleagues [3] identified a number of positive impacts associated with comprehensive PP involvement, including enhanced participant recruitment. If I were to complete the project again, I would have invited the PP to attend design meetings throughout the lifetime of the project, allowing them to play a much more important role in the study. In hindsight, use of best-practice guidelines, such as those provided by INVOLVE [4] and Hewlett et al. [5], would have been beneficial to ensure optimal PP involvement. For example, the INVOLVE guidelines specifically advocate: early PP involvement; development of a clear role description; and provision of an outline of the areas of the project in need of PP input [4]. Adoption of these suggestions may have helped to more fully incorporate our PP into the project.

Second, my follow up of patient recruitment across the five research sites in the study needed to be more organized, and more frequent. Follow up with local collaborators regarding recruitment rates at individual research sites was sporadic and not all sites were contacted. Having reflected on this I think that I felt I was becoming a 'bother' to research nurses who had already given my relatively small PhD study a great deal of time and attention during the initial qualitative study (reported in Chapter 2 of the thesis). This meant I was reticent to approach staff again to highlight site recruitment deficiencies. Ultimately this reticence may have contributed to the eventual failure to recruit to target: an important lesson.

Third, having now gained more experience of patient recruitment methods through my involvement with other projects I realise I should have approached patient interest groups earlier on in the design phase, and in greater numbers, to maximize the reach

of my study invitations and improve recruitment rates. I only approached one such group, speaking at a patient-led group event mid-way through the recruitment period. This event did generate some interest and two patients expressed a willingness to participate in the study, unfortunately in this instance they were both ineligible. However, I believe that a more coordinated targeting of appropriate patient interest groups of this type - from the start of the study, and assisted by greater PP involvement informed by best-practice guidelines [4,5] - would have boosted recruitment in the long-term.

I draw three main lessons from the experiences outlined above (1) the need to fully involve patient partners in all aspects of the design of a study, (2) the importance of a pre-planned and coordinated follow-up of research sites/staff involved in recruitment and (3) the need to consider multiple avenues of recruitment in the event the one or more methods prove unproductive.

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Appendix 3

Chapter 4 – Research ethics approval

Appendix 4

Chapters 4 and 5 – Survey instruments and pilot survey details

National Research Nurse Survey

Introduction

Thank you for your interest in this research

What is the purpose of this study?

The aim of this national survey is to gather information on how research nurses deal with quality of life and other patient-reported outcomes in clinical trials. We will donate £2 to Cancer Research UK for each completed survey we receive.

Who is doing this research?

This research is being conducted by the 'Patient-Reported Outcomes Research Group' based in Primary Care Clinical Sciences at the University of Birmingham. The study forms part of a PhD being undertaken by Derek Kyte MSc, supervised by Dr Melanie Calvert PhD, Professor Heather Draper PhD and Dr Jonathan Ives PhD. The West Midlands Research Ethics Committee have favorably reviewed the study (Reference number: 12/WM/0068).

How long will it take?

The questionnaire has 19 questions, expected completion time is 10–15 minutes. During the pilot phase, the average completion time was 11 minutes.

How will my data be protected?

All of the data collected from you will be kept anonymous. You will not be asked for any personal information, such as your name, date of birth or contact details, any other potentially identifying data will be kept confidential or anonymised. We will ask you about your work experience, but this information will be analysed at a group level and individual details will not be shared. The results of the questionnaire and any reports derived from it will be securely stored on the computer systems in Primary Care Clinical Sciences at the University of Birmingham for the duration of 10 years. After this period they will be deleted so that they cannot be recovered. Reports derived from the questionnaire results will be published in peer reviewed scientific journals, all data will be anonymous.

Once I agree to take part, can I change my mind?

You can exit the questionnaire at any point prior to submission and your answers will not be analysed. Once you have submitted the completed questionnaire you will not be able to withdraw as there is no way we can retrieve your anonymised answers.

Who can I contact to ask any questions?

Mr Derek Kyte

Who can I contact if I wish to make a complaint?

Dr Melanie Calvert

Please note: by advancing to the next page, you are consenting to take part in the study. Anonymity and confidentially will be ensured.

Explanation

Page 1

National Research Nurse Survey

DEFINITIONS OF TERMS USED IN THE SURVEY

Patient-reported outcome measures

Patient-Reported Outcome measures ask the patient a series of questions in order to gauge their views on their own health or care, i.e. an outcome directly reported by the patient.

Quality of Life

A Quality of Life measure is a Patient-Reported Outcome which is designed to evaluate the way in which physical, emotional and social well-being are affected by a disease or its treatment.

SECTION 1

The next section asks questions about your experience of the **last** clinical trial you worked on that used a quality of life or other patent-reported outcome measure. It does not matter is this was a primary or secondary outcome in the trial.

SECTION 1 - Last trial

1. First, some questions about yourself. How long have you been qualified as a nurse?

2. How long have you worked as a research nurse in total?

- Less than 1 year

3. Which of the following age groups do you belong to?

○ 25 or younger

4. Thinking about the last trial you worked on that used a Quality of Life or other Patient-Reported Outcome measure.

Were you employed as a research nurse in primary care or secondary care?

5. Which of the following clinical areas did the trial cover? PLEASE TICK ALL THAT APPLY

☐ naecology

6. Which of the following Patient-Reported Outcome Measures did the trial use?
PLEASE TICK ALL THAT APPLY

SECTION 1 - Last trial

7. Thinking about the last trial you worked on that used a Quality of Life or other Patient-Reported Outcome measure.

What assistance did you give to the trial participants during the completion of the questionnaire? PLEASE TICK ALL THAT APPLY

☐ uestionnaires independently.

8. During this trial, if the participant had to complete the Quality of Life or other Patient-Reported Outcome Measure questionnaire in clinic, when did they do so?

9. During this trial, which of the following did you do after trial participants had completed their Quality of Life/Patient-Reported Outcome questionnaires? PLEASE TICK ALL THAT APPLY

☐ ey had understood them correctly.

SECTION 1 - Last trial

10. Thinking about the last trial you worked on that used a Quality of Life or other Patient-Reported Outcome measure.

Please read the following statements. In each case, please answer 'yes', 'no', or 'not applicable'.

Yes

nd upon your answers here (optional)

11. Thinking about the last trial you worked on that used a Quality of Life or other Patient-Reported Outcome Measure.

Please read the following statements. In each case, please answer 'yes' or 'no'.

Yes

ere (optional)

SECTION 2

This section will ask about your **general** thoughts about working with Quality of Life/Patient-Reported Outcome Measures in trials.

12. Thinking about your general experience of Quality of Life/Patient-Reported Outcome measurement in trials.

Please read the following statements. In each case, tick one option: 'always', 'often', 'sometimes', 'never'.

Always ○

13. Some research nurses we have spoken to have reported encountering Quality of Life/Patient-Reported Outcome questionnaires containing answers which raise concern for the wellbeing of the trial participant in some way.

This information has been termed: 'concerning' Patient-Reported Outcome information.

In these reports, 'concerning' Patient-Reported Outcome information may simply have been particularly extreme questionnaire scores, or sometimes a participant might have written additional information on the questionnaire which raised concern (or attached a letter); finally, some nurses reported becoming concerned by things that the trial participant said to them either during, or after, the completion of the questionnaire.

Have you ever encountered any 'concerning' Patient-Reported Outcome information within a trial?

SECTION 2 - General thoughts

14. Have you ever taken action in response to 'concerning' Patient-Reported Outcome information you have encountered within a trial, in order to assist a trial participant?

15. Were you able to record all action(s) taken in response to the 'concerning' Patient-Reported Outcome information, in the trial documentation?

16. If you were to encounter 'concerning' Patient-Reported Outcome information in a future trial, for example, evidence of anxiety or depression, which of the following might you consider doing? PLEASE TICK ALL THAT APPLY

☐ riate healthcare professional.

17. Please read the following statements. In each case, please answer 'yes', 'no', or 'unsure'

	Yes		
ion.	○	○	○

SECTION 3 - The future

SECTION 3

This final section will ask about the changes you would like to see regarding Quality of Life/Patient-Reported Outcome measurement in **future trials**.

18. Thinking about the future.

Please read the following statements. In each case, please indicate whether you 'strongly agree', 'agree', 'have no opinion', 'disagree' or 'strongly disagree' with the statement.

Strongly Agree

nd upon your answers here (optional)

19. Thinking about the future.

What particular Quality of Life/Patient-Reported Outcome guidance should be included the trial protocol, what should be included in trial training, and what should be included in a standard operating procedure? PLEASE TICK ALL THAT APPLY

	Trial Protocol		
	☐	☐	☐
ons.			
How to deal with difficult situations.			

National Data Manager/Coordinator Survey

Introduction

Thank you for your interest in this research

What is the purpose of this study?

The aim of this national trials unit survey is to gather information on how data coordinators/inputters and data managers deal with quality of life and other patient-reported outcomes in clinical trials. We will donate £2 to Cancer Research UK for each completed survey we receive.

Who is doing this research?

This research is being conducted by the 'Patient-Reported Outcomes Research Group' based in Primary Care Clinical Sciences at the University of Birmingham. The study forms part of a PhD being undertaken by Derek Kyte MSc, supervised by Dr Melanie Calvert PhD, Professor Heather Draper PhD and Dr Jonathan Ives PhD. The West Midlands Research Ethics Committee have favorably reviewed the study (Reference number: 12/WM/0068).

How long will it take?

The questionnaire has 15 questions, expected completion time is 10-15 minutes.

How will my data be protected?

All of the data collected from you will be kept anonymous. You will not be asked for any personal information, such as your name, date of birth or contact details, any other potentially identifying data will be kept confidential or anonymised. We will ask you about your work experience, but this information will be analysed at a group level and individual details will not be shared. The results of the questionnaire will be securely stored on the computer systems in Primary Care Clinical Sciences at the University of Birmingham for the duration of 10 years. After this period they will be deleted so that they cannot be recovered. Reports derived from the questionnaire results will be published in peer reviewed scientific journals, all data will be anonymous.

Once I agree to take part, can I change my mind?

You can exit the questionnaire at any point prior to submission and your answers will not be analysed. Once you have submitted the completed questionnaire you will not be able to withdraw as there is no way we can retrieve your anonymised answers.

Who can I contact to ask any questions?

Mr Derek Kyte

Who can I contact if I wish to make a complaint?

Dr Melanie Calvert

Please note: by advancing to the next page, you are consenting to take part in the study. Anonymity and confidentially will be ensured.

Explanation

National Data Manager/Coordinator Survey

DEFINITIONS Of TERMS USED IN THE SURVEY

Patient-reported outcome measures

Patient-Reported Outcome measures ask the patient a series of questions in order to gauge their views on their own health or care, i.e. an outcome directly reported by the patient.

Quality of Life

A Quality of Life measure is a Patient-Reported Outcome which is designed to evaluate the way in which physical, emotional and social well-being are affected by a disease or its treatment.

SECTION 1

This section asks questions about your experience of the **last** clinical trial you worked on that used a quality of life or other patient-reported outcome measure. It does not matter if this was a primary or secondary outcome in the trial.

Please be aware that there are no 'right' or 'wrong' answers in this survey. We are simply interested in hearing about your experiences and opinions.

*1. Thinking about the last clinical trial you worked on that used a quality of life or other patent-reported outcome measure.

How would you describe your role?

2. How long have you worked as a [Q1], in total?

- 10 years or more

3. To which of the following age groups do you belong?

- 25 or younger

4. Thinking about the last trial you worked on that used a Quality of Life or other Patient-Reported Outcome measure.

Was the trial based in primary care or secondary care?

5. Which of the following clinical areas did the trial cover? PLEASE TICK ALL THAT APPLY

6. Which of the following Patient-Reported Outcome Measures did the trial use?
PLEASE TICK ALL THAT APPLY

SECTION 1 - Last trial

7. Thinking about the last trial you worked on that used a Quality of Life or other Patient-Reported Outcome measure.

When the Quality of Life/Patient-Reported Outcome questionnaire data were inputted, which of the following occurred? PLEASE TICK ALL THAT APPLY

☐ r research nurse) in order to correct them.

8. Again, thinking about the last trial you worked on that used a Quality of Life or other Patient-Reported Outcome measure.

Please read the following statements. In each case, please answer 'yes', 'no', 'don't know', or 'not applicable'.

Yes

ere (optional)

SECTION 2

This section will ask about your **general** thoughts about working with Quality of Life/Patient-Reported Outcome Measures in trials.

9. Some data managers/inputters we have spoken to have reported encountering Quality of Life/Patient-Reported Outcome data which raised concern for the wellbeing of the trial participant in some way.

This information has been termed: 'concerning' Patient-Reported Outcome information.

In these reports, 'concerning' Patient-Reported Outcome information may have been extreme questionnaire scores, or sometimes a participant might have written additional information on the questionnaire which raised concern (or attached a letter).

Thinking about your general experience. Have you ever encountered any 'concerning' Patient-Reported Outcome information within a trial?

SECTION 2 - General thoughts

10. Have you ever taken action in response to 'concerning' Patient-Reported Outcome information you have encountered within a trial, in order to assist a trial participant?

11. Were you able to record all action(s) taken in response to viewing 'concerning' Patient-Reported Outcome information, in the trial documentation?

○

12. If you were to encounter 'concerning' Patient-Reported Outcome information in a future trial, for example, evidence of anxiety or depression, which of the following might you consider doing? PLEASE TICK ALL THAT APPLY

please specify)

13. Please read the following statements. In each case, please answer 'yes', 'no', or 'don't know'.

Yes

SECTION 3

This final section will ask about the changes you would like to see regarding Quality of Life/Patient-Reported Outcome measurement in **future trials**.

14. Thinking about the future.

Please read the following statements. In each case, please indicate whether you 'strongly agree', 'agree', have 'no opinion', 'disagree' or 'strongly disagree' with the statement.

Strongly Agree

You may expand upon your answers here (optional)

15. Thinking about the future.

In your opinion, what particular Quality of Life/Patient-Reported Outcome data collection guidance do you feel is essential in helping you do your job well, and should be included the trial protocol, what should be included in trial training, and what should be included in a standard operating procedure? PLEASE TICK ALL THAT APPLY

Trial Protocol

orted

Outcome data.

National Trial Manager Survey

Introduction

Thank you for your interest in this research

What is the purpose of this study?

The aim of this national survey is to gather information on how trial managers coordinate quality of life and other patient-reported outcome measurement in clinical trials. We will donate £2 to Cancer Research UK for each completed survey we receive.

Who is doing this research?

This research is being conducted by the 'Patient-Reported Outcomes Research Group' based in Primary Care Clinical Sciences at the Universi y o Birmingham. The s udy farms prt o a PhD bi gu mer t akens Dek K yte M c, sper vi sed by D Ma i e Calvet PhD, Professor Heather Draper PhD and Dr Jonathan Ives PhD. The West Midlands Research Ethics Committee have favorably reviewed the study (Reference number: 12/WM/0068).

How long will it take?

The questionnaire has 14 questions, expected completion time is less than 10 minutes.

How will my data be protected?

All of the data collected from you will be kept anonymous. You will not be asked for any personal information, such as your name, date of birth or contact details, any other potentially identifying data will be kept confidential or anonymised. We will ask you about your work experience, but this information will be analysed at a group level and individual details will not be shared. The results of the questionnaire and any reports derived from it will be securely stored on the computer systems in Primary Care Clinical Sciences at the University of Birmingham for the duration of 10 years. After this period they will be deleted so that they cannot be recovered. Reports derived from the questionnaire results will be published in peer reviewed scientific journals, all data will be anonymous.

Once I agree to take part, can I change my mind?

You can exit the questionnaire at any point prior to submission and your answers will not be analysed. Once you have submitted the completed questionnaire you will not be able to withdraw as there is no way we can retrieve your anonymised answers.

Who can I contact to ask any questions?

Mr Derek Kyte

Who can I contact if I wish to make a complaint?

Dr Melanie Calvert

Please note: by advancing to the next page, you are consenting to take part in the study. Anonymity and confidentially will be ensured.

Explanation

National Trial Manager Survey

DEFINITIONS OF TERMS USED IN THE SURVEY

Patient-reported outcome measures

Patient-Reported Outcome measures ask the patient a series of questions in order to gauge their views on their own health or care, i.e. an outcome directly reported by the patient.

Quality of Life

A Quality of Life measure is a Patient-Reported Outcome which is designed to evaluate the way in which physical, emotional and social well-being are affected by a disease or its treatment.

SECTION 1

The next section asks questions about your experience of the **last** clinical trial you worked on that used a quality of life or other patent-reported outcome measure. It does not matter is this was a primary or secondary outcome in the trial.

SECTION 1 - Last trial

1. First, some questions about yourself. How long in total have you worked as a trial manager?

2. To which of the following age groups do you belong?

- ○ 25 or younger

3. Thinking about the last trial you worked on that used a Quality of Life or other Patient-Reported Outcome measure.

Which of the following clinical areas did the trial cover? PLEASE TICK ALL THAT APPLY

- [ ] General Practice

4. Was the trial based in primary or secondary care?

- ○
- ○ Secondary Care

5. Which of the following Patient-Reported Outcome Measures did the trial use?
PLEASE TICK ALL THAT APPLY

6. During the trial, were the staff involved in data collection given instructions on how to administer the quality of life/patient-reported outcome questionnaire?

Section 1 - Last trial

7. Again, thinking about the same trial. What particular information on Quality of Life/Patient-Reported Outcome measurement was given to the data collection staff? Please read the options below and in each case select either 'included in trial protocol, training or SOP', or 'not included'.

Included in trial protocol, training or SOP

ou may expand upon your answers here (optional)

SECTION 2

This section will ask about your **general** thoughts about working with Quality of Life/Patient-Reported Outcome Measures in trials.

SECTION 2 - General thoughts

8. Some research nurses/data mangers we have spoken to have reported encountering Quality of Life/Patient-Reported Outcome questionnaires containing answers which raise concern for the wellbeing of the trial participant in some way.

This information has been termed: 'concerning' Patient-Reported Outcome information.

In these reports, 'concerning' Patient-Reported Outcome information may simply have been particularly extreme questionnaire scores, or sometimes a participant might have written additional information on the questionnaire which raised concern (or attached a letter); finally, some research nurses reported becoming concerned by things that the trial participant said to them either during, or after, the completion of the questionnaire.

Have you ever encountered/been made aware of any 'concerning' Patient-Reported Outcome information within a trial?

- ○
- ○ Don't know

9. Have you ever taken action in response to 'concerning' Patient-Reported Outcome information you have encountered/been made aware of within a trial, in order to assist a trial participant?

10. Was there a mechanism in place to record all action(s) taken in response to the 'concerning' Patient-Reported Outcome information, in the trial documentation?

SECTION 2 - General thoughts

11. If your data collection staff were to encounter 'concerning' Patient-Reported Outcome information in a future trial, for example, evidence of anxiety or depression, which of the following would you expect them to do? PLEASE TICK ALL THAT APPLY

☐ patient's GP or other appropriate healthcare professional.

SECTION 3

This final section will ask about the changes you would like to see regarding Quality of Life/Patient-Reported Outcome measurement in **future trials**.

12. Thinking about the future.

Please read the following statements. In each case, please indicate whether you 'strongly agree', 'agree', 'have no opinion', 'disagree' or 'strongly disagree' with the statement.

Strongly Agree

e (optional)

13. Thinking about the future.

What particular Quality of Life/Patient-Reported Outcome guidance should be included the trial protocol, what should be included in trial training, what should be included in a standard operating procedure, and what guidance should not be included in any of the above? PLEASE TICK ALL THAT APPLY

Trial Protocol

Other(s) (please specify)

14. Has completing this questionnaire changed the way you will manage quality of life/patient-reported outcome measurement in future trials?

- Yes

National CTU CI/PI Survey

Introduction

Thank you for your interest in this research

What is the purpose of this study?

The aim of this national survey is to gather information on how CI's/PI's in trials coordinate quality of life and other patient-reported outcome measurement. We will donate £2 to Cancer Research UK for each completed survey we receive.

Who is doing this research?

This research is being conducted by the 'Patient-Reported Outcomes Research Group' based in Primary Care Clinical Sciences at the Universi o Birmingham. The s udy farms prt o a PhD bi g merit akens Derek Kyte M c, sper vised by D Mai e Calvet PhD, Professor Heather Draper PhD and Dr Jonathan Ives PhD. The West Midlands Research Ethics Committee have favorably reviewed the study (Reference number: 12/WM/0068).

How long will it take?

The questionnaire has 14 questions, expected completion time is less than 10 minutes.

How will my data be protected?

All of the data collected from you will be kept anonymous. You will not be asked for any personal information, such as your name, date of birth or contact details, any other potentially identifying data will be kept confidential or anonymised. We will ask you about your work experience, but this information will be analysed at a group level and individual details will not be shared. The results of the questionnaire and any reports derived from it will be securely stored on the computer systems in Primary Care Clinical Sciences at the University of Birmingham for the duration of 10 years. After this period they will be deleted so that they cannot be recovered. Reports derived from the questionnaire results will be published in peer reviewed scientific journals, all data will be anonymous.

Once I agree to take part, can I change my mind?

You can exit the questionnaire at any point prior to submission and your answers will not be analysed. Once you have submitted the completed questionnaire you will not be able to withdraw as there is no way we can retrieve your anonymised answers.

Who can I contact to ask any questions?

Mr Derek Kyte

Who can I contact if I wish to make a complaint?

Dr Melanie Calvert

Please note: by advancing to the next page, you are consenting to take part in the study. Anonymity and confidentially will be ensured.

Explanation

National CTU CI/PI Survey

DEFINITIONS OF TERMS USED IN THE SURVEY

Patient-reported outcome measures

Patient-Reported Outcome measures ask the patient a series of questions in order to gauge their views on their own health or care, i.e. an outcome directly reported by the patient.

Quality of Life

A Quality of Life measure is a Patient-Reported Outcome which is designed to evaluate the way in which physical, emotional and social well-being are affected by a disease or its treatment.

Chief Investigator

The Chief Investigator (CI) is defined as the lead investigator for a single site study, or in relation to a study conducted at more than one site, the investigator who takes primary responsibility for the conduct of the study across all sites.

Principal Investigator

The Principal Investigator (PI) is defined as the authorised health professional responsible for the conduct of that study at a study site, and if a team of authorised health professionals at a study site conducts the study, the Principal Investigator is the leader responsible for that team.

SECTION 1

The next section asks questions about your experience of the **last** clinical trial you worked on that used a quality of life or other patent-reported outcome measure. It does not matter is this was a primary or secondary outcome in the trial.

SECTION 1 - Last trial

1. First, some questions about yourself. How much experience in total have you had as a CI/PI?

- ○
- ○ 10 years or more

2. Which of the following age groups do you belong to?

- 25 or younger

3. Thinking about the last trial you worked on that used a Quality of Life or other Patient-Reported Outcome measure.

Which of the following clinical areas did the trial cover? PLEASE TICK ALL THAT APPLY

4. Was the trial based in primary or secondary care?

cify)

5. In the study, Were you a CI or PI?

○

6. Which of the following Patient-Reported Outcome Measures did the trial use?
PLEASE TICK ALL THAT APPLY

SECTION 1 - Last trial

7. At what stage of the trial design phase was the quality of life/patient-reported outcome element first discussed?

8. Was a quality of life/patient-reported outcomes expert involved in the design phase of the trial?

9. In your opinion, on a scale of 1 (not important at all) to 10 (extremely important), with what level of importance did the trial management group view the quality of life/patient reported outcome(s) within the trial?

1 (not important at all)

10. During the trial, were the staff involved in data collection given instructions on how to administer the quality of life/patient-reported outcome questionnaire?

11. Again, thinking about the same trial. What particular information on Quality of Life/Patient-Reported Outcome measurement was given to the data collection staff? Please read the option below and in each case select either 'included in trial protocol, training or SOP', or 'not included'.

Included in trial protocol, training or SOP

e (optional)

SECTION 2

This section will ask about your **general** thoughts about working with Quality of Life/Patient-Reported Outcome Measures in trials.

SECTION 2 - General thoughts

12. Some research nurses we have spoken to have reported encountering Quality of Life/Patient-Reported Outcome questionnaires containing answers which raise concern for the wellbeing of the trial participant in some way.

This information has been termed: 'concerning' Patient-Reported Outcome information.

In these reports, 'concerning' Patient-Reported Outcome information may simply have been particularly extreme questionnaire scores, or sometimes a participant might have written additional information on the questionnaire which raised concern (or attached a letter); finally, some nurses reported becoming concerned by things that the trial participant said to them either during, or after, the completion of the questionnaire.

Have you ever encountered/been made aware of any 'concerning' Patient-Reported Outcome information within a trial?

13. Have you ever taken action in response to 'concerning' Patient-Reported Outcome information you have encountered/been made aware of within a trial, in order to assist a trial participant?

details here (optional)

14. Was there a mechanism in place to record all action(s) taken in response to the 'concerning' Patient-Reported Outcome information, in the trial documentation?

SECTION 2 - General thoughts

15. If your data collection staff were to encounter 'concerning' Patient-Reported Outcome information in a future trial, for example, evidence of anxiety or depression, which of the following would you expect them to do? PLEASE TICK ALL THAT APPLY

☐ priate healthcare professional.

SECTION 3

This final section will ask about the changes you would like to see regarding Quality of Life/Patient-Reported Outcome measurement in **future trials**.

16. Thinking about the future.

Please read the following statements. In each case, please indicate whether you 'strongly agree', 'agree', 'have no opinion', 'disagree' or 'strongly disagree' with the statement.

Strongly Agree

17. Thinking about the future.

What particular Quality of Life/Patient-Reported Outcome guidance should be included the trial protocol, what should be included in trial training, what should be included in a standard operating procedure, and what guidance should not be included in any of the above? PLEASE TICK ALL THAT APPLY

Trial Protocol

rted

Outcome questions.

Other(s) (please specify)

18. Has completing this questionnaire changed the way you will manage quality of life/patient-reported outcome measurement in future trials?

n your answer here (optional)

Survey Pilot Testing

The online survey was piloted within the Birmingham & Black Country Comprehensive Local Research Network between 13/05/2013 and 11/06/20013.

9 Research nurses completed the pilot survey (Figure 1).

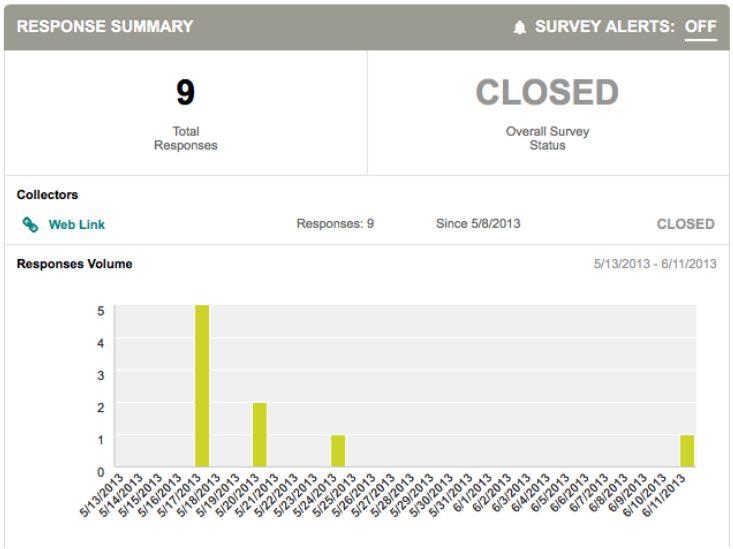


Figure 1. Pilot Survey Response Summary

Summary of the main findings of the pilot:

- All questions were completed by respondents
- Nurses reported taking an average of 12 minutes to complete the survey
- 1 respondent suggested we include more comments box's throughout the survey (Figure 2)

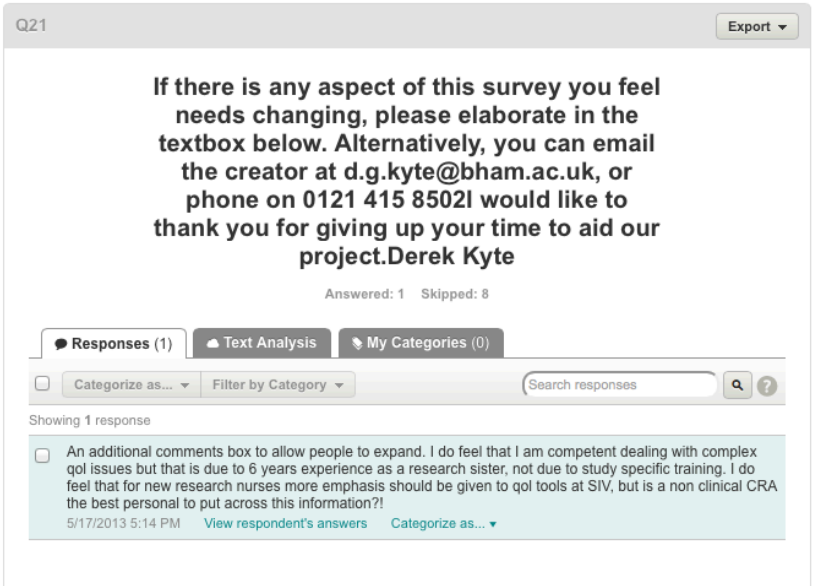


Figure 2. Pilot Survey – Suggested Changes

Appendix 5

Chapter 4 - Full Logistic Regression Model

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	95% C.I.for EXP(B) Upper
Step 1[a]	Research_Role(1)	.667	.879	.575	1	.448	1.948	.348	10.918
	Research_Experience			5.659	4	.226			
	Research_Experience(1)	-.442	1.227	.130	1	.719	.643	.058	7.122
	Research_Experience(2)	-20.314	28420.777	.000	1	.999	.000	.000	.
	Research_Experience(3)	-20.099	40193.049	.000	1	1.000	.000	.000	.
	Research_Experience(4)	.814	.386	4.444	1	.035	2.258	1.059	4.815
	Trial_Protocol(1)	.028	.347	.007	1	.935	1.029	.521	2.032
	Trial_Training(1)	.617	1.315	.220	1	.639	1.854	.141	24.405
	Research_Experience * Research_Role			1.000	3	.801			
	Research_Experience(1) by Research_Role(1)	1.190	1.190	1.000	1	.317	3.286	.319	33.826
	Research_Experience(2) by Research_Role(1)	20.623	28420.777	.000	1	.999	904623446	.000	.
	Research_Experience(3) by Research_Role(1)	20.592	40193.049	.000	1	1.000	876813138	.000	.
	Trial_Protocol(1) by Trial_Training(1)	-.860	1.332	.417	1	.519	.423	.031	5.759
	Constant	-.889	.961	.855	1	.355	.411		

a. Variable(s) entered on step 1: Research_Role, Research_Experience, Trial_Protocol, Trial_Training, Research_Experience * Research_Role , Trial_Protocol * Trial_Training .

Key: Research_Role, Research_Experience, number of years of research experience (1=0 to 3 years, 2=4 to 6 years, 3=7 to 10 years, 4= 10+ years); Trial_Protocol, whether PRO-specific information was reportedly included in the trial protocol (1=yes); Trial_Training, whether PRO-specific information was reportedly included in trial training (1=yes)

Appendix 6

Chapter 6 – Search strategies (Appendix S1)

MEDLINE

1 - "Patient reported outcome*".ti.
2 - "Patient-reported outcome*".ti.
3 - "Health-related quality of life".ti.
4 - "Health related quality of life".ti.
5 - "Quality of Life".ti.
6 - *"Quality of Life"/
7 - 1 or 2 or 3 or 4 or 5 or 6
8 - exp Guideline/ or exp Practice Guideline/
9 - *Health Policy/
10 - (guideline* or Guide or Guidance or Recommendations or Standards).m_titl.
11 - 8 or 9 or 10
12 - 7 and 11

AMED/CINHAL+ (EBSCO)

S1 - TI Patient reported outcome*
S2 - TI patient-reported outcome*
S3 - TI Health related quality of life
S4 - TI Health-related quality of life
S5 - TI quality of life
S6 - S1 or S2 or S3 or S4 or S5
S7 - Guideline* or Practice Guideline*
S8 - Health policy
S9 - TI Guide or Guidance or Recommendations or Standards
S10 - S7 or S8 or S9
S11 -S6 and S10

EMBASE

1 - "Patient reported outcome*".ti.
2 - "Patient-reported outcome*".ti.
3 - "Health-related quality of life".ti.
4 - "Health related quality of life".ti.
5 - "Quality of Life".ti.
6 - *"Quality of Life"/
7 - 1 or 2 or 3 or 4 or 5 or 6
8 - exp Guideline/ or exp Practice Guideline/
9 - *Health Policy/
10 - (guideline* or Guide or Guidance or Recommendations or Standards).m_titl.
11 - 8 or 9 or 10
12 - 7 and 11

Appendix 7

Chapter 7 – Search strategies

Initial search strategies were designed by Calvert and Kyte drawing upon the guidelines presented in the Cochrane Handbook (http://www.cochrane.org/handbook) and the work of Terwee et al[150]. These were distributed to the following international PRO experts for comments, edits and additions: Blazeby J, Duffy H, Gheorghe A, Draper H, Ives J (all UK); King M and Mercica-Bebber R (Australia), Brundage M (Canada). The final search strategies are presented below.

Eligibility criteria:

Papers must provide (1) Guidelines/Checklist, on (2) PRO-related, (3) trial protocol content.

Databases:

MEDLINE (OVID), EMBASE, CINHAL, COCHRANE LIBRARY

Search Strategy (MEDLINE)

MEDLINE
PRO terms
1) Patient reported outcome*.tw.
2) Self-reported outcome*.tw.
3) exp "Quality of Life"/
4) Patient Satisfaction/
5) adherence.mp.
6) Fatigue/
7) exp *Health Status/
8) "Activities of Daily Living"/
9) life qualit$.tw.
10) exp self concept/
11) health level.tw.
12) level of health.tw.
13) wellness.tw.
14) well being.tw.
15) (activities of daily life or daily living activities).tw.
16) functional ability.tw.
17) good health.tw.
18) healthiness.tw.
19) social adjustment/
20) physical limitations.tw.
21) psychiatric status.tw.

22) pain measurement/
23) functional assessment.tw.
24) QoL.tw.
25) hrql.tw.
26) hrqol.tw.
27) exp *"Outcome Assessment (Health Care)"/
28) health status.tw.
29) lifestyle.tw.
30) questionnaire*.tw.
31) symptom assessment.tw.
32) needs assessment.tw.
33) quality of life.tw.
34) exp *Questionnaires/
35) (patient$ adj2 reported).tw.
36) self report$.tw.
37) patient$ experience$.tw.
38) PROM$1.tw.
39) *Pain/
40) Pain, Postoperative/
41) *"Severity of Illness Index"/
42) wellbeing.tw.
Invalid term so removed as covered elsewhere
43) Health Utility.tw.
44) Health Status/
45) psychosocial.tw.
46) psycho-social.tw.
47) exp Patient Satisfaction/
48) (outcome$ adj5 expectation$).tw.
49) (outcome$ adj5 satisfaction).tw.
50) (outcome$ adj5 (satisfaction or satisfied)).tw.
51) "Interviews as Topic"/
52) (symptom$ adj5 (improv$ or change$ or deteriorat$)).tw.
53) (patient$ adj5 priorit$).tw.
54) (scale or scales).tw.
55) expectations.tw.
56) satisfaction.tw.
57) "Recovery of Function"/
58) Or/1-57
Guideline/checklist terms
59) exp Guideline/
60) exp Practice Guideline/
61) (Guidance or Recommendation* or Standard*).mp

62) exp Checklist/
63) exp Medical Ethics/
64) exp Research Ethics/
65) exp informed consent/
66) Professional Obligation.tw.
67) Duty of Care.tw.
68) Or/59-67
Trial Protocol terms
69) (Trial design or study design).mp
70) (Trial Protocol* or study protocol*).mp
71) Or/69-70 72) And /58, 68,71

Search Strategy (EMBASE)

EMBASE
PRO terms
1) Patient reported outcome*.tw.
2) Self-reported outcome*.tw.
3) exp "Quality of Life"/
4) Patient Satisfaction/
5) adherence.mp.
6) Fatigue/
7) exp *Health Status/
8) "Activities of Daily Living"/
9) life qualit$.tw.
10) exp self concept/
11) health level.tw.
12) level of health.tw.
13) wellness.tw.
14) well being.tw.
15) (activities of daily life or daily living activities).tw.
16) functional ability.tw.
17) good health.tw.
18) healthiness.tw.
19) social adjustment/
20) physical limitations.tw.
21) psychiatric status.tw.
22) pain measurement/
23) functional assessment.tw.
24) QoL.tw.
25) hrql.tw.
26) hrqol.tw.
27) exp *"Outcome Assessment (Health Care)"/

28) health status.tw.
29) lifestyle.tw.
30) questionnaire*.tw.
31) symptom assessment.tw.
32) needs assessment.tw.
33) quality of life.tw.
34) exp *Questionnaires/
35) (patient$ adj2 reported).tw.
36) self report$.tw.
37) patient$ experience$.tw.
38) PROM$1.tw.
39) *Pain/
40) Pain, Postoperative/
41) *"Severity of Illness Index"/
42) wellbeing.tw.
43) Health Utility.tw.
44) Health Status/
45) psychosocial.tw.
46) psycho-social.tw.
47) exp Patient Satisfaction/
48) (outcome$ adj5 expectation$).tw.
49) (outcome$ adj5 satisfaction).tw.
50) (outcome$ adj5 (satisfaction or satisfied)).tw.
51) "Interviews as Topic"/
52) (symptom$ adj5 (improv$ or change$ or deteriorat$)).tw.
53) (patient$ adj5 priorit$).tw.
54) (scale or scales).tw.
55) expectations.tw.
56) satisfaction.tw.
57) "Recovery of Function"/
58) Or/1-57
Guideline/checklist terms
59) exp Guidelines/
60) exp Practice Guideline/
61) (Guidance or Recommendation* or Standard*).mp
62) exp Checklist/
63) exp Medical Ethics/
64) exp Research Ethics/
65) exp informed consent/
66) Professional Obligation.tw.
67) Duty of Care.tw.

68) Or/59-67
Trial Protocol terms
69) (Trial design or study design).mp
70) (Trial Protocol* or study protocol*).mp
71) Or/69-70 72) And /58, 68,71

Search Strategy (CINHAL)

CINAHL
PRO terms
1) (MH "Outcome Assessment")
2)TI Patient reported outcome* or AB Patient reported outcome*
3)(MH "Self Report")
4)TI Self-reported outcome* or AB Self-reported outcome*
5)(MH "Quality of Life+")
6)(MH "Patient Satisfaction")
7)TX adherence
8)(MH "Fatigue")
9)(MH "Health Status+")
10)(MH "Health")
11)(MH "Activities of Daily Living")
12)TI life quality OR AB life quality
13) (MH "Self Concept+")
14)TI health level OR AB health level
15)TI level of health OR AB level of health
16)TI Wellness or AB Wellness
17)TI well being OR AB well being
18)TI activities of daily life OR AB activities of daily life
19)TI daily living activities OR AB daily living activities
20)TI functional ability OR AB functional ability
21)TI good health OR AB good health
22)TI healthiness OR AB healthiness
23)(MH "Social Adjustment")
24)TI physical limitations OR AB physical limitations
25)TI psychiatric status OR AB psychiatric status
26)(MH "Pain Measurement")
27)TI Functional Assessment OR AB Functional Assessment
28)TI QoL OR AB QoL
29)TI hrql OR AB hrql
30)TI hrqol OR AB hrqol
31)(MH "Outcomes (Health Care)+")

32)TI health status OR AB health status
33)TI lifestyle OR AB lifestyle
34)TI Questionnaire OR AB Questionnaire
35)TI symptom assessment OR AB symptom assessment
36)TI needs assessment OR AB needs assessment
37)TI quality of life OR AB quality of life
38)(MH "Questionnaires+")
39)TI patient* N2 reported OR AB patient* N2 reported
40)TI self report* OR AB self report*
41)TI patient* experience* OR AB patient* experience*
42)TI PROMS* OR AB PROMS*
43)(MH "Pain")
44)(MH "Postoperative Pain")
45)(MH "Severity of Illness Indices")
46)TI wellbeing OR AB wellbeing
47)(MH "Health Resource Utilization")
48)(MH "Health Resource Allocation")
49)TI Health Utility OR AB Health Utility
50)(MH "Health Status")
51)TI psychosocial OR AB psychosocial
52)TI psycho-social OR AB psycho-social
53)TI outcome* N5 expectation* OR AB outcome* N5 expectation*
54)TI outcome* N5 satisfaction OR TI outcome* N5 satisfaction
55)(TI outcome* N5 (satisfaction or satisfied)) OR (AB outcome* N5 (satisfaction or satisfied))
56)(MH "Interviews")
57)(TI symptom* N5 (improv* or change* or deteriorat*)) OR (AB symptom* N5 (improv* or change* or deteriorat*))
58)TI patient* N5 priorit* OR AB patient* N5 priorit*
59)(TI (scale or scales)) OR (AB (scale or scales))
60)TI expectations OR AB expectations
61)TI satisfaction OR AB satisfaction
62)(MH "Functional Status")
63)(MH "Functional Assessment")
64) Or/1-63
Guideline/checklist terms
65)TX Guideline*
66)TI Guideline* or AB Guideline*
67)(MH "Guideline Adherence")
68)(MH "Practice Guidelines")
69)TX Guidance

70)TX Recommendation*
71)TX Standard*
72)(MH "Checklists")
73)(MH "Ethics, Medical")
74)(MH "Research Ethics+")
75)(MH "Consent+")
76)(MH "Consent (Research)")
77)TI Professional Obligation OR AB Professional Obligation
78)TI Duty of Care OR AB Duty of Care
79) Or/65-78
Trial Protocol terms
80)(MH "Study Design")
81)TX Trial design or study design
82)(MH "Research Protocols")
83)TX Trial protocol or study protocol
84) Or/80-83
85) And/64,79,84

Search Strategy (COCHRANE LIBRARY)

Cochrane
PRO terms
1)Patient reported outcome*:ti or Patient reported outcome*:ab (Word variations have been searched)
2)Self-reported outcome*:ti or Self-reported outcome*:ab (Word variations have been searched)
3)MeSH descriptor: [Quality of Life] explode all trees
4)MeSH descriptor: [Patient Satisfaction] explode all trees
adherence (Word variations have been searched)
5)MeSH descriptor: [Fatigue] explode all trees
6)MeSH descriptor: [Health Status] explode all trees
7)MeSH descriptor: [Activities of Daily Living] explode all trees
8)life quality:ti or life quality:ab (Word variations have been searched)
9)MeSH descriptor: [Self Concept] explode all trees
10)health level:ti or health level:ab (Word variations have been searched)
11)level of health:ti or level of health:ab (Word variations have been searched)
12)wellness:ti or wellness:ab (Word variations have been searched)

13)well being:ti or well being:ab (Word variations have been searched)
14)(activities of daily life or daily living activities):ti or (activities of daily life or daily living activities):ab (Word variations have been searched)
15)functional ability:ti or functional ability:ab (Word variations have been searched)
16)good health:ti or good health:ab (Word variations have been searched)
17)healthiness:ti or healthiness:ab (Word variations have been searched)
18)MeSH descriptor: [Social Adjustment] explode all trees
19)physical limitations:ti or physical limitations:ab (Word variations have been searched)
20)psychiatric status:ti or psychiatric status:ab (Word variations have been searched)
21)MeSH descriptor: [Pain Measurement] explode all trees
22)functional assessment:ti or functional assessment:ab (Word variations have been searched)
23)QoL:ti or QoL:ab (Word variations have been searched)
24)hrql:ti or hrql:ab (Word variations have been searched)
25)hrqol:ti or hrqol:ab (Word variations have been searched)
26)MeSH descriptor: [Outcome Assessment (Health Care)] explode all trees
27)health status:ti or health status:ab (Word variations have been searched)
28)lifestyle:ti or lifestyle:ab (Word variations have been searched)
29)questionnaire*:ti or questionnaire*:ab (Word variations have been searched)
30)symptom assessment:ti or symptom assessment:ab (Word variations have been searched)
31)needs assessment:ti or needs assessment:ab (Word variations have been searched)
32)quality of life:ti or quality of life:ab (Word variations have been searched)
33)MeSH descriptor: [Questionnaires] explode all trees
34)patient* next reported:ti or patient* next reported:ab (Word variations have been searched)
35)self report*:ti or self report*:ab (Word variations have been searched)

36)patient* experience*:ti or patient* experience*:ab (Word variations have been searched)
37)PROM*:ti or PROM*:ab (Word variations have been searched)
38)MeSH descriptor: [Pain] explode all trees
39)MeSH descriptor: [Pain, Postoperative] explode all trees
40)MeSH descriptor: [Severity of Illness Index] explode all trees
41)wellbeing:ti or wellbeing:ab (Word variations have been searched)
42)Health Utility:ti or Health Utility:ab (Word variations have been searched)
43)MeSH descriptor: [Health Status] explode all trees
44) psychosocial:ti or psychosocial:ab (Word variations have been searched)
45) psycho-social:ti or psycho-social:ab (Word variations have been searched)
46) outcome* near/5 expectation*:ti or outcome* near/5 expectation*:ab (Word variations have been searched)
47) outcome* near/5 satisfaction:ti or outcome* near/5 satisfaction:ab (Word variations have been searched)
48)(outcome* near/5 (satisfaction or satisfied)):ti or (outcome* near/5 (satisfaction or satisfied)):ab (Word variations have been searched)
49)MeSH descriptor: [Interviews as Topic] explode all trees
50)(symptom* near/5 (improv* or change* or deteriorat*)):ti or (symptom* near/5 (improv* or change* or deteriorat*)):ab (Word variations have been searched)
51) patient* near/5 priorit*:ti or patient* near/5 priorit*:ab (Word variations have been searched)
52)scale or scales:ti or scale or scales:ab (Word variations have been searched)
53) expectations:ti or expectations:ab (Word variations have been searched)
54) satisfaction:ti or satisfaction:ab (Word variations have been searched)
55) MeSH descriptor: [Recovery of Function] explode all trees
56) Or/01-55
Guideline/checklist terms
57) MeSH descriptor: [Guideline] explode all trees
58) MeSH descriptor: [Practice Guideline] explode all trees

59) (Guidance or Recommendation* or Standard*) (Word variations have been searched)
60) MeSH descriptor: [Checklist] explode all trees
61) MeSH descriptor: [Ethics, Medical] explode all trees
62) MeSH descriptor: [Ethics, Research] explode all trees
63) MeSH descriptor: [Informed Consent] explode all trees
64) Professional Obligation:ti or Professional Obligation:ab (Word variations have been searched
65) Duty of Care:ti or Duty of Care:ab (Word variations have been searched)
66) Or/57-65
Trial Protocol terms
67) (Trial design or study design) (Word variations have been searched)
68) (Trial Protocol* or study protocol*) (Word variations have been searched)
69) Or/67-68
70) And/56,66,69

Appendix 8

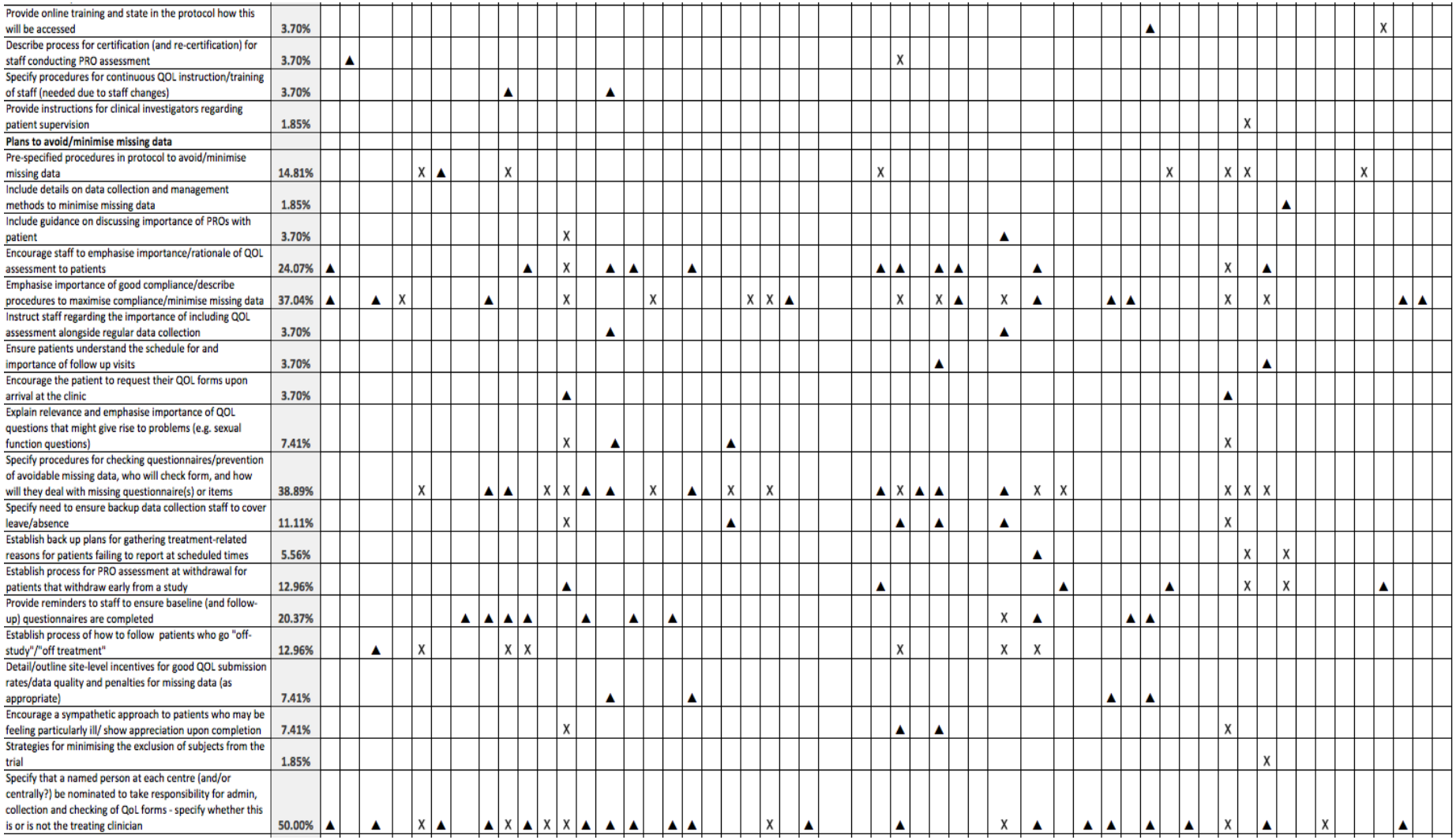
Chapter 7 – Summary of protocol recommendations

Recommendations extracted from n=54 guidance documents	% of Guidance Documents	Mohipour et al. (1989)	Schron & Schumaker (1992)	Gotay et al. (1992a)	Osoba (1992)	Gotay et al. (1992b)	Nayfield et al. (1992)	Sadura et al. (1992)	Hayden et al. (1993)	Cella et al. (1993)	Spilker (1995)	Molin & Arrigo (1995)	Fayers et al. (1997)	Kiebert et al. (1997)	Bernhard et al. (1998a)	Bernhard et al. (1998b)	Osoba (1998)	Simes et al. (1998)	Mohipour & Lovato (1998)	Brooks et al. (1998)	Leidy et al. (1999)	Osoba (1999)	de Haes et al. (2000)	Revicki et al. (2000)	Bottomley (2001)	Hakamies-Blomqvist et al. (2001)	Santanello et al. (2002)	Chassany et al. (2002)	EORTC QLG (2002)	Movsas (2003)	Calvert & Freemantle (2004)	Wiklund (2004)	Buchanan et al. (2005)	Fayers & Hays (2005)	Lipscomb (2005)	Avery & Blazeby (2006)	TROG (2007)	Ganz & Gotay (2007)	Lipscomb et al. (2007)	Land et al. (2007)	Patrick et al. (2007)	Sloan et al. (2007)	Revicki et al. (2007)	Fayers & Machin (2007)	FDA (2009)	Fairclough (2010)	Hao (2010)	NCIC CTG (2010)	Basch et al. (2011)	King (2011)	Efficace & Taphoorn (2012)	Jensen et al. (2012)	Novik et al. (2013)	Macfield et al. (2013)	Kyte et al. (2013)
Number of recommendations -->		16	10	8	31	35	13	9	9	26	21	19	34	28	26	8	14	5	20	1	33	11	23	16	16	4	10	42	38	13	41	30	10	23	26	28	15	12	12	6	19	16	2	37	38	42	9	23	21	35	6	31	23	12	1
ADMINISTRATIVE INFORMATION																																																							
Roles & Responsibilities of PRO Personnel																																																						
Research nurses should be involved in protocol development	1.85%								▲																																													
Name the QOL sub-study coordinator - include contact details & institution	3.70%																																															X		X				
Name the QOL sub-study manager/assistant/officer - include contact details & institution	1.85%																																																X				
The involvement of personnel other than those listed in the study should be specified (e.g. Psychologists, social workers etc)	1.85%				X																																																	
INTRODUCTION																																																							
Background, Rationale & Objectives																																																						
Background PRO-specific information																																																						
Describe what is currently known about QOL in this area and explain the gaps in literature	9.26%				X	X																		X																											X		X				
Describe the population of interest	5.56%		▲											▲																																							X				
PRO-specific rationale																																																						
Describe why PROs have been included appropriate to the study population, intervention, context objectives and setting	9.26%					X																										▲	▲												▲					▲						
Justify the relevance of assessing HRQL for disease and population under investigation	9.26%																								▲			▲			X	▲		X																					
Provide a clinical justification for QOL outcome measurement	22.22%				X	X							X											▲				▲			X	X	▲												X		X		X					
Provide a rationale for measuring QOL- e.g. superior intervention/negative impact of intervention/equivalence	48.15%	▲						X		X			X	X			X		X			X	X	X	X			X	X		X	X	X	X	X								X		X		X		X	X	X	▲	X	
Emphasise importance of QOL assessment to the study	11.11%					X							X	▲	▲																																X		▲									
Pro-specific hypotheses/objectives																																																						
State the QOL hypothesis (and corresponding null hypothesis) and to which outcome the hypothesis relates	42.59%				X	X	X							X							X	X	X	X	X		X	▲	X	▲				X		X	▲			▲		X	X	X		X		X		X			
Identify QOL as an objective/state research objective of HRQL component in relation to dimensions, population and timeframe	40.74%		▲		X	X		▲		▲	X	X	▲	X			X	X				X						X				▲	▲		▲	▲								X		X		X		X			X		
State whether the study is exploratory or confirmatory.	1.85%																																																	X				
Protocols addressing comparative effectiveness research in oncology should include Core Outcome Set symptoms	3.70%	▲																																															X						
METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES																																																						
PRO study setting																																																						
Description and rationale of sampling method (representativeness of population and/or centres, as appropriate)	5.56%										▲												▲					X																													

PRO eligibility criteria																																																							
Describe patient eligibility criteria	14.81%			▲						▲				X	▲								X													▲												X					X		
State the inclusion/exclusion criteria for QOL endpoint(s) and analyses (e.g., language/reading requirements)	12.96%				X	X				▲		X									X																									X				X					
Specify if QOL completion is a pre-randomisation eligibility condition	33.33%				X	X		▲		▲	▲	▲	▲		▲		▲	▲	X	X									▲	X	▲													X				▲				X			
PRO endpoint specification																																																							
Identify QOL as an endpoint	9.26%																		X																	▲												X		X		X			
Define the role of the PRO endpoint (primary, important secondary, exploratory)	25.93%													▲							X			X				X			X		▲			▲		▲	▲			X	X		X	▲						X			
Describe the constructs used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom	7.41%																																			X										X				X				▲	
Specify the timeframe of interest/primary time-point for analysis and the rationale for this	25.93%	▲				▲				X	▲								▲		X							X	X		X	▲				▲										X				X		▲			
Include a conceptual model to define exactly what is being measured, which domains are covered and what is the intended HRQL claim	9.26%																											▲					X								▲					X							▲		
Timing of PRO assessments																																																							
Include QOL assessment timings in main protocol schedule of assessments	12.96%							▲		▲		X							X																													X		X		▲			
Specify which measures will be used at each assessment	1.85%																																																	X					
Specify if baseline assessment is pre-randomisation	35.19%				▲	X	▲		▲		▲		X	▲								▲							▲	▲	▲				▲	▲	▲							X		▲						▲	X	▲	
Specify acceptable time windows for each assessment	29.63%											X	X				X				X					▲			X		▲	▲		X	X		▲							X		X				X		▲		▲	
Specify standardised timing of questionnaire delivery (e.g. before/whilst/after seeing clinician)	29.63%				X		▲						X		▲		▲				▲		▲					▲	▲		X	▲					▲							X	X							▲	▲		
For open label trials - PRO instruments administered in a clinic visit should be administered before other clinical assessments or procedures	1.85%																																												▲										
Outline standardised order for administration of PRO and clinical assessments	3.70%																				▲																								X										
Justification for timing of PRO assessments																																																							
Timing should link to research questions, length of recall, disease/Tx natural history, planned analysis/ must be fair for both arms	16.67%	▲												▲													X	▲		▲					▲										▲	▲						X			
Specify the timing of QOL assessments - link to hypotheses	68.52%		▲	▲		X	▲			▲	▲		X	X	X	▲	X	X			X	X	X		X	X		X	X	▲	X	X		▲	▲	▲	▲	▲	▲					X	X	X		X	▲	X		X	▲	▲	
Long-term assessments in different treatment groups should be at similar times in relation to the date of randomisation to avoid bias	5.56%																												X															▲		▲									
Other timing information																																																							
Minimum assessment at baseline, end of study or at withdrawal	9.26%														▲										X			▲				▲									▲														
Conduct clinical and QOL assessment simultaneously	5.56%								▲			▲		▲																																									
PRO sample size																																																							
State the sample size and power requirements in relation to the rationale/objectives/hypothesis	40.74%				X	X	▲				▲			X							X		X		X		X	X	X		X	▲	▲			▲						▲		X		X		X		X		▲	X		
If the sample size required for HRQL assessment is substantially less than for primary endpoint an unbiased strategy for selection of a subset of patients in whom HRQL will be assessed is possible provided that this strategy is clearly defined and justified in the protocol	7.41%				X	X	▲																					X																											

PROs in relation to blinding																																																							
In a blinded study detail the use of PRO administration techniques to minimise the possibility of unblinding	1.85%																																												▲										
Research protocol must specify that interviewers be blind to intervention	1.85%																											X																											
METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS																																																							
METHODS: DATA COLLECTION																																																							
PRO instrument description																																																							
Describe the questionnaire(s) (including, number of items/domains, instrument scaling/scoring, reliability, content and construct validity, responsiveness, sensitivity, respondent burden, cultural adaptation/validity, recall period)+/- validation plan if appropriate	35.19%	X	▲		X	X						X			▲						X		X					X			X	X				▲	▲				▲			▲		▲			▲		X			▲	
number of items and domains	1.85%																											▲																											
Detail availability of instrument in different languages and their use on the study	1.85%																																															X							
If appropriate describe administering different QOL forms to subgroups of patients	1.85%																				X																																		
PRO instrument justification																																																							
Specify which QOL questionnaires will be used - link to clinical justifications and hypotheses via specific domains/items	59.26%		▲		X	X	▲				▲			X							X	X	X	X	X		X	X	X	▲	▲	▲	X	▲		▲	▲	▲	▲			▲				X		X	X	X	X	▲	X	▲	
Selection of questionnaire should be discussed and justified	5.56%	▲											X																																				▲						
Specify why the particular questionnaire was chosen in preference to others	1.85%				X																																																		
Describe PROM recall period - link to treatment effects	9.26%	▲																											▲			X			▲										▲										
Reference the validity, reliability and responsiveness of the instrument (may be more succinct with refs if PROM widely used)	25.93%					X						▲									X		X	▲	▲			X		▲	X			▲		▲									▲					X				▲	
Provide evidence of measurement equivalence across modes (when mixing modes of PRO data collection)	1.85%																																																X						
Outline plans for validation of measurement properties, if appropriate	12.96%					X																						▲			▲						▲				X				X								X		
Specify the HRQL domains the study intervention is expected to effect	31.48%					X								▲							X		X	X	X			X	X		X	▲	▲			▲						X			▲	X	▲					X			
Discuss respondent burden	3.70%																											▲																								▲			
Justify use of questionnaires that take longer than 10 mins to complete (or 20 mins at baseline)	1.85%																																																X						
Describe questionnaire completion time	7.41%				X							▲																				X					▲																		
Provide evidence that questionnaire is acceptable to patients	3.70%																																									▲												▲	
International trials should include cultural validity of questionnaire, documentation of any procedures/events that differ across countries, analysis of cross culture equivalence	3.70%									▲																										▲																			

PRO data collection plan																																																							
Include a pre-specified data collection plan	31.48%					X		▲			X			X	▲				X		X					▲					▲	▲		X	X				▲		X								▲			▲	▲		
Specify how QOL will be assessed - pencil and paper, online, etc	40.74%		▲		X	X		▲		X				X	▲						▲		X		X			▲	X		X	▲		X	X	▲									▲	X			▲	X		▲			
Specify how patients will be managed if translations unavailable	1.85%																▲																																						
Specify where QOL will be assessed - clinic, home, etc	22.22%			▲	X	X		▲							▲							X	X					▲				▲				▲										▲				X					
Specify whether the QOL instrument will be used in other languages – if so, which	1.85%																																																	X					
Specify location (e.g. quiet area [an example but not formal recommendation])	3.70%												▲																																▲										
Substantiate use of proxies (conditions under which proxy permissible)	1.85%																							▲																															
State who will administer the measure (e.g., a physician, nurse etc)	1.85%				X																																																		
Specify if help and or proxy assessments are permitted (and what level of assistance allowed)	25.93%					X				X		X	X		▲	▲												▲	▲		▲			X	X	▲								X		▲									
Ensure privacy and confidentiality of planned data collection	5.56%				X																						X	▲																											
PRO data collection guidelines/training infromation																																																							
Provide guidelines and/or training plan for PRO data collection	66.67%	▲	▲	▲	X		▲	▲	X	X	▲	▲	X	▲	▲	▲	X		X		X	X	X		X	▲		▲	▲	▲	▲			▲	▲	▲		▲	▲		X	▲		X	X	X						▲			
Specify procedures for minimising inconsistencies in trial conduct	1.85%																																												X										
A plan should be included in protocol for systematically training and contacting local site personnel to ensure that they understand the content and importance of collecting PRO data. Ideally coordinated by a lead data manager who monitors patient adherence in real time and communicates with sites if patient non-adherent	9.26%																		▲										▲		▲	▲																	X						
Provide interviewer training plan/format guidelines for PROs administered by interviewer (plus guidance on recording of interviews)	11.11%	▲			X					▲											▲																								X							▲			
Provide instructions on how the patient should complete the form (e.g. without conferring with friends/relatives, all questions should be answered even if the patient feels them to be irrelevant)	38.89%	▲				X				▲			X	▲	▲	▲					▲		X					▲	▲		▲			▲	▲		▲				X			▲	▲	X						▲	X		
Provide training plan and instructions to patients for self-administered PROs	1.85%																																												X										
Instruct site staff to give patients a full explanation about QoL assessment procedures	5.56%										▲																									▲								▲											
Instruct site staff to routinely record the source of PRO data in studies that allow proxies	5.56%												▲															▲																					▲						
Instruct site staff to routinely record (on clinical follow-up form) whether QOL assessment completed	3.70%												X						▲																																				
Instruct site staff to routinely record (on clinical follow-up form) if the patient needed help to complete the questionnaire	3.70%												▲																																				▲						
Instruct site staff to routinely record (on clinical follow-up form) the reasons for any missing data	7.41%												X																		X													▲					▲						
Instruct data collection staff to record the specific mode of PRO administration (in studies with mixed modes of PRO data collection)	1.85%																																																X						


Provide online training and state in the protocol how this will be accessed
3.70%
Describe process for certification (and re-certification) for staff conducting PRO assessment
3.70%
Specify procedures for continuous QOL instruction/training of staff (needed due to staff changes)
3.70%
Provide instructions for clinical investigators regarding patient supervision
1.85%
Plans to avoid/minimise missing data
Pre-specified procedures in protocol to avoid/minimise missing data
14.81%
Include details on data collection and management methods to minimise missing data
1.85%
Include guidance on discussing importance of PROs with patient
3.70%
Encourage staff to emphasise importance/rationale of QOL assessment to patients
24.07%
Emphasise importance of good compliance/describe procedures to maximise compliance/minimise missing data
37.04%
Instruct staff regarding the importance of including QOL assessment alongside regular data collection
3.70%
Ensure patients understand the schedule for and importance of follow up visits
3.70%
Encourage the patient to request their QOL forms upon arrival at the clinic
3.70%
Explain relevance and emphasise importance of QOL questions that might give rise to problems (e.g. sexual function questions)
7.41%
Specify procedures for checking questionnaires/prevention of avoidable missing data, who will check form, and how will they deal with missing questionnaire(s) or items
38.89%
Specify need to ensure backup data collection staff to cover leave/absence
11.11%
Establish back up plans for gathering treatment-related reasons for patients failing to report at scheduled times
5.56%
Establish process for PRO assessment at withdrawal for patients that withdraw early from a study
12.96%
Provide reminders to staff to ensure baseline (and follow-up) questionnaires are completed
20.37%
Establish process of how to follow patients who go "off-study"/"off treatment"
12.96%
Detail/outline site-level incentives for good QOL submission rates/data quality and penalties for missing data (as appropriate)
7.41%
Encourage a sympathetic approach to patients who may be feeling particularly ill/ show appreciation upon completion
7.41%
Strategies for minimising the exclusion of subjects from the trial
1.85%
Specify that a named person at each centre (and/or centrally?) be nominated to take responsibility for admin, collection and checking of QoL forms - specify whether this is or is not the treating clinician
50.00%

METHODS: DATA MANAGEMENT																																																							
PRO-specific Quality Assurance																																																							
Include guidance for data entry on coding responses, missing responses or ambiguous responses	1.85%																														▲																									
Specify procedures for a central PRO data monitoring system (aimed at identifying and rectifying potential data collection problems)	24.07%	▲		▲					▲		▲	▲			▲				▲										X					▲	X			▲	▲	▲															
Specify how an electronic PRO source will be maintained and how investigator will meet regulatory requirements and ensure data integrity and security	3.70%																															▲													X										
Specify plan to monitor compliance	12.96%													▲														X		▲				▲				▲														▲	X		
Include data collection, data storage and data handling/transmission procedures	9.26%				X														X		X																				X				X										
Ensure plans for administration consistent with user manual	1.85%																																												X										
Specify procedure for monitoring adherence to 'timing windows'	3.70%														X																															▲									
METHODS: DATA ANALYSIS																																																							
PRO Statistical Analysis																																																							
All analyses should be clearly defined a priori in the protocol	53.70%				X					▲	▲	X		X			X		X		X	X	X	X	▲		X	X			X	▲	▲				▲		▲		X	X		X	X	X		X	▲	X		X	X		
Explain the assumptions of analyses	1.85%																																																	X					
State the anticipated response rate/effect size	7.41%													X									X																					X						X					
Include an a priori estimation of expected change in PRO score	1.85%																											X																											
Specify conditions for positive outcome	5.56%																					▲																			X				X										
Specify ITT or per-protocol analysis.	11.11%																							X							▲						▲				X					X						▲			
Include a priori identified summary statistics (as appropriate)	1.85%																																									▲													
Specify minimum amount of QOL data and acceptable degree of timing deviation before compromise of study question	1.85%														▲																																								
Describe approach to controlling for QOL related comorbidity	1.85%																				X																																		
Describe methods for scoring endpoints. Where possible, reference scoring manuals for summated scales from questionnaires (domain-specific and/or total),and methodological papers for composite endpoints (e.g. QTWiST)	3.70%																																													▲				X					
Ensure plans for scoring are consistent with those used in development	5.56%																											X			X														X										
Include appropriate procedures for minimising assessment bias	1.85%																				X																																		
Pre-specify scoring	11.11%					X															▲			▲				X				X				▲										X									
Plans to address multiplicity of PRO data																																																							
Plan for multiplicity/controlling type 1 error - summary measures/adjustments	35.19%					X	X				▲			▲							X			▲			X	X	X		X	X			▲	▲					X	X			X	X	X					▲			
Pre-specification of sequence of testing (regulatory trials)/exploratory analyses to control for multiplicity or prespecify domains for a labelling claim	12.96%																													X	X	▲									X	▲				▲	▲								

PRO clinical significance																																																							
Specify the criteria for statistical and clinical significance	7.41%																				X								X							▲			▲																
Define clinical response/method of analysis for response/cumulative distribution function	7.41%																							▲							X										X				X										
State and justify minimal [clinical] important difference/change	20.37%																				▲				X							▲					▲				▲			X				X		X	X	X		X	
Identify and state score change meaningful to patient	3.70%																										X																						▲						
Describe QOL responder definitions (size and duration of benefit) where relevant	1.85%																																																	X					
Investigators should indicate how the results will be used.	1.85%				X																																																		
Statisitical methods to deal with missing PRO data																																																							
Describe methods for handling missing data	40.74%				X	X					▲										X			▲	X		X	X	▲		X	▲			▲		▲				X	X			X	X	X		X	X			▲	▲	
Include approach to imputation	7.41%																																									X			X				X			▲			
Include proposed sensitivity analyses for imputation methods.	11.11%																														▲				▲							▲			X	X	X								
Sate how missing data will be described	5.56%																											▲			X															X									
MONITORING																																																							
PRO data monitoring																																																							
Role of DMC and QA in relation to PROs should be defined.	22.22%		▲		X	X	▲			X					▲				▲								X	▲						▲										▲									X		
PRO alerts																																																							
Provide guidance for staff on where they should refer patients for appropriate help, should completion of the QoL questionnaire prompt them to seek more information or support	1.85%																												▲																										
Specify mechanism for alerting clinical staff about symptoms reported by patients that exceed a pre-defined level of severity	3.70%									▲																																							▲						
Include an a priori plan for consistent/standardised management of PRO alerts that is clearly communicated to all appropriate trial staff	1.85%																																																						X
ETHICS AND DISSEMINATION																																																							
PRO-specific consent information																																																							
Explain the QOL assessment procedure within the PIS/consent (including: reasons for evaluating QoL, what it will involve, risks and benefits, frequency and timing/timeframe, the need to answer all questions, the importance of completing questions without being influenced by the opinions of others) and, if appropriate, identify if consent to QOL assessment is required for entry into the trial	25.93%				X	X				▲		X	X		▲		X						▲						X					▲	▲	▲								X		X									
Describe informed consent procedure.	1.85%													X																																									
Inform patients who they may contact for help in completing the questionnaire	1.85%																																			▲																			
Pro-specific confidentiality procedures																																																							
Include guidance on discussing PRO confidentiality with patients (e.g. patients told how their questionnaires will be used)	16.67%									▲		X	X		▲			▲											▲		▲	X												X											
Specify whether QOL forms will be used to influence therapy or patient management (i.e. will clinician have knowledge)	7.41%												X																▲		▲													X											

PRO dissemination policy																																																							
Include detailed plans for regular feedback to participants via letter/newsletter on QOL aspect of study	3.70%								▲								▲																																						
Include QOL publication policy	1.85%																																															X							
APPENDICES																																																							
PRO components of informed consent materials																																																							
A sample PIS and consent form (in which QOL assessment requirements are mentioned) should be included in an appendix of the protocol	14.81%					X							X	X									X						X																				X		X			X		
Patients should be provided with QOL information leaflet to take home	3.70%												X																																X											
PIS/Consent form should inform patients what will happen to their completed questionnaires	9.26%					X						X																	▲	▲						▲																			
PRO assessment checklist and/or flowsheet																																																							
Details about the characteristics of the PRO should be included in an appendix	1.85%																																																			X		
Formal statement on QOL data collection policy should be included in the appendix	1.85%																		X																																				
Include a QOL Assessment checklist in a protocol appendix	3.70%																																															▲		X					
Include statistical analysis plan in protocol appendix	5.56%												X																																X	▲									
Checklist should be provided in the protocol	1.85%																																																	X					
Include a QOL patient evaluation flow sheet in the appendix	1.85%																																															X							
PRO questionnaire																																																							
Provide exact version/format of PROM in the protocol within the CRF (or in a separate appendix as appropriate)	18.52%	▲				X	▲												X		X				X																X				X			X					X		
Present evidence of permission to use QOL questionnaire (where applicable)	3.70%																																															X		X					
Include translations of core questionnaire in appendix	1.85%																																															▲							
PROM completion instructions																																																							
Ensure clear written patient instructions accompany QOL/PRO questionnaire	16.67%				X						▲			X			X						X						X																X						X			X		
General Referencing																																																							
References should be provided to support key statements	3.70%				X																																											▲							

▲ = implicit recommendation
X = explicit recommendation

Appendix 9

Chapter 7 – PRO recommendations related to other supporting trial documentation

Recommendations extracted from n=54 guidance documents	Moinpour et al. (1989)	Schron & Schumaker (1992)	Gotay et al. (1992a)	Osoba (1992)	Gotay et al. (1992b)	Nayfield et al. (1992)	Sadura et al. (1992)	Hayden et al. (1993)	Cella et al. (1993)	Spilker (1995)	Molin & Arrigo (1995)	Fayers et al. (1997)	Kiebert et al. (1997)	Bernhard et al. (1998a)	Bernhard et al. (1998b)	Osoba (1998)	Simes et al. (1998)	Moinpour & Lovato (1998)	Brooks et al. (1998)	Leidy et al. (1999)	Osoba (1999)	de Haes et al. (2000)	Revicki et al. (2000)	Bottomley (2001)	Hakamies-Blomqvist et al. (2001)	Santanello et al. (2002)	Chassany et al. (2002)	EORTC QLG (2002)	Movsas (2003)	Calvert & Freemantle (2004)	Wiklund (2004)	Buchanan et al. (2005)	Fayers & Hays (2005)	Lipscomb (2005)	Avery & Blazeby (2006)	TRoG (2007)	Ganz & Gotay (2007)	Lipscomb et al. (2007)	Land et al. (2007)	Patrick et al. (2007)	Sloan et al. (2007)	Revicki et al. (2007)	Fayers & Machin (2007)	FDA (2009)	Fairclough (2010)	Hao (2010)	NCIC CTG (2010)	Basch et al. (2011)	King (2011)	Efficace & Taphoorn (2012)	Jensen et al. (2012)	Novik et al. (2012)	Macefield et al. (2013)	Kyte et al. (2013)
GENERAL APPROACH TO PROTOCOL																																																						
PROs should be addressed in a separate chapter in the protocol	▲										X																												X											X				
PRO endpoints should be fully integrated in trial protocol/data collection		▲		X						X								▲			▲							▲	X				▲	▲		X	X	▲			X	X			X	X					X	X		
Relevant sections pertaining to QOL should be identified in the table of contents																																															X							
OTHER TRIAL DOCUMENTATION																																																						
Include SOPs for administration of QoL assessments												X																															X											
SOPs should describe how incomplete data should be disclosed - e.g. notes of missing items in questionnaire. Explanations of why a questionnaire was not completed by the Pt should be initialed by the investigator																											▲																											
Include PRO completion Reminders in CRF																											▲	X															X		X									
Include area in CRF to document whether patient required help from proxy or other assistance																												X		X			X	X									X											
Include area in CRF to document the reason for non-completion/missing data (or include a specific missing data reporting form or 'face sheet' alongside the PROM)														▲		X		X		X								X		X			X	▲	▲				▲				X		X							X	▲	
randomisation checklist with QOL completion as eligibility criteria							▲											X										X															X											
Training manual with written instructions for staff responsible for administering Q's should be provided (e.g. investigators guide/booklet/QL manual/QL assessment schedule/Manual of operations)		▲		X								X			▲					X							X						X																					
Training manual should include guidelines for handling common patient questions																				X																																		
Training manual should include guidance on what to do if patient refuses to complete certain items																				X																																		
Training manual should include plans for ongoing training and follow-up																				X																																		

▲ = implicit recommendation
X = explicit recommendation

Appendix 10

Chapter 8 – Full PRO Protocol Checklist

SPIRIT HEADINGS	CODE	PRO checklist items (in bold) and sub-categories
ADMINISTRATIVE INFORMATION		
Roles & Responsibilities		
	P1	**ROLES & RESPONSIBILITIES OF PRO PERSONNEL IDENTIFIED?**
	P1a	Research nurse involved in protocol development?
	P1b	Composition, roles and responsibilities of PRO study coordinator outlined?
	P1c	Composition, roles and responsibilities of other PRO personnel outlined?
	P1d	PRO expert named on Trial Management Group/TMC?
INTRODUCTION		
Background & Rationale		
	P2	**BACKGROUND PRO-SPECIFIC INFORMATION PROVIDED?**
	P2a	Describes what is currently known about PROs in this area and explain the gaps in literature?
	P2b	Describes the population of interest for the PRO?
	P3	**PRO-SPECIFIC RATIONALE PROVIDED?**
	P3a	Description of why PROs have been included appropriate to the study population, intervention, context, objectives and setting provided?
	P3b	Clinical justification for PRO assessment provided?
	P4	**PRO-SPECIFIC HYPOTHESIS PROVIDED?**
	P4a	PRO hypothesis provided? e.g. superior intervention/negative impact of intervention/equivalence
	P5	**PRO-SPECIFIC OBJECTIVES STATED (IN RELATION TO DIMENSIONS, POPULATION AND TIMEFRAME)?**
	P5a	Stated whether study exploratory or confirmatory?
	P5b	Core outcome set symptoms included? (for CER)
METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES		
	P6	**DETAILS & RATIONALE OF PRO STUDY SAMPLE/SETTING PROVIDED?**
	P6a	Description and rationale of sampling method provided?(representativeness of population and/or centres, as appropriate)
	P7	**PRO CONSIDERATIONS DISCUSSED IN THE ELIGIBILITY CRITERIA?**
	P7a	Described patient eligibility criteria for PRO assessment?
	P7b	PRO inclusion criteria outlined?
	P7c	PRO exclusion criteria outlined?
	P7d	Specified if PRO completion a pre-randomisation eligibility condition?
INTERVENTION		
	P8	**PRO ENDPOINT SPECIFIED?**
	P8a	PRO identified as endpoint?
	P8b	Role of PRO endpoint defined (primary, important secondary, exploratory)?
	P8c	Constructs used to evaluate the intervention outlined (e.g. overall QOL,

		specific domain, specific symptom)?
	P8d	Primary time-point for analysis/timeframe of interest specified?
	P8e	Included a conceptual model to define exactly what is being measured, which domains are covered and what is the intended HRQL Claim?
	P9	**TIMING OF PRO ASSESSMENTS SPECIFIED?**
	P9a	Assessment timings for each PROM included in main protocol schedule?
	P9b	Specified if baseline assessment is pre-randomisation?
	P9c	Specified time windows for each PRO assessment?
	P9d	Specified timing of questionnaire delivery (before/whilst/after seeing clinician)?
	P9e	Outlined standardised order for administration of PRO and clinical assessments?
	P9f	Open label trials: Is PRO administered before other clinical assessments or procedures?
	P9g	Is PRO assessment at baseline and at end of study (or withdrawal)?
	P9h	Are clinical and PRO assessment conducted simultaneously?
	P10	**TIMINGS OF PRO ASSESSMENT JUSTIFIED?**
	P10a	Timings justified in relation to research question/hypothesis?
	P10b	Timings justified in relation to length of recall?
	P10c	Timings justified in relation to intervention/natural history?
	P10d	Timings justified in relation to planned analysis?
	P10e	Established timings fair for both arms of study (e.g. similar times in relation to the date of randomisation)?
	P11	**PRO SAMPLE SIZE DISCUSSED & JUSTIFIED?**
	P11a	Specified the sample size and power requirements?
	P11b	Justified sample size/power (with reference to rationale/objectives/hypothesis as appropriate)?
	P11c	Strategy for selection of subset of patients in trial for PRO assessment defined and justified?
METHODS: ASSIGNMENT OF INTERVENTIONS (FOR CONTROLLED TRIALS)		
BLINDING		
	P12	**PROs DISCUSSED IN RELATION TO BLINDING?**
	P12a	Detailed use of PRO administration techniques to minimise the possibility of unblinding?
	P12b	Specified that PRO interviewers be blind to intervention?
METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS		
Data Collection Methods		
	P13	**PROM IDENTIFIED & DESCRIBED?**
	P13a	Described the questionnaire(s) (including, number of items/domains, instrument scaling/scoring)?
	P13b	Described the administration of different PROMs to subgroups of patients (if appropriate)?
	P13c	Detailed availability of instrument in different languages and their use on the study (if appropriate)?

	P14	**CHOICE OF PROM JUSTIFIED IN RELATION TO STUDY HYPOTHESES?**
	P14a	Justification provided for specified PROs - linked to hypotheses via specific domains/items?
	P14b	Justification provided for PROM recall period (link to treatment effects)?
	P15	**CHOICE OF PROM JUSTIFIED IN RELATION TO MEASUREMENT PROPERTIES?**
	P15a	Provided evidence of PROM reliability?
	P15b	Provided evidence of PROM validity?
	P15c	Provided evidence of PROM content and/or construct validity?
	P15d	Provided evidence of PROM responsiveness?
	P15e	Provided evidence of PROM sensitivity?
	P15f	References provided for all measurement property claims?
	P15g	Provided evidence of PROM cultural adaptation/validity?
	P15h	International trials: provided evidence of cultural validity of questionnaire, documented of any procedures/events that differ across countries and provided evidence of cross-cultural equivalence?
	P15i	Discussed plan for the validation of PROM measurement properties (if appropriate)?
	P16	**CHOICE OF PROM JUSTIFIED IN RELATION TO ACCEPTABILITY & PATIENT BURDEN?**
	P16a	Provided evidence of PROM acceptability?
	P16b	Discussed PROM questionnaire completion time/respondent burden?
	P17	**PRO DATA COLLECTION PLAN INCLUDED?**
	P17a	Specified mode of PRO assessment (pencil and paper, online, etc)?
	P17b	Specified site of PRO assessment (clinic, home etc)?
	P17c	Specified if PROM to be used in other languages (if so, which) and how patients will be managed if translations unavailable?
	P17d	Specified location of PROM completion (e.g. quiet/private area)?
	P17e	Specified who would administer the PROM?
	P17f	Specified if assistance and/or proxy assessments are permitted (and what level of assistance allowed)?
	P17g	Specified plans to ensure privacy and confidentiality of planned data collection?
	P18	**PRO DATA COLLECTION GUIDELINES/TRAINING INFORMATION PROVIDED FOR TRIAL PERSONNEL?**
	P18a	PRO data collection guidelines and/or training information provided for trial staff?

	P18b	Included information for trial personnel regarding the importance of PRO to the trial?
	P18c	Interviewer guidelines and/or training information provided for PRO administered by interview?
	P18d	Instructions provided on how the patient should complete PROM?
	P18e	Included instructions for trial personnel to give patients a full explanation about PRO assessment procedures?
	P18f	Included instructions for trial personnel to routinely record the source of PRO data in studies that allow proxies?
	P18g	Included instructions for trial personnel to routinely record whether PRO assessment completed?
	P18h	Included instructions for trial personnel to routinely record if the patient needed help to complete the questionnaire?
	P18i	Included instructions for trial personnel to routinely record the reasons for any missing data?
	P18j	Included instructions for trial personnel to record the specific mode of PRO administration (in mixed-mode studies)?
	P18k	Included instructions regarding access to any PRO-specific online training modules (if appropriate)?
	P18L	Outlined process for certification (and re-certification) for trial personnel conducting PRO assessment?
	P18m	Described procedure for updated/continuous PRO instruction/training of trial personnel (needed due to staff changes)?
	P18n	Included instructions for clinical investigators regarding patient supervision?
	P19	**PLANS TO MINIMISE AVOIDABLE MISSING DATA PROVIDED?**
	P19a	Guidance included on the need to discuss with the patient the importance of the PRO to the trial, and of attending all follow-up PRO assessment visits?
	P19b	Outlined importance of good PRO assessment compliance?
	P19c	Specified importance of including PRO assessment alongside regular data collection?
	P19d	Instructed trial personnel to encourage patients to request (or bring) their PRO forms on arrival at the clinic?
	P19e	Explained relevance and emphasised importance of PRO questions that might give rise to problems (e.g. sexual function questions)?
	P19f	Specified procedures for checking questionnaires to prevent avoidable missing data?
	P19g	Specified procedures for dealing with missing questionnaires or items?
	P19h	Specified need to ensure backup data collection staff to cover leave/absence?
	P19i	Specified back up plans for gathering treatment-related reasons for patients failing to report at scheduled times?
	P19k	Specified process for PRO assessment at withdrawal for patients that withdraw early from a study?
	P19L	Specified plans to provide reminders to staff/participants to ensure baseline (and follow-up) PROMs are completed?
	P19m	Specified plans for following patients who go off treatment/off study?
	P19n	Outlined site-level incentives in-place aimed at good PROM submission rates/data quality (as well as penalties for missing data if appropriate)?
	P19o	Guidance included on the need to adopt a sympathetic approach to patients who may be feeling particularly ill?
	P19p	Guidance included on the need to show appreciation to the patient upon PROM completion?
	P19q	Included strategies for minimizing the exclusion of subjects from the trial?
	P20	**PRO-SPECIFIC QUALITY ASSURANCE (QA) DESCRIBED?**
	P20a	Guidance included on data entry of PROM coding responses, missing responses or ambiguous responses ?
	P20b	Specified how electronic PRO source will be (i) maintained, (ii) procedures for meeting regulatory requirements and (iii) ensuring data integrity and security?

	P20c	Specified plan for data management centre to monitor compliance?
	P20c(i)	Sub-category for above: Specified plans for lead data manager coordinated central PRO data monitoring system (aimed at identifying and rectifying potential data collection problems) to monitor patient adherence in real time and communicate with study sites in the event of non-adherence?
	P20d	Specified PRO data storage and data handling/transmission procedures?
	P20e	Specified if data handling plans aligned with PROM user instructions?
	P20f	Specified procedure for monitoring adherence to 'timing windows'?
Statistical methods		
	P21	**PRO STATISTICAL ANALYSIS PLAN PROVIDED?**
	P21a	Provided explanation for assumptions of PRO analyses?
	P21b	Included an *a priori* estimation of expected change in PRO score?
	P21c	Stated the anticipated response rate/effect size?
	P21d	Specified conditions for positive outcome?
	P21e	Plans for scoring consistent with those used in development?
	P21f	Specified ITT or per-protocol analysis plans for PROs?
	P21g	Included *a priori* identified summary statistics (as appropriate)?
	P21h	Specified minimum amount of PRO data and acceptable degree of timing deviation before compromise of study question?
	P21i	Described approach to controlling for PRO related comorbidity?
	P21j	Specified procedures for minimising assessment bias?
	P21k	Described methods for scoring endpoints? Where possible, referenced scoring manuals for summated scales from questionnaires (domain-specific and/or total), and methodological papers for composite endpoints (e.g. QTWiST).
	P22	**PLANS TO ADDRESS MULTIPLICITY OF PRO DATA PROVIDED?**
	P22a	Specified plan for multiplicity/controlling type 1 error - summary measures/adjustments?
	P22b	Specified sequence of testing (regulatory trials)/exploratory analyses to control for multiplicity or prespecify domains for claim?
	P23	**PRO CLINICAL SIGNIFICANCE DEFINED?**
	P23a	Specified the criteria for statistical and clinical significance?
	P23b	Defined clinical response/method of analysis for response/cumulative distribution function?
	P23c	Stated and justified minimal [Clinical] important difference/change?
	P23d	Provided score change meaningful to patient?
	P23e	Described PRO responder definitions (size and duration of benefit) where relevant?
	P23f	Specified how PRO results would be used?
	P24	**STATISTICAL METHODS TO DEAL WITH MISSING PRO DATA DEFINED?**
	P24a	Described methods for handling missing data?
	P24b	Described approach to imputation?
	P24c	Specified proposed sensitivity analyses for imputation methods?
	P24d	Specified how missing data would be described?
MONITORING		
Data monitoring		
	P25	**PRO DATA MONITORING DEFINED?**
	P25a	Role of DMC and QA in relation to PROs defined?
	P26	**PLAN FOR THE IDENTIFICATION AND MANAGEMENT OF PRO ALERTS INCLUDED?**

	P26a	Specify mechanism for alerting clinical staff about symptoms reported by patients that exceed a pre-defined level of severity and procedure for consistent/standardized management of PRO alerts
	P26b	Included guidelines for trial personnel on where they should refer patients for appropriate help, should completion of the PROM prompt them to seek more information or support?
ETHICS AND DISSEMINATION		
	P27	**PRO-SPECIFIC CONSENT INFORMATION PROVIDED?**
	P27a	Provided guidance on PRO-specific consent content (for example: reasons for evaluating QoL, what it will involve, risks and benefits, frequency and timing/timeframe, the need to answer all questions, the importance of completing questions without being influenced by the opinions of others)?
	P27b	Specified if consent to PRO assessment required for entry into the trial?
	P27c	Provided information on who patients should contact for help in completing the questionnaire?
	P28	**PRO-SPECIFIC CONFIDENTIALITY PROCEDURES DESCRIBED?**
	P28a	Specified whether PROMS will be used to influence therapy or patient management (i.e. will clinician have knowledge)?
	P28b	Included guidance on discussing PRO confidentiality with patients (e.g. patients told how their questionnaires will be used)
Dissemination Policy		
	P29	**PRO DISSEMINATION POLICY OUTLINED?**
	P29a	Included plans for regular feedback to participants on PRO aspect of study?
APPENDICES		
	P30	**PRO INFORMATION INCLUDED IN CONSENT MATERIALS?**
	P30a	PRO-specific information leaflet provided for patients to take away?
	P30b	Patient information/consent provides information for patients on what will happen to their completed questionnaires?
	P30c	Information on PRO assessment requirements included in the model patient information/consent form (protocol appendix)?
	P31	**PRO ASSESSMENT CHECKLIST AND/OR FLOWSHEET PROVIDED IN APPENDIX?**
	P31a	Details about the characteristics of the PRO should included in an appendix?
	P31b	Formal statement on PRO data collection policy included in the appendix?
	P31c	PRO statistical analysis Plan Provided in appendix?
	P32	**EXACT VERSION OF PROM PROVIDED IN CRF/APPENDIX (WITH TRANSLATED VERSIONS IF APPROPRIATE)?**
	P32a	Present evidence of permission to use QOL questionnaire (where applicable)
	P33	**PROM COMPLETION INSTRUCTIONS PROVIDED IN CRF/APPENDIX?**

Appendix 11

Chapter 8 – List of Total PROMS used in n=75 protocols

PROMS	No. (%)	Notes
Aberdeen Varicose Vein Questionnaire (AVVQ)	1 (1.33)	
Acceptability Questionnaire (measure not named)	1 (1.33)	
Activities of Daily Living (Barthel Index)	1 (1.33)	
Activity of Daily Living (measure not named)	1 (1.33)	
Adapted Client Service Receipt Inventory (CSRI)	1 (1.33)	
Adherence Questionnaire (measure not named)	1 (1.33)	
Adult Service Use Questionnaire (ASUS)	1 (1.33)	
Anti Depressant Side Effect Checklist (ASEC)	1 (1.33)	
Anxious Thoughts Inventory (AnTI)	1 (1.33)	
Asthma Control Questionnaire (ACQ)	1 (1.33)	
Asthma Specific Health Status Questionnaire (AQLQ - short version)	1 (1.33)	
Attitudes and Beliefs about Falls Prevention (AFRIS)	1 (1.33)	
A patient generated index (PGI) of aspects of life affected by a fear of falling	1 (1.33)	
Bangor Life Events Schedule of Intellectual Disabilities (BLESID)	1 (1.33)	
Beck Depression Inventory (BDI)	3 (4.00)	
Behavioural Adherence (Self Report)	1 (1.33)	
Behavioural Regulation in Exercise Questionnaire (BREQ 2)	1 (1.33)	
Beliefs about Paranoia Scale (BAPS)	1 (1.33)	
Birchwood Social Function Scale (SFS)	1 (1.33)	

Bowel Diary	1 (1.33)	
Brief Core Schema Scale (BCSS)	1 (1.33)	
Bristol Activities of Daily Living Scale (BADLS) - Carer Completion	1 (1.33)	
Calgary Sleep Apnoea Quality of Life Index (SAQLI) Secondary	3 (4.00)	
Cambridge Exeter Repetitive Thought Scale (CERT)	1 (1.33)	
Cardiff Wound Impact Schedule (CWIS)	1 (1.33)	
Caregiver Burden Inventory (CBI)	1 (1.33)	
Caregiver Strain Index (CSI)	1 (1.33)	
Caregiver Uplift / Burden Scale - Carer Completion	1 (1.33)	
Caregiving Difficulty Scale - Intellectual Disability (CDS-ID) Carer Completion	1 (1.33)	
Childhood Trauma Questionnaire (CTQ)	1 (1.33)	
Cleveland Clinic Score	1 (1.33)	
Client Satisfaction Questionnaire	1 (1.33)	
Client Service Receipt Inventory (CSRI)	1 (1.33)	
Client Services Receipt Inventory (CSRI) Carer Completion	2 (2.67)	
Clinical Outcomes in Routine Evaluation Outcome Measure (CORE-OM)	2 (2.67)	
Cognitive Emotion Regulation Questionnaire – Short version (CERQ)	1 (1.33)	
Community Healthy Activities Model Program for Seniors (CHAMPS - Activities Questionnaire for Older Adults)	1 (1.33)	
ConfBal Scale (measure of balance confidence)	1 (1.33)	
Connor-Davidson Resilience Scale (CD-RISC2)	1 (1.33)	
Consultation Satisfaction Questionnaire (CSQ)	1 (1.33)	
Contingent Valuation Questionnaire (Measure not named)	1 (1.33)	

Curiosity for Internal and External Experiences	1 (1.33)	
Custom PROM (subjective quality of life and satisfaction with medication 11 item scale not named)	1 (1.33)	
Daily Sleep Diary	1 (1.33)	
Day in the Life (DILQ)	1 (1.33)	
Depressed States Checklist (DSC)	1 (1.33)	
Depression Carer Self Efficacy Scale	1 (1.33)	
Dermatitis Family Impact Instrument (DFI)	1 (1.33)	
Dermatology Life Quality Index (DLQI)	1 (1.33)	
Device Specific Quality of Life Questionnaire (not named)	1 (1.33)	
Diabetes Family Responsibility Questionnaire (DFRQ)	1 (1.33)	
Diabetes Specific Quality of Life (DSQOL)	1 (1.33)	
Diabetes Treatment Satisfaction Questionnaire (DTSQ)	1 (1.33)	
Dietary Instrument for Nutrition Education (DINE)	1 (1.33)	
Disabilities of Arm Shoulder and Hand Score (DASH)	1 (1.33)	
Disability Rating Index (DRI)	1 (1.33)	
Dispositional Positive Emotions Scale (DPES)	1 (1.33)	
Eating Disorder Examination Questionnaire (EDE-Q)	1 (1.33)	
Eczema area and severity index (EASI)	1 (1.33)	
Edinburgh Postnatal Depression Scale (EPDS)	1 (1.33)	
EORTC QLQ-C30	1 (1.33)	
Epworth Sleepiness Scale (ESS)	3 (4.00)	
EQ-5D	56 (74.66)	inc 1 EQ5D 3L and 1 EQ5D 5L and 1 EQ5D_Y (young people version)

EQ-5D - Carers, proxy, parent completion	3 (4.00)	merged EQ5D Carers and EQ5D (proxy where necessary) and EQ5D (parent completion)
EUROHIS-QOL-8	1 (1.33)	
European Brain Injury Qr - patient version (EBIQ-p) and relative version (EBIQ-r)	1 (1.33)	
Everyday Memory Questionnaire (EMQ - Patient Version)	1 (1.33)	
Everyday Memory Questionnaire (EMQ - relative version)	1 (1.33)	
Exercise Expectations	1 (1.33)	
Experience of Services	1 (1.33)	
Fagerstrom Nictotine Dependence Questionnaire (FTND)	1 (1.33)	
Falls Efficacy Scale - International (FES-I)	2 (2.67)	
Family Eating and Activity Habits questionnaire (FEAHQ)	1 (1.33)	
Family Emotional Involvement and Criticism Scale (FEICS)	1 (1.33)	
Fear of Falling (measure not named)	1 (1.33)	
Fear of Falling when Walking Numeric Rating Scale	1 (1.33)	
Fecal Incontinence Quality of Life Score (FI-QOL)	1 (1.33)	
Five-factor Mindfulness Questionnaire (FFMQ)	1 (1.33)	
Food Frequency Questionnaires (FFQ)	1 (1.33)	
Functional Assessment of Cancer Therapy-Prostate (Fact P)	1 (1.33)	
Functional Outcome of Sleep Questionnaire (FOSQ)	1 (1.33)	
Further Treatment Questionnaire (Measure Not Identified)	1 (1.33)	
Functional Assessment of Cancer Therapy Questionnaire for Breast Cancer (FACT-B+4)	1 (1.33)	
Functional Health Status Measure (OMQ-14)	1 (1.33)	

General Health Questionnaire (GHQ 12)	1 (1.33)	
General Health Questionnaire (GHQ12) Carer Completion	1 (1.33)	
General Health Questionnaire (GHQ-30)	1 (1.33)	
General Practice Physical Activity Questionnaire (GPPAQ)	1 (1.33)	
General Self-efficacy Scale (GSS)	1 (1.33)	
Generalised Anxiety Disorder (GAD-7)	3 (4.00)	
Geriatric Depression Scale (GDS)	1 (1.33)	
Geriatric Depression Scale (GDS-15)	1 (1.33)	
Glasgow Anxiety Scale (GAS-ID)	1 (1.33)	
Glasgow Depression Scale for people with a learning disability (GDS-LD)	1 (1.33)	
Global self report measures of satisfaction with treatment (PROM not Named)	1 (1.33)	
Godin Leisure Time Physical Activity Questionnaire	1 (1.33)	
Guernsey community participation and leisure activities scale (GCPLAS)	1 (1.33)	
Health and Social Care Resource Use Questionnaire	1 (1.33)	
Health care usage and driving questionnaire (RTAs) Secondary	1 (1.33)	
Health Economics Questionnaire (Measure not named)	1 (1.33)	
Health Economics/Service Utilisation Questionnaire (measure not named)	1 (1.33)	
Health Resource Questionnaire	1 (1.33)	
Health Utilities Index (HUI)	1 (1.33)	
Health Utilities Index Mark 2/3 (HUI2/3 - Parent & child completion)	1 (1.33)	
Health-related Quality of Life for People with Dementia (DEMQOL)	1 (1.33)	
Hospital Anxiety and Depression Scale (HADS)	9 (12.00)	including 1 - carer completion

Hypoglycemia Fear Scale (HFS)	1 (1.33)	
Impact of Epilepsy Scale	1 (1.33)	
Improving Access to Psychological Therapies Employment Status Questionnaire (IAPT Employment Status)	1 (1.33)	
Infant or Children Dermatology Quality of Life (IDQOL or CDLQI)	1 (1.33)	
Intellectual Disabilities Scale (IDDS) - Proxy (carer) completion	1 (1.33)	
International Consultation on Incontinence Modular Questionnaire - Female Lower Urinary Tract Symptoms (ICIQ-FLUTS)	1 (1.33)	
International Consultation on Incontinence Modular Questionnaire - Urinary Incontinence Symptoms Quality of Life (ICIQ-UIQOL)	1 (1.33)	
International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SHORT FORM)	1 (1.33)	
International Consultation on Incontinence Modular Questionnaire - Vaginal Symptoms (ICI - Vaginal Symptoms Questionnaire)	1 (1.33)	
International Physical Activity Questionnaire (IPAQ)	2 (2.67)	
Interpretation of Voices Inventory (IVI)	1 (1.33)	
Kidney Disease Quality of Life Instrument (KDQOL)	1 (1.33)	
Likert scales of patients global impression of success (0-10)	1 (1.33)	
Local Pain Visual Analogue Scale (VAS)	1 (1.33)	
Manchester Short Assessment of Quality of Life (MANSA)	1 (1.33)	
Mastery/control over epilepsy (6 item epilepsy specific scale)	1 (1.33)	
Maternal Satisfaction Questionnaire (Not Identified)	1 (1.33)	
Measure of Capability Wellbeing for Adults (ICECAP A)	1 (1.33)	
Medical Symptom Checklist (MSCL)	1 (1.33)	
Medication Adherence (10 item sub scale from Epilepsy Self Management Scale (ESMS))	1 (1.33)	
Medication Adverse Effects (2 items from QOLIE31)	1 (1.33)	

Menorrhagia Multi Attribute Scale (MMAS)	1 (1.33)	
Mental Health Inventory (MHI-5)	1 (1.33)	
Minnesota Living with Heart Failure Score (MLWHF)	1 (1.33)	
Modified client service receipt inventory (CSRI)	1 (1.33)	
Modified Falls Efficacy Scale (MFES)	1 (1.33)	
Modified Index of Community Involvement (ICI)	1 (1.33)	
Modified Index of Domestic participation (IPDL)	1 (1.33)	
Morisky 4 item Self Report Measure of Medication Taking Behaviour (MMAS-4)	1 (1.33)	
Morisky Medication Adherence Scale	2 (2.67)	
Motivation to Quit Questionnaire	1 (1.33)	
Multidimensional Scale of Perceived Social Support (MSPSS)	1 (1.33)	
Moods and Feelings Questionnaire (MFQ)	1 (1.33)	
Neurological Disorders Inventory for Epilepsy (NDDI-E)	1 (1.33)	
Nijmegen Hyperventilation Questionnaire	1 (1.33)	
Nottingham Extended Activities of Daily Living (NEADL)	2 (2.67)	
Numerical Rating Scale (NRS) for breathlessness	1 (1.33)	
Older People's Quality of Life Questionnaire (OPQOL)	1 (1.33)	
Olerud and Molander Ankle Score (OMAS)	2 (2.67)	
Brief Illness Perception Questionnaire (B-IPQ)	1 (1.33)	
Pain Diary	1 (1.33)	
Oxford Handicap Score (OHS)	1 (1.33)	
Oxford Hip / Knee Score	1 (1.33)	

Oxford Shoulder Score (OSS)	1 (1.33)	
Pain Visual Analogue Scale (VAS)	1 (1.33)	
Parenting Styles and Dimensions Questionnaire (PSDQ)	1 (1.33)	
Pathway Questionnaire not named (Patient Progression through Mental Health Service)	1 (1.33)	
Patient 4 week diary (falls, exercise, service use)	1 (1.33)	
Patient Costs Questionnaire Secondary	1 (1.33)	
Patient Diary (Meds Adherence, Illness Severity and Symptoms)	1 (1.33)	
Patient Diary/Calendar of Resource Use	1 (1.33)	
Patient Experience of Care - Modified version of the National GP Patient Survey (NGPPS)	1 (1.33)	
Patient Health Questionnaire 9 (PHQ-9)	6 (8.00)	1 added = listed as other PROMS PHQ9
Patient Health Questionnaire 9 (PHQ-15)	1 (1.33)	
Patient Satisfaction (Measure not named)	1 (1.33)	
Perceived Criticism Scale (PCS)	1 (1.33)	
Phone_FITT Questionnaire	1 (1.33)	
Physical Activity Scale for the Elderly (PASE) Primary	1 (1.33)	
Preference Questionnaire	1 (1.33)	
Psychosis Attachment Measure (PAM-SR)	1 (1.33)	
Pain Diary	1 (1.33)	
Participant log of UTI Symptoms	1 (1.33)	
Patient Diary for Health Utilisation	1 (1.33)	
Patient Global Impression of Improvement in their Urinary Infection (PGI-I)	1 (1.33)	
Patient Orientated Eczema Measure (POEM)	1 (1.33)	

Patient Rated Wrist Evaluation Questionnaire	1 (1.33)	
Patient Reported Symptom Recurrence	1 (1.33)	
Patient Satisfaction Measure - study tailored questionnaire	1 (1.33)	
Paediatric Quality of Life Inventory (PEDSQL)	5 (6.67)	includes 1 parent completion and 1 parent & child completion
Pelvic Floor Muscle Exercise Self Efficacy Scale (PFME)	1 (1.33)	
Pelvic Organ Prolapse Symptom Scale (POP-SS)	1 (1.33)	
Pressure Ulcer Quality of Life – Utility Index (PUQOL-UI)	1 (1.33)	
Pressure Ulcer Quality of Life (PU-QOL)	1 (1.33)	
Quality of Life - Alzheimer's Disease Scale (QOL-AD)	1 (1.33)	
Quality of Life in Epilepsy Inventory (QOLIE 31)	1 (1.33)	
Quality of Life in Epilepsy Inventory (QOLIE 31)	1 (1.33)	
Quality of the Carer Patient Relationship (QCPR) completed by patient and carer	1 (1.33)	
Quit Attempts and changes in Motivation and Intention to Quit	1 (1.33)	
Relationship Scales Questionnaire (RSQ)	1 (1.33)	
Resilience Scale (RS-14)	1 (1.33)	
Resource Use questionnaire	2 (2.67)	
Response to Depression Questionnaire	1 (1.33)	
Scottish Physical Activity Questionnaire (SPAQ)	1 (1.33)	
Self Complete Behavioural Recovery Questionnaire	1 (1.33)	
Self Efficacy in Diabetes Scale (SED)	1 (1.33)	
Self Report Breathlessness Visual Analogue Scale (VAS)	1 (1.33)	
Self Report Confidence for Quitting	1 (1.33)	

Self Report Daily Urges to Smoke	1 (1.33)	
Self Report desire to smoke before and after intervention	1 (1.33)	
Self Report of Physical Activity Levels	1 (1.33)	
Self Report of Smoking Abstinence	1 (1.33)	
Self Report Self Confidence for Physical Activity	1 (1.33)	
Self Report Thoracic Pain Visual Analogue Scale (VAS)	1 (1.33)	
Self Report Use of Community Facilities for Physical Activity	1 (1.33)	
Self Report Weekly Urges to Smoke	1 (1.33)	
Self Reported Abstinence	1 (1.33)	
Self Reported Attendance	1 (1.33)	
Self Reported Costs Incurred Patient and Carer completion	1 (1.33)	
Self Reported Daily Cigarette Consumption	1 (1.33)	
Self Reported Falls Calendar	1 (1.33)	
Self Reported Further Falls	1 (1.33)	
Self Reported Health and Social Care Contacts	1 (1.33)	
Self-Compassion Scale (SCS)	1 (1.33)	
Service Use Questionnaire	1 (1.33)	
Severity of Alcohol Dependence Questionnaire (SADQ)	1 (1.33)	
Sexual Activity Questionnaire (SAQ)	1 (1.33)	
SF-12 Secondary	12 (16.00)	includes 1 SF-12 (v2) Secondary and 1 SF-12 (v2+4) Secondary
SF-36 Secondary	13 (17.33)	includes 1 = SF-36 (v2) Secondary
Short Falls Efficacy Scale (FES)	1 (1.33)	

Shoulder Pain and Disability Index (SPADI)	1 (1.33)	
Side Effect Scale (Not Named)	1 (1.33)	
Social Functioning Questionnaire (SFQ)	1 (1.33)	
Social Participation Questionnaire (SPQ)	1 (1.33)	
State Trait Anxiety Inventory (STAI)	1 (1.33)	
Stigma Scale of Epilepsy (SSE)	1 (1.33)	
Stool Chart	1 (1.33)	
Strengths and Difficulties Questionnaire (SDQ) - Parent and child versions	1 (1.33)	
Study Specific Questionnaire - NHS resource use	1 (1.33)	
Study Specific Questionnaire - evaluation of compliance	1 (1.33)	
Study Specific Questionnaire - positives/negatives about the device	1 (1.33)	
Symptom Diary - completed by parents	1 (1.33)	
Symptom Severity Score (SSS)	1 (1.33)	
The De Jong-Gierveld Loneliness Scale Primary	1 (1.33)	
The Guernsey Community and Leisure Participation Assessment (GPLA)	1 (1.33)	
The Internalised Stigma of Mental Illness Scale (ISMIS)	1 (1.33)	
The Lubben Social Network Scale (LSNS)	2 (2.67)	
Townsend Disability Scale (TDS)	1 (1.33)	
Treatment Satisfaction Questionnaire	1 (1.33)	
Trial Specific Seizure Diary	1 (1.33)	
Ulcer Related Pain Scale	1 (1.33)	
Urinary Tract Infection Questionnaire (UTI)	1 (1.33)	

Urinary Incontinence Questionnaire (ICI)	1 (1.33)	
Use of Medical Services	1 (1.33)	
Vaizey Incontinence Score	1 (1.33)	
Venous Insufficiency Epidemiological and Economic Study (VEINES-QOL)	1 (1.33)	
Warwick Edinburgh Mental Well-Being Scale (WEMWBS)	1 (1.33)	
Weekly Adverse Event Diary	1 (1.33)	
Weekly Symptom Diary	1 (1.33)	
WHOOLEY QUESTIONS	1 (1.33)	
WHOQOL-BREF	2 (2.67)	
WHOQOL-OLD	1 (1.33)	
Work Stress Assessment Questionnaire (WSA)	1 (1.33)	
Working Alliance Inventory (WAI)	1 (1.33)	
Yale Brown Obsessive Compulsive Scale (YBOCs self rated)	1 (1.33)	
Zung Self Rating Depression Scale (ZDS)	1 (1.33)	

Appendix 12

Chapter 8 – Full (first) multiple linear regression model

EFFECT	CLINICAL AREA	ESTIMATE	P-VALUE	95% CI - LOWER	95% CI - UPPER
INTERCEPT		10.459	<0.001	5.281	15.636
SPIRIT SCORE		0.081	0.167	-0.035	0.198
PRO NOT PRIMARY OUTCOME		-4.993	<0.001	-6.358	3.628
NOT PRIMARY CARE		-1.447	0.052	-2.908	0.014
YEAR 2012		1.253	0.091	-0.212	2.718
CLINICAL AREA	AIDS	-0.205	0.946	-6.240	5.829
CLINICAL AREA	CARDIAC	1.464	0.522	-3.105	6.032
CLINICAL AREA	COLORECTAL	1.729	0.586	-4.618	8.075
CLINICAL AREA	DERMATOLOGY	-0.360	0.908	-6.601	5.882
CLINICAL AREA	DIABETES	7.212	0.022	1.098	13.324
CLINICAL AREA	ELDERLY CARE	6.292	0.044	0.187	12.396
CLINICAL AREA	EMERGENCY SERVICES	-0.593	0.839	-6.417	5.232
CLINICAL AREA	FALLS PREVENTION	4.864	0.052	-0.041	9.770
CLINICAL AREA	GASTROENTEROLOGY	-1.846	0.463	-6.861	3.169
CLINICAL AREA	GENERAL PRACTICE WAITING TIMES	6.163	0.038	0.363	11.963
CLINICAL AREA	HEPATOLOGY	-0.879	0.769	-6.867	5.108
CLINICAL AREA	MENTAL HEALTH	0.713	0.701	-3.006	4.432
CLINICAL AREA	NEPHROLOGY	1.438	0.637	-4.643	7.519
CLINICAL AREA	NEUROLOGY	1.107	0.584	-2.932	5.146
CLINICAL AREA	OBSTETRICS AND GYNAECOLOGY	1.712	0.457	-2.874	6.298

CLINICAL AREA	ONCOLOGY	1.814	0.425	-2.720	6.348
CLINICAL AREA	ORTHOPAEDICS	2.231	0.321	-2.243	6.705
CLINICAL AREA	PAEDIATRICS	2.053	0.313	-1.993	6.099
CLINICAL AREA	PHYSICAL ACTIVITY	-0.150	0.946	-4.580	4.279
CLINICAL AREA	RESPIRATORY	2.226	0.315	-2.180	6.632
CLINICAL AREA	SMOKING CESSATION	-0.898	0.687	-5.358	3.562
CLINICAL AREA	UROLOGY	2.445	0.430	-3.728	8.619
CLINICAL AREA	VASCULAR	0.820	0.689	-3.270	4.909
CLINICAL AREA	WEIGHT LOSS	0*			
COMBINED CLINICAL AREA			0.158		
SCALE		5.532	1.1411		

Abbreviations: PRO, Patient-reported outcome. *Comparator