DEVELOPING A CORE OUTCOME SET FOR TWIN PREGNANCY

By

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Abstract

Introduction

Twin pregnancy is a pregnancy with two fetusus. One in 42 babies are born a twin (1). There are multiple pathophysiological processes that cause twin pregnancy which results in different twin pregnancy types, each attributing an associated risk (2–4). Consequently, mothers and twins are at a significant increased risk of morbidity and mortality (5–7) which has resulted large body of research aiming to improve outcomes for them (8).

In order to provide strong evidence to support the clinical guidance of these patients, research is often combined in the form of meta-analysis. However, this can be hindered by the heterogeneity within outcome reporting in clinical trials. A solution to this, is the use of Core Outcome Set's (COS). A COS is '*an agreed standardised collection of outcomes which should be measured and reported as a minimum, in all trials for a specific clinical area'* (9) and are based on what key stakeholders (patients and medical experts) believe are essential for research. A COS for twin pregnancy will therefore standardise outcome reporting in twin pregnancy which will enable data synthesis, ensure future research remains relevant to patients and improve outcomes for mothers and twins.

COS development is broken down into the three distinct stages as defined by The COMET Initiative (9). Stage one is outcome identification, stage two is outcome consensus and stage three is COS finalisation. The aim of this research is to create the initial COS as set out in stages one and two of COS development which will lay the foundation for the final COS for twin pregnancy.

Methods

Stage one: outcome identification

Systematic review

A systematic review was completed according to recommended methods and reported according to Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) (10). All Randomised Control Trials (RCT) and their follow up studies reporting prediction, prognosis, intervention or management outcomes in twin pregnancy were included. The study characteristics, outcomes definitions and measurement tools were extracted and descriptively analysed.

Qualitative interviews

Qualitative interviews and Reflective Thematic Analysis (RTA) were undertaken in accordance with Braun (11), and the six steps for RTA (12) were followed using NVIVO Software ®. A deductive codebook informed by the systematic review was created and 'new' outcomes were formed inductively and iteratively by two independent researchers.

Stage two

Delphi Survey

Outcomes identified from the systematic review and Qualitative interviews were combined to form a comprehensive outcome inventory. Three stakeholder panels (Obstetricians and Midwives, Neonatologists and Neonatal Nurses and parents

with a lived experience of twin pregnancy) completed a two round online Modified Delphi Survey using the DelphiManager software® from The University of Liverpool.

Results

Systematic review

57 RCT's and their follow up studies were identified for inclusion. 1257 verbatim outcome were reported which were categorised into 170 unique outcomes. Massive heterogeneity was seen within outcome reporting across all RCT's, as most trials did not report the same outcomes and those that did often did not use the same outcome definitions or measures meaning data synthesis would be limited. Furthermore, long-term outcomes were underrepresented in RCT's.

Qualitative interview

20 participants were interviewed and generated 57 important outcomes, of which 16 were potentially new outcomes. There were similarities between researcher and patients shot-term physiological outcome priorities, however, there remains a degree of difference as half of RCT's did not report the most important theme of 'death'. Likewise, most 'new' outcomes inductively created were long-term outcomes which shows that researchers have not addressed these previously.

Delphi Survey

72 outcomes formed the comprehensive outcome inventory and were considered for consensus by 176 twin pregnancy experts. 20 outcomes met the pre-defined ‘consensus in’ criteria and will therefore be taken through to the third stage of COS development. A further 7 outcomes met the pre-defined ‘dissensus’ and will be discussed as optional.

Conclusion

This research highlights the diverse and complex nature of twin pregnancy research which is related to the need to address maternal, single and double fetal outcomes as well as different types of chorionicity. There is a clear lack of standardisation in outcome selection, definition and reporting which currently hinders evidence synthesis and limits the effectiveness of research. The COS for twin pregnancy will standardise outcome reporting and enable data synthesis in future twin pregnancy research which in turn will reduce adverse outcomes for mothers and twins.

Future research

The initial COS for twin pregnancy created within this body of work will be taken forward and finalised during a consensus meeting with international twin pregnancy experts.

Dedication

I would like to dedicate this thesis to my two supervisors Professor Katie Morris and Dr Victoria Hodgetts-Morton. Thank you for continuing to support me to complete this Masters and for believing in me in times when I didn’t believe in myself.

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List of Abbreviations

ACOG American Congress of Obstetricians and Gynaecologists

AR assisted reproduction

BAPM Gynaecologists and British Association of Perinatal Medicine

BMFMS British Maternal and Fetal Medicine Society

CS caesarean section

COMET Core Outcome Measures in Effectiveness Trials Initiative

COS core outcome set.

DCDA Dichorionic diamniotic

DZ dizygotic

FGR fetal growth restriction

FOGSI Federation of Obstetric and Gynaecological Societies of India

GRADE Grading of Recommendations Assessment, Development and Evaluation

HCP health care professional

HEFA Human Fertilisation and Embryology Authority

ISTS International Society of Twin Studies

IVF In-Vitro Fertilisation

MBBRACE Mothers and Babies Reducing Risk through Audit and Confidential enquiries across the UK.

MC monochorionic

MCDA monochorionic diamniotic

MCMA monochorionic monoamniotic

MZ monozygotic

NHS National Health Service

NIHR National institute for Health and Social Care Research

NNU Neonatal unit

OMERACT Outcome Measures in Rheumatology

PE pre-eclampsia

PPH post-partum haemorrhage

PPI Patient and Public Involvement

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO International prospective register of systematic reviews

PTB preterm birth

RCOG Royal College of Obstetricians and Gynaecologists

RCT randomised controlled trial.

RoB2 A revised Cochrane risk-of-bias tool for randomized trials

RTA Reflective thematic analysis

sFGR selective fetal growth restriction

TAPS twin anaemia-polycythaemia sequence.

TRAPS twin reversed arterial perfusion sequence.

TTTS twin to twin transfusion syndrome

UK United Kingdom

USA United States of America

WHO World Health Organisation

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Chapter 1:

Introduction

Twin pregnancy is a pregnancy with two fetusus and can occur due to polyovulation i.e. two ova are released (dizygotic twinning) and fertilised rather than one, or when one fertilised ovum divides in two (monozygotic twinning) (5). The differing pathophysiological processes result in different twin pregnancy types, each carrying an associated risk. All twin pregnancy types are at a greater risk of pregnancy complications compared to those with a singleton pregnancy (5–7) and certain twin pregnancy types have additional risks specific to them (2–4,13). Consequently, both mothers and twins are at a significantly increased risk of morbidity and mortality compared to a singleton pregnancy (5–7). It is thought that one in 42 babies in the world is born a twin (1). Twin pregnancy rates have increased dramatically over the last 40 years due to the increase in older mothers having children and the use of fertility treatment, both of which increase the chance of twin pregnancy (14). In Africa alone, where 80% of the worlds twin population are born, it is thought that two to three hundred thousand twins have died within their first year of life (1). Furthermore, the increased risk of long-term morbidity associated with twins (15) can not only be life-changing but has a potential significant economic impact on healthcare providers (16). Consequently, in a bid to try and reduce risk to mothers and twins, several countries released legal legislation limiting the number of embryos transferred during fertility treatment (17) which has subsequently caused their twins pregnancy rates to steady (18) Nevertheless, the risks to those experiencing twin pregnancy remains high and a vast amount of research has been undertaken aiming to improve outcomes for mothers and twins (8). However, to provide strong evidence and change clinical practice, data is often combined in the form of a

meta-analysis. Heterogeneity within the clinical trials within a meta-analysis, and in particular the outcome reporting can make this challenging. The standardisation of outcome selection, collection and reporting would help to combat this (9).

A Core Outcome Set (COS) is an agreed set of outcomes that should be defined, collected, and reported in a standardised manner, as a minimum, in all clinical trials within a given condition (9). Utilising a COS within research reduces the heterogeneity within outcome reporting by minimising inconsistencies (9). It enables data from different trials to be combined, facilitates accurate data synthesis, reduces reporting bias, and ensures all trials report useable data. This in turn reduces research waste and enhances the value of the findings within research.

Furthermore, key stakeholder involvement is embedded throughout COS development methodology which ensures that the COS remains patient-centred and clinically relevant. This facilitates clinical practice to be based on the best research evidence and this has been shown to result in improved outcomes for patients (9). For this reason, the National Institute for Health and Social Care Research (NIHR) in the United Kingdom (UK) and The Cochrane Collaboration advocate their use, as have many other research funders and policy makers. Thus, over the last decade, the popularity of COS development has greatly increased and to date there are 63 Core Outcome Set's within the field of Obstetrics, the majority of which have been designed for singleton pregnancies e.g. preterm birth (PTB), pre-eclampsia (PE) with only two developed for specific conditions in twins (19). There are outcomes that are specific for multiple

pregnancy, due to the inherent increased morbidity and mortality, as well as outcomes due to specific pathologies that can occur in twins e.g. those related to monochorionicity such as Twin-to-twin Transfusion Syndrome (TTTS) and Selective Fetal Growth Restriction (sFGR). Therefore, due to the complexities of twin pregnancy and the associated risk to both mother and twins it is paramount a COS specific for twin pregnancy is created for the use in future twin pregnancy research and ultimately to improve outcomes for mothers and their babies.

1.1 Background

1.1.1 Prevalence

The prevalence of twin pregnancy varies between 0.9% - 3.1% and significantly differs between countries and/ or continents (1,20–22). For instance, Central Africa has the highest twin pregnancy rates with 18 per 1000 births, whereas the rate in East Asia is only 6-9 per 1000 births. The variation observed is due to dizygotic (DZ) twinning, as monozygotic (MZ) twinning rate has stayed constant between 3.5-4 per 1000 births globally (1) DZ twinning on the other hand, has seen noticeable variations across different populations with Japan reporting a twin birth rate of 1.3 per 1000 births compared to Nigeria reporting one of the highest at 50 per 1000 births (1,23). This is thought to be associated with their genetics, and reflective of their racial and ethical differences (23). In addition to this, there has been a substantial increase in DZ twinning rates over time especially in Europe, North America, and Asia likely due to a shift towards older mothers and the use of assisted reproduction (AR) (14) but there are still large variations within these countries as well. For instance, in 2021 the United States of America (USA) had a twin birth rate of 31.2 per 1000 births whereas the UK had a rate of 13.7 per 100

births (21,22). This may be due to the differences in AR legal legislation. Historically, the incidence of twin pregnancy in England and Wales had continually risen (22). However, in 2006 the Human Fertilisation and Embryology Authority (HEFA) published a set of policies aiming to reduce the incidence of twin and higher order multiple births due to AR. One of the policies within the Code of Practice recommends single embryo transfer in women under the age of 35 (17). The legislation resulted in a reduction of multiple embryo transfers from 87% of In-Vitro Fertilisation (IVF) cycles in 1991 to 25% in 2019 (18). Consequently, there was a 21% decrease in the number of multiple pregnancies due to AR between 2007 and 2019 in women under the age of 35 (18) and so the rates of twin pregnancy in England and Wales have continued to decline (21).

1.1.2 Twin development

The aetiology of twin pregnancy is not simple as there are several pathophysiological processes that result in different types of twin pregnancy, each attributing to their own fetal growth pathology and risks. Twin pregnancies can either be DZ or MZ.

1.1.2.1 Dizygotic Twinning

DZ twins account for over two-thirds of all twin pregnancies (23) and are commonly known as ‘nonidentical’ because their genetic relationship is the same as ordinary siblings, whereby approximately 50% of their genes are shared and because of this they can be different sexes (Male / Female) (24). DZ twinning occurs due to polyovulation during a single menstrual cycle i.e. two ova (eggs) are fertilised by two sperm. The mechanism leading to DZ twinning transpires when

multiple follicles within the ovary/ovaries mature at one time and two ova are released instead of one (5). In 50% of cases one ovum is released from the right ovary and one is released from the left ovary (5). Similarly, AR, specifically when two embryos are transferred into the uterus during one cycle, is also a cause of DZ twinning (5).

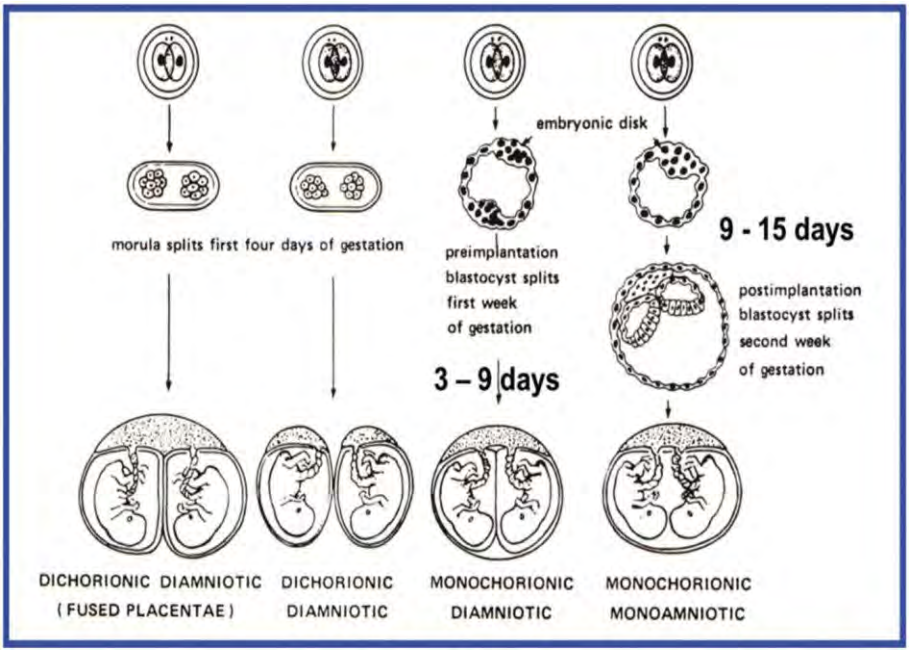
After fertilisation, each zygote implants into the uterus at approximately 6-7 days and develops as would a singleton pregnancy. Thereafter, each embryo will develop their own placenta and placental circulation, chorion, and amnion (gestational sac) thus their twin type is known as dichorionic diamniotic (DCDA) (5). However, not all DCDA twins are DZ, approximately 15% can develop from MZ twinning (5).

1.1.2.2 Monozygotic Twinning

MZ twinning occurs when a single ovum is fertilised by a single sperm to form one zygote, this subsequently divides into two individual zygotes and develops into 'identical' twins (5). There is a misconception that identical twins share 100% of their genes but there are minor genotypic and phenotypic differences that materialise after the zygote divides (5). That said, MZ twins carry a remarkably greater genetic concordance compared DZ twins or any other relative and will therefore always be the same sex as one another (5) There are three different types of MZ twinning; the pathophysiology for these is the timing of the division. If division happens within three days of fertilisation, the MZ will develop dichorionic placentation and so, like DZ twinning, each embryo will have their own placental circulation, chorion and amnion and therefore be classified as DCDA (25). Division

between 3-9 days produces monochorionic (MC) placentation whereby one placenta is shared between both twins; this means they will also share the same placental circulation. However, their amnionicity will be separate as they will have two separate gestational sacs, this twin type is classified as Monochorionic Diamniotic (MCDA) (25). If division occurs between 9-12 days the twins will share the same placenta, placenta circulation, chorion, and amnion. This type of twinning is classified as Monochorionic Monoamniotic (MCMA) and is the rarest form of twin pregnancy representing less than 1% of twin pregnancies (25). In summary, the later the zygote divides after fertilisation the less independent they are from one another and consequently the risks to the pregnancy and fetusus increase.

Figure 1: Monozygotic twins: relationship between chorionicity and amnionicity. Reproduced with permission from Ward RH, Whittle MJ (eds), Multiple Pregnancy. London: RCOG Press, 1995. (23)



1.1.3 Twin pregnancy risks

Women with a twin pregnancy and the twin fetuses, are at an increased risk of many of the complications of pregnancy e.g. PTB and PE. Furthermore, these complications are often more severe than those in a singleton pregnancy (3,5–7,13,26,27). In addition, MC pregnancies, which make up 30% of the UK twin pregnancy population, are at further risk of complications specific to monochorionicity (5–7).

1.1.3.1 Fetal risks

1.1.3.1.1 Congenital abnormalities

The prevalence of congenital abnormalities is 27% higher in twins compared to singletons (8). This has slowly increased over the years from 5.9 per 10,000 births in 1984 to 10.7 per 10,000 in 2007 (28) and is thought to be due to the increased use of AR with recent data suggesting an increased risk of heart defects in pregnancies conceived by AR (7). The chromosomal abnormality risk rate of a DZ twin is the same as a singleton however is it 2-3 times higher in MZ twins likely due to the abnormal cleavage and midline structural defects (7). Furthermore, MZ twins will generally be concordant for chromosomal or genetic defects (5) whereas DZ twins are much more likely to be discordant (3,29).

1.1.3.1.2 Fetal Growth Restriction (FGR) and Selective Growth Restriction (sFGR)

Around 25% of twin pregnancies will be affected by FGR which is much greater than singletons (8%) (30). Initially, the twins' growth will be similar to a singleton until 32 weeks gestation when it tends to slow down which can result in FGR or growth discordance between twins, all of which are associated with greater

perinatal adverse outcomes (30). There are several factors thought to be linked to this including, unequal placental perfusion to each twin, congenital infection, genetic differences between twins or differences in umbilical cord insertion into the placenta (4,31,32). In addition to this, maternal factor such as AR, hypertension, and increased maternal age could also be relevant (14). MC pregnancies are at further risk of sFGR, this is when unequal placental sharing effects one twin and results in a growth discordance of at least 25% between twins (33). It is thought to occur in 10-46% of MC pregnancies (34). 15% of those affected by sFGR will suffer a sudden fetal demise without signs of fetal deterioration of the smaller twin, which confers a 50% risk of demise of the larger 'surviving' twin (35).

1.1.3.1.3 Twin entrapment

Twin entrapment is unique to twins and is a rare but life-threatening emergency. It occurs when the presenting twin is breech, and the second twin is cephalic. This leads to their heads becoming interlocked at birth and results in the babies becoming trapped. It is more common in MA twins and is thought to occur in 1 in 1000 births with a strong association with hypoxia and fetal death (36).

1.1.3.1.4 Twin Reversed Arterial Perfusion Sequence (TRAPS)

TRAPS is unique to MC twins; the reported incidence is 1:100 (37) and develops due to an abnormal cardiac structure in one twin so their heart does not pump. This results in the acardiac twin becoming haemodynamically dependant on the other twin (pump twin) which is structurally normal. This in turn causes cardiac failure in the 'normal' twin, as well as the potential for long term neurological impairment due to chronic hypoxia. TRAPS also carries a high risk of PTB (37).

1.1.3.1.5 Twin-to-Twin Transfusion Syndrome (TTTS)

TTTS is unique to MC twins and occurs in 10%-15% of MC pregnancies (38). It is associated with a very high risk of perinatal morbidity and mortality accounting for 20% of all stillbirths in twin pregnancies (39). If not recognised and treated appropriately 90% -100% of twin fetuses will die (40). TTTS is a consequence of unequal distribution of the placental circulation. This causes one twin (recipient) to have a high blood volume and one twin (donor) to have a reduced blood volume. The mortality rates are primarily associated with the extreme prematurity and very low birthweight (41).

1.1.3.1.6 Twin Anaemia-Polycythaemia Sequence (TAPS)

TAPS is unique to MC twins and complicates 5% of MC pregnancies (42). It can occur spontaneously or due to laser ablation for TTTS. It is like TTTS, in that there is unequal sharing of the placental circulation, however one twin (recipient) will have a high red blood cell count and one twin (donor) will have a low red blood cell count. This causes severe anaemia in the donor twin leading to hydrops and severe polycythaemia in the recipient twin leading to cardiac failure (42).

1.1.3.1.7 Complications unique to Monoanmionicity

Monoamnionicity adds further complexities to an MC pregnancy as not only do they share the same placental circulation, but they also share the same gestational sac. This can lead to close umbilical cord insertions and result in cord entanglement causing fetal hypoxia (13). MA twins are also at a much greater risk of congenital malformation and discordant anomalies, affecting 15-35%, due to the

late embryonic cleavage and imbalances in placental circulation. This ultimately means MCMA twins have the highest risk of PTB, morbidity and mortality (13).

1.1.3.1.8 Fetal morbidity and mortality

The prevalence of mortality of in one or more of twins during the first trimester, known as early pregnancy loss, is considerably higher in twins, affecting 15% - 35% compared to 5.4% of singleton pregnancies (6,7). Due to the increased complications associated with MC twins they have an even greater risk of early pregnancy loss compared to DC twins (43). In addition to this, MA twins are twice as likely to suffer a single twin demise twins (44,45) which is heightened between 16 -22 weeks gestation due to the corresponding incidence peak of Twin-to-Twin Transfusion Syndrome (TTTS) (43). A UK based study in 2020 demonstrated that 47% of women who suffered a single twin fetal demise were diagnosed with TTTS (45). Furthermore, there is also an increased likelihood of stillbirth and neonatal mortality in MC twins compared to DC twins even in the absence of conditions specific to MC twins (43,46). Nevertheless, the risk of stillbirth and neonatal mortality in all twin pregnancies remains significantly higher than a singleton pregnancy (46).

1.1.3.1.9 Pre-term birth

The most significant risk in twin pregnancy and the leading cause of mortality and morbidity in twins is PTB (birth <37weeks gestation) (47). This was highlighted in the 2020 Mothers and Babies Reducing Risk through Audit and Confidential enquiries across the UK (MBBRACE) report where they found that PTB was the

number one cause of perinatal loss in twins in the UK (8). The aetiology of PTB in twin pregnancy is different to that in a singleton pregnancy as it is much more multifactorial due to the greater risk of complications (26). Thus, the prevalence of PTB in twin pregnancy (60.3%) is much greater than a singleton pregnancy (8.2%) and their gestational age at birth is more likely to be earlier (22).

Monochorionicity has been found to be to one of the most significant risk factors for PTB, even in the absence of TTTS, and so MC twins are much more likely to encounter extreme PTB (birth <28 weeks) compared to DC twins (48). A prospective study of 1000 twin pregnancies found that 29% of DC twins were born before 36 weeks whereas 34% of MC twins were born before 34 weeks (27). Not only does PTB have a major psychological impact on the family (49), but it also has a substantial economic impact to health care providers (16). Furthermore, although survival rates of PTB have improved as technology has advanced (50), the risk of both short-term and long-term morbidities remain (51) and decreased gestational age at birth is a strong predictor of severe morbidity (15).

For instance, the incidence of PTB associated asphyxia and cerebral palsy, a complication that can result in disorders that require life-long medical support, is increased three-fold in twin pregnancy compared to a singleton pregnancy (52). Thus, the economic impact is significant; a UK population-based study in 2023 found that those born extremely premature had a hospital admission cost of £80,559 within the first 8 years of life compared to those born at full term, costing £1894 and much of this cost was during the first year of life, £71,866 Vs £848 (16).

1.1.3.2 Maternal risks

1.1.3.2.1 Maternal morbidity and mortality

Women with a twin pregnancy are at a higher risk of both minor complications such as poor sleep, abdominal pain, and constipation, as well as major complications compared to a singleton pregnancy (53,54). They are not only at a greater risk of severe morbidity, 6.2% Vs 1.3% (55), but are also 2.5 times more likely to die in the UK compared to a singleton pregnancy (56). Furthermore, The World Health Organisation (WHO) reported a four-fold increased risk of mortality worldwide compared to a singleton pregnancy (53). The reason for this is multifactorial with no single contributor but is thought to be related to the higher incidence of PE, placental abruption, caesarean section (CS) and postpartum haemorrhage (PPH) that is associated with twin pregnancy (57).

1.1.3.2.2 Maternal complications associated with twin pregnancy.

The incidence of PE/ gestational hypertension is 2-5 times higher than a singleton pregnancy and complicates 10-20% of all twin pregnancies (58,59), however, this may be greatly underestimated. This is because hypertensive disorders often go undiagnosed as symptoms may only present themselves towards the later stages of pregnancy by which time, due to the increased risk of PTB, the birth has already occurred. PE is a condition that causes a sudden rise in blood pressure which if left untreated increases the risk of placental abruption and can also result in multiorgan failure and death. Women with a twin pregnancy have a greater risk of this because the onset is sooner, the progression is quicker, and severity is more severe than those with a singleton pregnancy (60,61).

Another major cause of placental abruption in twin pregnancy is the over distention of the uterus followed by rapid decompression after the birth of the first twin (57) this consequently leads to major haemorrhage, and adverse maternal and neonatal outcomes (60,61). Furthermore, due to the larger surface area of the placental site, uterine over distention and a higher CS rate, which is thought to be 75% worldwide (62) vs 23.8% with a singleton pregnancy (63), women are at an increased risk of placenta praevia (64) and PPH. Average blood loss is >500 ml more than those with a singleton pregnancy (57,65). This is further compounded by the increased risk of anaemia (67.3% vs 38.7%) compared to a singleton pregnancy which is due to plasma volume expansion and oxygen requirements that are 30% greater than those with a singleton pregnancy (66).

1.2 Core Outcome Set

Due to the complexities of twin pregnancies and the immense risk to both the mother and twins, there is a vast amount of research focused on reducing mortality and morbidity rates (8). The primary aim of clinical trials in medicine is to guide clinical practice and ultimately improve outcomes for patients and their families. This in turn will often have an added economic benefit as well, for instance preventing the birth of one baby born extremely prematurely in the UK could save the National Health Service (NHS) £78,665 (16).

Clinical trials show effect by evaluating interventions and demonstrating their beneficial or detrimental effect; these are known as outcomes. To provide stronger evidence for a change in clinical practice, data from research is often combined in

the form of a meta-analyses. This is because, meta-analyses increase the sample size and generalisability of the findings by minimising bias, as well as improving the statistical power of the results and thus the precision of measurements of treatment effect (67).

However, ‘Clinical trials are only as credible as their outcomes’ (68). It has been reported that 85% of all clinical research is wasted (69) and therefore does not lead to any patient benefit, wastes large quantities of research funding and enormous amounts of patients/ healthcare professionals (HCP)/ researchers’ time. One of the causes of research waste is poor outcome selection (9).

Heterogeneity within outcome reporting is a leading cause of research waste as it hampers the ability to compare data by meta-analysis (70). This is because researchers investigating a similar question may choose to report different outcomes, or if reporting the same outcome, they may define the outcome differently or use different methods and/or measures to collect the data making data synthesis difficult and prohibits any meaningful comparisons within it. For instance, trials in twin sFGR reported 93 different outcomes within 39 trials and for each outcome there were multiple different measures used to collect the data (71).

Likewise, ‘selective outcome reporting’ is also a problem within research. Often researchers will select what outcomes to report depending on their results which consequently introduces bias (72). So much so, that often once selective reporting has been minimised during Cochrane reviews, evidence that previously appeared

to report an intervention as being of benefit, indicates the intervention being of no benefit (73). In addition to this, the outcomes selected to be reported frequently lack stakeholder engagement, such as patients, yet for outcomes to be meaningful they need to be important to all stakeholders including people with a lived experience of the condition, HCPs and researchers.

Nevertheless, outcomes are frequently chosen to meet the needs of the researchers and there is rarely any patient involvement when selecting them (74). Therefore, even if clinical trials are reporting an intervention as being beneficial it may not actually be beneficial to the patient, their families, or HCPs and will not actually improve outcomes. This was highlighted when patients identified the outcome of 'fatigue' as being important in rheumatoid arthritis clinical trials which previously had not been considered (74).

A solution to problems within outcome reporting and research waste is the development of a COS. A COS is '*an agreed standardised collection of outcomes which should be measured and reported as a minimum, in all trials for a specific clinical area'* (9) and are based on what key stakeholders (people with a lived experience of the condition, HCPs, researchers) believe are essential for clinical decision making within the management of a specific condition (9). Furthermore, the COS will also standardise how each outcome is defined and measured which means each trial within a given condition will be defining, collecting, measuring, and reporting the same outcomes in the same way. This does not imply that researchers should not be innovative and collect 'new' outcomes, but the COS

should be collected in conjunction with any additional outcomes they wish to collect.

The gold standard for COS development has been outlined by the Core Outcome Measures in Effectiveness Trials Initiative (COMET) which was launched in 2010 (9). The development and use of COS across all clinical specialities is widespread. To date there are over 63 COS for conditions within pregnancy and childbirth alone; two of which are based on twin pregnancy, specifically TTTS and sFGR (19). However, these conditions relate only to MC pregnancies which accounts for 30% of the twin pregnancy population (2) Therefore there is an urgent need for a COS that can be utilised in all twin pregnancy research due to the complexities and risks these pregnancies carry.

Furthermore, twin pregnancy research also has an added statistical complication not seen in other research. This is the reporting of different common denominators. For instance, some researchers may choose to report the number of mothers affected by an outcome and some researchers may choose to report the number of babies affected by an outcome, which potentially will double the results and bring in the issue of clustering of events. Thus, even if clinical trials define, collect, and measure the same outcome in the same way, data cannot be synthesised unless they have reported the same common denominator. A COS in twin pregnancy should also standardise how each outcome is reported and eliminate this statistical complication that is specific to twin pregnancy research.

The COMET initiative recommends that the COS is created in three stages (9). Stage one is outcome identification and can be completed in two distinctive parts. Firstly, outcomes important to researchers and HCPs are collected via a systematic review of all published clinical trials within a specific condition. Secondly, to extract outcomes important to patients, qualitative interviews are conducted with people with a lived experience of the condition. The outcomes collected from both the systematic review and interviews are combined to from a comprehensive outcome inventory.

Stage two is outcome consensus, during this stage key stakeholders, including people with a lived experience of the condition and HCPs, refine the comprehensive outcome inventory using a formal consensus method such as The Delphi Survey Method which results in the initial COS. The third and final stage, determines the final list of core outcomes, their definitions and how they will be reported via a consensus meeting with key stakeholders.

1.3 Aim

The aim of this research is to commence the development of a twin pregnancy COS. This research will focus on stages one and two of COS development as defined by the COMET initiative and lay the foundation for the final COS development in twin pregnancy. The aim of the COS is to allow all future research in twin pregnancy to be combined; providing stronger evidence to support clinical guidance and decision making and ultimately reduce adverse outcomes for women with a twin pregnancy and twins.

A project steering group, including HCP's, researchers, and parents with a lived experience of twin pregnancy will be established and responsible for the overall conduct of the study.

Chapter 2:

Outcomes in intervention and management of multiple pregnancies trials: A systematic Review

2.1 Abstract

2.1.1 Introduction

Twin pregnancy has risks of adverse outcomes for mother and baby. Data synthesis is required to gain evidence to aid recommendations but is hampered by variations in outcome reporting.

2.1.2 Materials and Methods

Systematically review outcomes reported in twin pregnancy trials (PROSPERO - CRD42019133805). Searches were performed in MEDLINE, EMBASE, CINHAL, Cochrane library (inception-January 2019) for randomised control trials or their follow-up studies reporting prediction, prognosis, intervention or management outcomes in twin pregnancy. The study characteristics, outcomes definitions and measurements were extracted and descriptively analysed.

2.1.3 Results

49 RCTs and 8 follow-up studies evaluated 21 interventions, 1257 outcomes, categorised into 170 unique outcomes. 65% of trials included all twin pregnancies, 12% DCDA and 11% MCDA only or MCMA and MCDA. Five (9%) papers were prediction/ prognosis RCT's and 52 (91%) related to an intervention. Of interventions, 40 (77%) were medical, 34 (85%) for preterm birth; 12 (23%) surgical, 6 (50%) related to TTTS interventions (83% for monochrorionic studies). Commonest domains were: 'Neonatal' 77%, 'Delivery' 70% and 'Survival' 67%. Least reported were longer term outcomes for 'Infant' or 'Parental'.

2.1.4 Conclusions

Twin pregnancy outcomes are diverse and complex. This is related to the need to address maternal, single and double fetal outcomes and different types of chorionicity. The lack of outcome standardisation in selection, definition and reporting hinders evidence synthesis and the selection of outcomes important to women and health care professionals thus limiting the effectiveness of research.

2.2 Introduction

This chapter reports stage 1 of the COS development; a systematic review of outcomes reported in randomised controlled trials (RCTs) for interventions and management in twin pregnancy. The work contained in this chapter has been published as Farmer N, Hillier M, Kilby MD, Hodgetts-Morton V, Morris RK. Outcomes in intervention and management of multiple pregnancies trials: a systematic review. European Journal of Obstetrics & Gynecology and Reproductive Biology 261 (2021) 178-192 (72)

2.3 Materials and methods

This systematic review was registered on the International prospective register of systematic reviews (PROSPERO) (CRD42019133805) and COMET database. It was performed according to recommended methods and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and COMET guidance (75) (Appendix 1 contains the protocol for the systematic review, Appendix 2 contains the PRISMA checklist).

2.3.1 Data Sources

Electronic database searches were executed to obtain articles reporting RCTs of intervention or management in twin pregnancies. The search was completed in MEDLINE (database inception – 25 Jan 2019), CINHAL (database inception – 25 Jan 2019), EMBASE (database inception – 25 Jan 2019) and the Cochrane library (database inception – 02 Feb 2019) using a pre-defined search strategy. The Web of Science was used to search for grey literature.

The pre-defined search strategy based on the eligibility criteria incorporated all relevant keywords and variations. 'Twin pregnancy' OR 'twin pregnancies' were combined with more twin specific definitions 'monoamniotic' OR 'monochorionic' OR 'diamniotic' OR 'dichorionic' and limited to 'randomised control trials' and 'clinical trials' if the database allowed (Appendix 3 Search strategy in MEDLINE). The reference lists of included studies were cross-checked and authors were contacted for further information where necessary.

2.3.2 Eligibility criteria for selecting studies.

Studies were eligible if they reported a specific therapeutic intervention (medical or surgical) in pregnancy and/or a management pathway (e.g. ultrasound screening) in twin pregnancies and were of RCT design. Planned RCT follow-up studies, documented in the original protocol, were also included to capture longer-term outcomes. This is unlike systematic reviews and meta-analysis of effectiveness where participant duplication in statistical analysis is an issue, as it is only

outcomes being captured and not their numerical value. Secondary analyses investigating a new hypothesis were not included.

All three variations of twin pregnancy were included i.e. DCDA, MCDA, MCMA, but trials including higher order multiples (e.g. triplets) were excluded as these pregnancies include variations of DC and MC placentation. All therapeutic interventions and comparators were considered regardless of type, setting or mode of administration and all outcomes were included and collected. No dates, country of origin or language restrictions were applied. Studies that met the eligibility criteria following review of their title and abstract were selected for full manuscript review.

2.3.3 Data extraction and analysis:

Manuscripts were reviewed independently in duplicate to confirm eligibility and data extraction was performed using a piloted data extraction proforma. The following study characteristics were extracted: study design, year of study, place of study, sample size, multicentre vs. single centre, intervention, comparator as well as outcome definition, measurement, and classification.

To overcome differing definitions, outcomes were categorised into unique outcomes with the same semantic meaning e.g. admission to the neonatal unit and admission to a level three unit was grouped into one unique outcome.

Outcomes that were defined at different time points but had the same meaning were also grouped into a unique outcome e.g. neonatal death before discharge and neonatal death before 28 days was grouped as 'neonatal death'. Likewise, authors were mindful not to over aggregate outcomes during a categorisation as this may have resulted in crucial outcomes being lost. For instance, RCTs often reported the number of babies with one or more specified condition as a single composite outcome and would also report each condition that formed the composite outcome as an outcome in itself. It was agreed that composite outcomes would be separated into the measures/definitions used within it to form separate unique outcomes as each had a different semantic meaning.

Unique outcomes were grouped according to the OMERACT 2.0 framework which consists of four core areas – life impact, pathophysiological/manifestations, resource use/economical and death. Dodd et al (76) was considered for outcome taxonomy, however as there is a maternity specific sub-classification, the majority of unique outcomes may have potentially been placed in a signal sub-classification and therefore the Outcome Measures in Rheumatology (OMERACT 2.0) framework was utilised. If needed there would be further organisation into domains within each main area if needed. Each grouping and categorisation were agreed by all the authors who are experts in research and twin pregnancy and by the patient representative. Raw data were inputted into Microsoft EXCEL©.

2.3.4 Quality assessment:

Studies were subjected to methodological quality assessment using the Cochrane risk of bias Tool for RCTs (RoB2) (77). The quality assessment was performed independently in duplicate.

2.4 Results

Figure 2 shows the process of selection for inclusion with a total of 1113 citations identified in the electronic search; 57 were deemed eligible for inclusion following full paper review. There were 48 RCTS and 9 follow-up studies.

2.4.1 Study characteristics

The majority of trials (61%) were published between 2011- 2019 (Table 1). 59% recruited participants from multiple centres and 21% recruited across multiple continents including low-, middle-, and high-income countries. Sample sizes ranged from 12 to 4603 participants with 51% having a sample size between 101-500 participants. 65% of the trials included all twin pregnancies, 12% included only DCDA twin pregnancies and 23% included only MCDA or MCMA and MCDA twin pregnancies.

Figure 2: Flow diagram demonstrating inclusion of studies in systematic review of outcomes in intervention and management of multiple pregnancy trials."

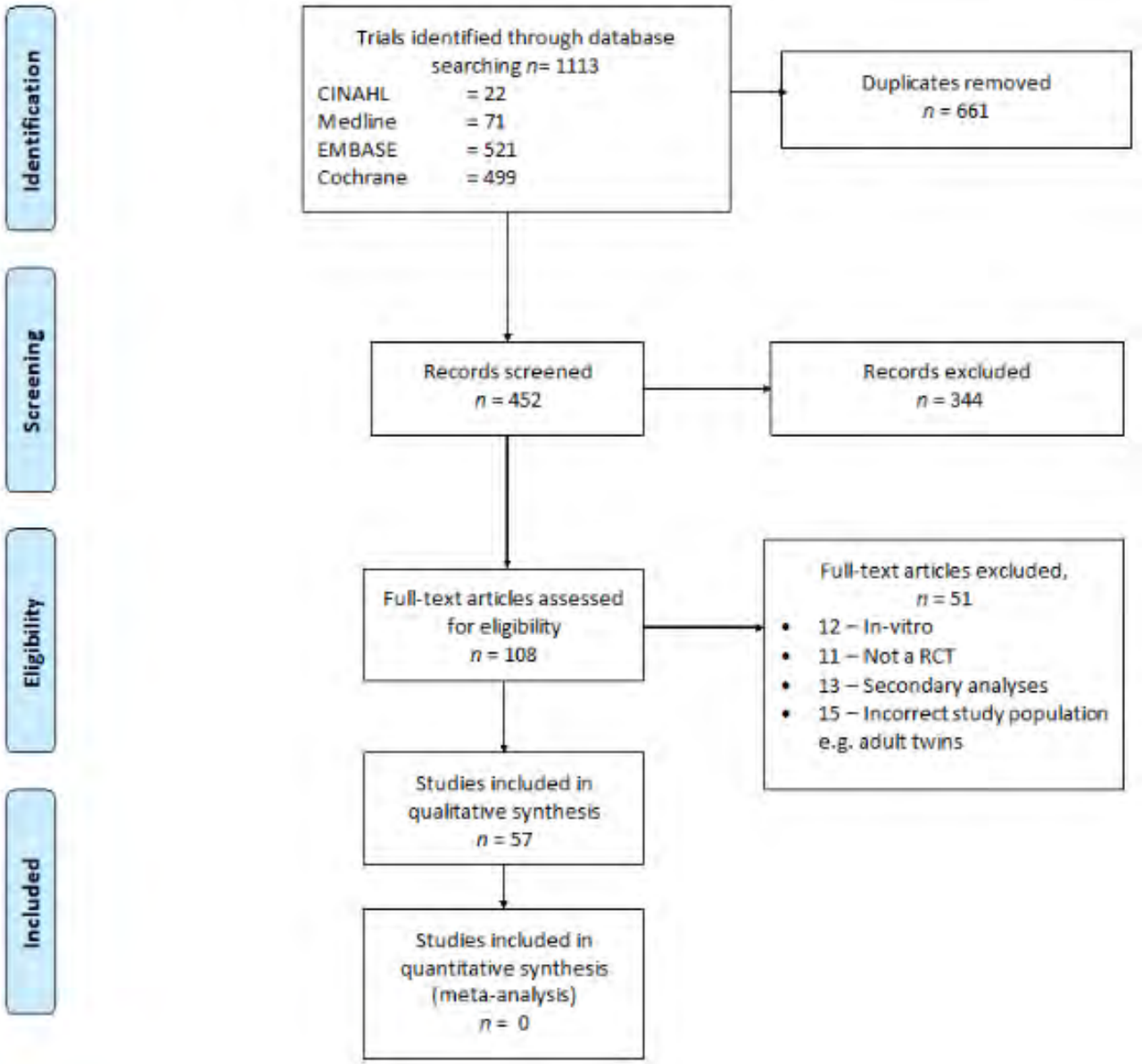


Table 1: Summary of study characteristics

		No. of trials (n= 57)	%
Year of publication	1971-1980	2	4
	1981-1990	8	14
	1991-2000	3	5
	2001-2010	9	16
	2011-2019	35	61
Multi-centre		33	59
Continent	Africa	9	16
	Asia	7	12
	Australia	1	2
	Europe	17	30
	North America	10	17
	South America	1	2
	Multiple continents	12	21
Sample size	< 50	11	19
	51-100	5	9
	101-200	13	23
	201-500	16	28
	501-2000	6	11
	2001-5000	4	7
	not documented	2	3
Twin type	All twins	37	65
	DCDA	7	12
	MCDA & DCDA	7	12
	MCDA	2	4
	MCMA & MCDA	4	7
RCT type	Prediction/ Prognosis	5	9
	Intervention	52	91
	-Medical	40	77
	-Surgical	12	23
Maximum length of follow up	0 months - ≤ 6 months	44	77
	> 6 months - ≤ 12 months	1	2
	> 12 months - ≤ 24 months	4	7
	> 24 months	3	5

Intervention and prediction/ prognosis RCTs were both reported; 5 (9%) papers were prediction/ prognosis RCTs and 52 (91%) were intervention RCTs. Of the 52 intervention RCTs, 40 (77%) were medical management and 12 (23%) surgical management. Of those reporting medical interventions, 34 (85%) related to interventions for preterm birth; RCTs investigating progesterone accounted for 28% of all trials. Of the 12 RCTs reporting a surgical intervention, 6 (50%) were related to interventions for TTTS (83% of those whose inclusion criteria were MCMA or MCDA related to laser coagulation). Appendix 4 reports detailed characteristics of each included trial. 44 (77%) trials followed up their participants within six months (77%) and 3 (5%) trials followed up their participants for more than two years, the maximum length of follow up was eight years.

2.4.2 Outcomes

There were 1257 verbatim outcomes reported within 57 trials between the years 1971–2019.

2.4.2.1 Outcome classification

Of the 1257 outcomes, 20% were classified as primary outcomes, 64% as secondary outcomes and 16% were unclassified which was observed in 16/57 trials (28%). Outcome classification has increased over recent years from 0 - 50% between 1971-2000 to 78 - 83% between 2001-2019.

2.4.2.2 Outcome domains and Unique Outcomes

The 1257 outcomes were then grouped and classified into outcome domains according to the OMERACT 2.0 filter and further classified into 170 unique outcomes. The core area 'Life impact' consisted of 2 outcome domains: - 'Parental' which had 8 unique outcomes and 'Infant' which has 7 unique outcomes. The core area 'Pathophysiology/Manifestations' comprised of the 5 outcome domains labelled as: - 'Fetal' which has 12 unique outcomes; 'Delivery' which has 29 unique outcomes; 'Neonatal' which has 50 unique outcomes; 'Maternal Investigations' which has 9 unique outcomes and 'Maternal Morbidity' which has 29 unique outcomes. The core area 'Resource use/Economical impacts' consists of 12 outcomes. The core area 'Death' has 13 unique outcomes. (Appendix 5 Summarises the outcomes classified according to OMERACT 2.0)

Figure 3 shows the proportion of outcome domains that were reported by trials within different timeframes. Initially only four outcome domains were reported (Neonatal, Delivery, Survival, and Maternal Investigations) this increased over time and consequently nine domains have been reported. The most frequent and consistent domains reported by trials are 'Neonatal' which was reported in 44/57 (77%) of trials, 'Delivery' which was reported in 40/57 (70%) of trials and 'Survival' which was reported in 38/57 (67%) of trials (Figure 3). The outcome domains that are least reported by trials are 'Infant' which has been reported in 10/57 trials (18%) and 'Parental' which was reported in 5/57 (9%) trials (Figure 3). The outcomes within these domains are long term outcomes and/ or patient reported outcomes and it wasn't until 2001 that both Infant and Parental outcomes were reported more frequently (Figure 4).

Figure 3: Percentage of trials that reported each outcome domain (n=57)

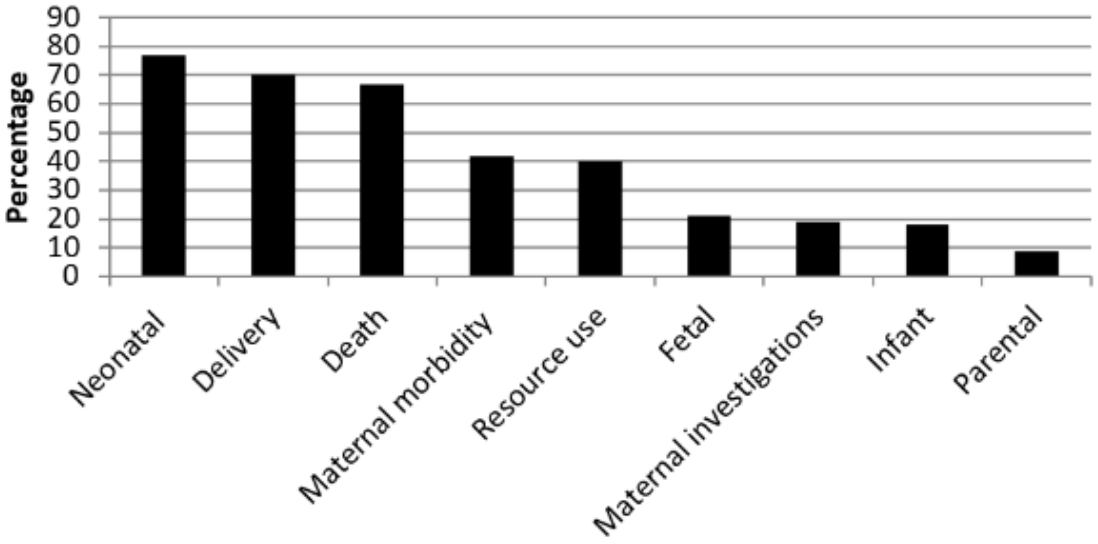
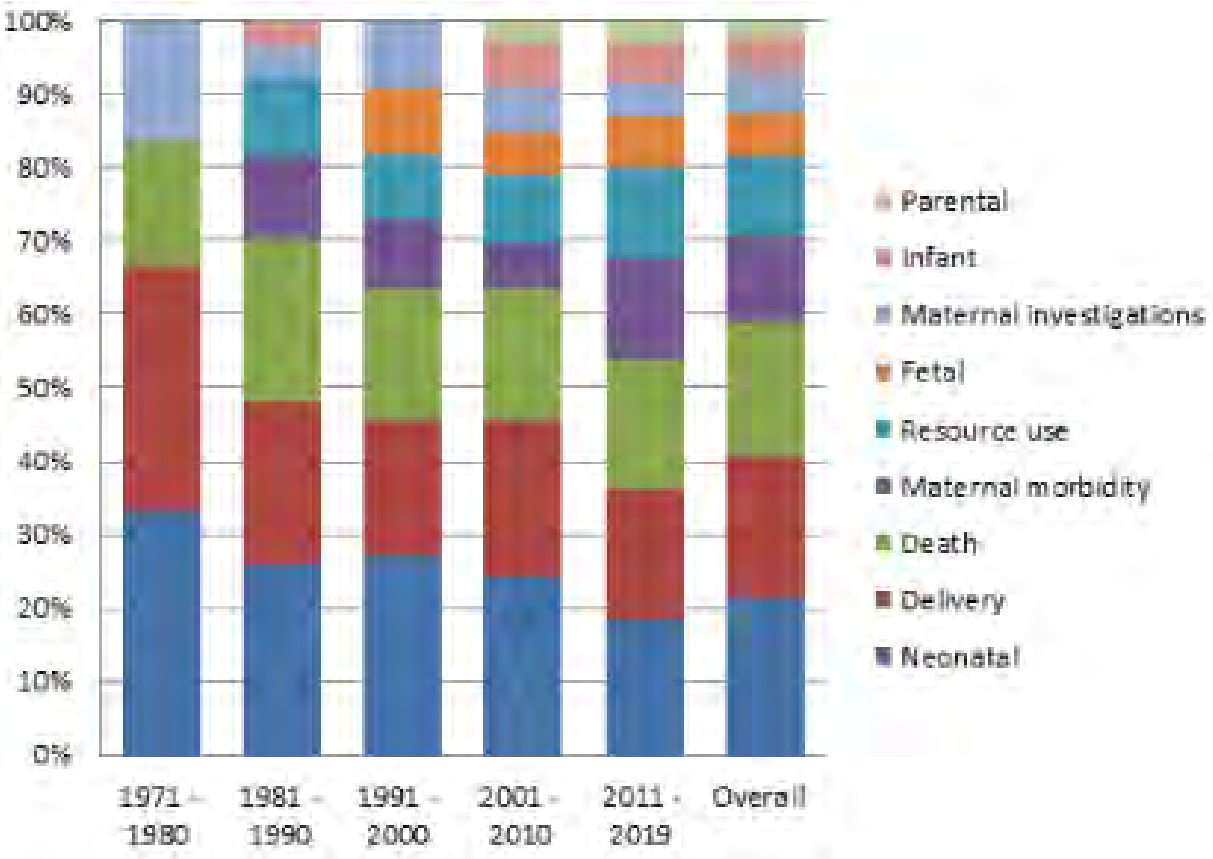


Figure 4: Proportion of outcome domains reported by trials within each timeframe.



As shown in Table 2 the three most frequently reported outcomes were ‘Side effects from the intervention’ which was reported 85/1257 (7%) times by 12/57 (21%) trials and was measured in 72 different ways. ‘Preterm Birth’ was reported 77/1257 (6%) times in 26/57 (45%) trials and measured in 18 different ways; and ‘Mode of Delivery’ was reported 54/1257 (4%) times in 24/57 (42%) trials and measured in 16 different ways (Appendix 6 shows the different measurement variations and definitions used for each of the three most reported outcomes).

Table 2: Outcomes most frequently reported.

Outcome Domain	**Outcome**	**Number of times reported.** (*n*=1257)	**Number of trials that reported the outcome.** (*n*=57)	**Number of different definitions/ measures**
Maternal morbidity	Side effects from intervention	85 (7%)	12 (21%)	72
Delivery	Preterm delivery	77 (6%)	26 (45%)	18
Delivery	Mode of delivery	54 (4%)	24 (42%)	16

Is it important to note that the number of times an outcome is reported will not correlate to the number of trials that have reported the outcome; this is because each trial will often use more than one outcome measure to report a unique outcome. For instance, one trial may have measured ‘Mode of Delivery’ as the number of CS and the number of vaginal births; in this case one trial will have reported the outcome ‘Mode of Delivery’ twice. Therefore, if unique outcomes’ measures are heterogeneous it may appear to be more frequently reported e.g. ‘Side effects from intervention’ is the most heterogeneous with 72 different measures and although it has been reported 85 times is has only been reported by 12 trials. Thus, it is important to evaluate which outcomes were most commonly

reported by each trial. As seen in Table 3, the three outcomes reported most by trials are: - ‘Birthweight’, which was reported by 29/57 (50%) trials and was reported 42/1257 (3%) times using 7 different measures; ‘Gestation at delivery’ which was reported in 29/57 (50%) trials and was reported 34/1257 (3%) times using 7 different measures; ‘Neonatal death’ was reported by 27/57 (47%) trials and was reported 36/1257 (3%) times using 13 different measures (Appendix 7 shows the variation in their outcome measures).

Table 3: Outcomes that trials most frequently reported.

Outcome Domain	**Outcome**	**Number of trials that reported the outcome.** (n= 57)	**Number of times reported** (*n*=1257)	**Number of different definitions/measures**
Neonatal	Birthweight	29 (50%)	42 (3%)	6
Neonatal	Gestation at delivery	29 (50%)	34 (3%)	6
Survival	Neonatal death	27 (47%)	36 (3%)	12

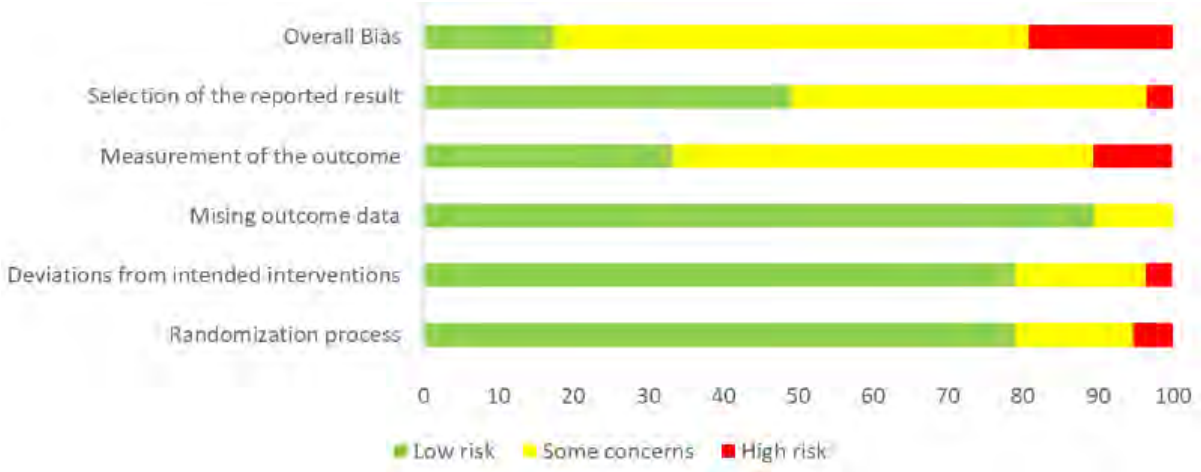
The large variety of outcome measurements and definitions is seen across all unique outcomes with no single measure or definition being utilised for any of the 170 unique outcomes that were reported more than once. Furthermore, 23% of verbatim outcomes had not been defined; and those that were defined, were poorly defined and often not based on any standardised measurement. This was further complicated as some trials reported their outcomes as a continuous variable whilst others reported the outcome dichotomised. For instance, PTB was measured by the number of gestational weeks the baby was at birth and others reported the number of babies that were born before 37 weeks. Trials also differed in their choice of common denominator, as some trials reported the number of

pregnancies and others reported the number of babies that were affected by an outcome.

2.4.3 Quality assessment

Figure 5 shows that 18% of trials scored at a low risk of bias, with the area at highest risk being ‘outcome measures’ and ‘selection of the reported result’. This reflects the findings that most trials did not clearly define their outcome and report it.

Figure 5: Quality assessment of included trials in in systematic review of “Outcomes in intervention and management of multiple pregnancy trials.” Assessed using the Cochrane risk of bias tool. (75)



2.5 Discussion

2.5.1 Main findings

This systematic review highlights the complexities and heterogeneity of outcomes in twin pregnancy clinical trials and a lack of standardisation of outcomes and their measures. Of note, this review identified that longer term outcomes for mother and baby(s) are rarely collected, and long-term parent related outcomes have only been included in research since 2001. Furthermore, the inconsistencies within the outcome definitions and measurements identified and use of denominators for reporting of results introduces further diversity and bias. The three most reported outcomes were ‘side effects of intervention’, ‘Pre-term delivery’ and ‘Mode of delivery’. The three most frequently reported outcomes by trials were ‘Birth weight’, ‘Gestation at delivery’ and ‘Neonatal death’.

2.5.2 Strengths and Limitations

To the author’s knowledge this review is the first to provide a comprehensive summary and analysis of all outcome reporting in twin pregnancy RCTs and RCT follow-up studies and the strength lies within the methodology employed.

Currently there is on-going work aiming to establish the most efficient methodology for systematic reviews for COS development. It has been suggested that it may not be necessary to search multiple databases as outcome saturation can be reached regardless. Furthermore, it has also been suggested that outcomes need only be collected by one reviewer as there is a low risk of error when collecting outcomes as opposed to numerical data (78). However, this

review has followed the standardised data collection within systematic review methodology to ensure a rigorous approach. Additionally, all outcomes were collected regardless of classification. Some COS developers have collected primary outcome data only; deeming them to be of upmost importance, yet of the 1257 outcomes collected in this review, 80% were not classified as primary outcomes and therefore would have been missed. Furthermore, bias would also be introduced during the data collection as outcome classification has only been adopted recently meaning the outcomes gathered would only be from the latter years. However, it could be argued that older outcomes may be outdated as they reflect the interventions/ complications of that era and that as medicine advances the complications of that era change and outcomes that are reported will adapt to this. Nevertheless, if outcomes have truly become outdated, they will be eliminated during the Delphi survey.

A limitation of this review is that the inclusion criteria were restricted to RCTs and RCT follow up studies; it could be argued that some outcomes may only be present in observational studies. However, RCTs are considered to be of the highest quality and so are most likely to influence clinical practice, therefore outcomes reported in these trials should be the most important and relevant. In addition, in the next phase of the COS development during the Delphi Survey (see chapter four) twin experts had the opportunity to suggest outcomes that they feel were missed thus minimising this risk. Moreover, the RCT follow up trials included within this review identified important long-term patient reported outcomes such as ’infant neurodevelopmental impairment’, ‘Cerebral Palsy’, and ‘visual impairment’.

These outcomes may be crucial as they not only have lifelong consequences for the child and their family but will also increase health care costs significantly.

Another limitation of this review was the degree of subjectivity when categorising verbatim outcomes into unique outcomes as many were poorly defined or closely inter-related. For instance, one trials' outcome may have been PPH measured by the requirement of a blood transfusion however another trial may have reported blood transfusion as an outcome but not defining its measure i.e. a blood transfusion due to PPH. This was exacerbated by the use of neonatal composite outcomes which was an unforeseen challenge during categorisation. To overcome this consensus-led clear decisions were made involving all authors and a patient representative. At the time of outcome categorisation there was no clear guidance for COS developers clarifying or standardising the way in which outcomes were categorised. However, literature has since been published which discusses the importance of verbatim outcomes being categorised into outcomes with the same 'original meaning' (79) and so supports the method used.

2.5.3 Interpretation

This review suggests that outcomes likely to be of importance to parents and long-term outcomes are not well incorporated within research. One possible reason for this is the lack of patient involvement when trials are designed. This research supports this, as the outcome domains most frequently and consistently reported by trials were 'Neonatal', 'Delivery' and Survival' and these outcomes reflect the questions identified by clinicians and researchers. The lack of patient involvement

has become widely recognised and the importance of engaging them in research is being increasingly acknowledged (78,80–83). This is vital as researchers can only be certain that interventions are being evaluated in a way that is relevant to the target population if parents' perspectives are considered (84). Likewise, it is debatable whether trials have followed up their participants for long enough to understand the effects of the intervention as only three trials followed up their participants for more than two years and prior to 2014 no trials had followed up their participants for more than six months. Fortunately, the scope of research has widened, and researchers have recognised the importance of long-term follow up with one trial's follow up being over eight years. However, as this gains momentum COS developers need to be mindful as implementing such methods can be costly on resources and time.

The heterogeneity and inconsistencies within outcome definitions and measurements reduces the quality of the results produced by data synthesis, which ultimately affects the validity of conclusions and reduces the meaningfulness of evidence-based guidelines. The use of different common denominators in twin pregnancy research, introduces bias as it will significantly affect the overall percentages. This is relatively unique to multiple pregnancy research. Therefore, even if trials utilise the same outcome definitions, evidence could not be synthesised because of the diversity within the variable reporting.

Developing a COS for multiple pregnancy will overcome the inadequacies of current practice by developing a range of approved outcomes with agreed

definitions, measurements, and common denominators which will be reported as a minimum in all trials. The outcomes gathered in this review are those that are deemed important by clinicians and researchers and were collected from RCTs in low-, middle-, and high-income countries which will aid the international generalisability of the COS.

The next step in the COS development is identifying outcomes that are important to parents via interviews (Chapter 3). The outcomes identified will be combined with the outcomes from this review to form a comprehensive outcome inventory (Chapter 4). The outcomes for the COS will be determined using the modified Delphi method and a consensus meeting, with all stakeholders, will then need to take place to finalise the measurements and common denominators for each outcome (85,86).

The development of a COS for twin pregnancy will ultimately improve patient care as it will enable clinicians to make better informed decisions and ensure that research is meaningful to patients. However, it is important that clinicians also recognise that the COS for twin pregnancy will provide an overview of all twin pregnancies. This systematic review details the difficulty of assessing outcomes in twin pregnancy which was mainly due to the vast number of variables e.g. outcomes could evaluate the pregnancy as whole, or they could evaluate each individual baby, or they could depend on the type of twin pregnancy. Therefore, there is also a need for a COS relevant to unique conditions to be developed - such as a COS for Twin-to-Twin Transfusion syndrome (87) to further aid data

synthesis in such conditions. Researchers also need to be aware of the complexities of statistical analysis related to outcomes in multiple pregnancies (88).

2.6 Conclusion

Our review has demonstrated the complexity of outcome reporting in twin pregnancy clinical trials and the clear deficiency of patient-centred outcomes and long-term outcomes for the babies. The heterogeneity of outcome selection results from the need to address maternal, single fetal, double fetal and different types of twinning.

Chapter 3:

Developing a Core Outcome Set for twin pregnancy: Patient experiences and perspectives in qualitative interviews.

3.1 Introduction

Stakeholder engagement is a key component of COS development as it ensures it is important and meaningful to those in which research is aiming to benefit. One of the essential stakeholder groups within COS development is patients, and early involvement is crucial and recommended by COMET(9). Patient and public involvement (PPI) is interlaced throughout the COS development process and there are several ways it can be achieved such as PPI inclusion in the project steering group, nominal group work and Delphi Survey, as well as qualitative interviews or focus groups (9).

Consequently, there is variation in how COS developers choose to include PPIs within their research. For instance, during stage 1 (outcome identification) some COS developers carry out qualitative research adjunctively to the systematic review (89,90), whereas others choose not to, instead only including PPI's during outcome consensus (stage 2 & 3) (71,91). This is currently the most common method of PPI inclusion which is likely due to the increased workload and additional costs, resources and time needed for qualitative research (9,92). However, this means that outcome identification is restricted to the outcomes gathered from the systematic review, yet studies have demonstrated differing priorities between patients and researchers (93–95) and historically there has also been limited PPI involvement during outcome selection within trials (74). Thus, although there is PPI involvement with this method, it is likely they will only consider outcomes for consensus that have been deemed valuable by researchers. It is therefore important to undertake qualitative research in order to exhaust outcome identification.

Aside from comprehensive outcome identification, qualitative research serves several other purposes within COS development. The term ‘outcome’ can be obscure to those outside of research and participants often find it difficult to interpret what an ‘outcome’ is (96). Qualitative research allows participants to explain outcomes in their own terms which will ensure both PPIs and researchers have an in-depth understanding of what the outcome means (97). In addition to this, it enables researchers to explore why an outcome is important and confirms the context is correct (97). This is vital as during the development of PARTNER2 COS, ‘employment’ was highlighted as an important outcome in both the systematic review and qualitative interviews (98). However, qualitative interviews gave researchers a deeper understanding of the context and found that having ‘suitable’ employment rather than employment alone was important to stakeholders (98). This allowed researchers to take the accurate outcome through to the Delphi Survey which would have otherwise been potentially meaningless to stakeholders.

In addition to this, researchers can utilise the language used by the participants when describing an outcome of importance. Appropriate language use during the stage 2 & 3 is crucial as outcome descriptions in clinical trials are often differ to that used by PPI’s (97). Therefore, identifying the appropriate language to use for the lay outcome definitions in stage 2 & 3 will ensure all participants are interpreting the outcome correctly when considering it for consensus.

One of the guiding principles of COS development is to ensure outcomes are relevant and reflect the priorities of key stakeholders (9), therefore the mixed method approach, that employs qualitative research alongside the systematic review during outcome identification, is increasing in popularity (89,99). This is also reflected in the current COS development guidance which recommends outcome identification comes from multiple sources, including interviews and/or focus groups (9). In doing so, it will ensure all potentially relevant outcomes are taken through for consensus which will promote confidence in the final COS and maximise the impact of future research (97).

A systematic review of outcome reporting in twin pregnancy clinical trials (Chapter 2) demonstrated that outcomes which may have been important to patients are poorly reported (100). Furthermore, to date, there has been two core outcome sets developed in twin pregnancy (specifically TTTS & sFGR) but neither carried out qualitative research during COS development (71,91). Therefore, in order to gain a deeper understanding of patients views within this field and establish what outcomes are important to them it is important qualitative research is undertaken. This research has not been performed to date in this area.

3.2 Aim

The research in this Chapter forms part of the development of a COS for twin pregnancy (9). The primary aim is to identify outcomes that are important to parents with a lived experience of twin pregnancy (stage 1) and why. Furthermore, exploring their priorities, experiences and perceptions of twin pregnancy may

identify outcomes that have previously been unreported in clinical trials and ensure outcome identification is exhaustive. Following this study, outcomes identified from both interviews and the systematic review will be combined to form a comprehensive outcome inventory, this will be considered for consensus by key stakeholders via a Delphi Survey (Chapter 4). To aid patient understanding during the Delphi Survey, the language used to describe outcomes during the interviews will also be utilised when creating the Delphi Survey lay outcome definitions.

3.3 Method

3.3.1 Study design

A qualitative interview study was used to achieve the primary aim of identifying outcomes important to people with a lived experience of twin pregnancy; this is advocated by COMET (9). Semi-structured interviews were undertaken to enable in-depth discussion whilst ensuring the researcher could maintain the focus of the interview. To aid this, an interview guide, informed by the systematic review, was created (Appendix 8). To elicit important outcomes, participants were initially asked open questions; they were asked to describe their twin pregnancy experience, which was followed by more focused questioning to address the research questions and identify outcomes that were important for the participant and, importantly, why these were important for them. This enabled inductive exploration into participants' narratives (101).

3.3.2 Sampling and participants

This study purposively sampled a population of mothers, and/or their partners, that had experienced twin pregnancy, were over the age of 18, and were able to understand and speak English. To achieve heterogeneity within the sample, parents were eligible for recruitment if they were currently pregnant with twins or had experienced twin pregnancy within the last 10 years, with or without complications. The project steering group thought it was important to include parents that have birthed within 10 years as they may provide long-term outcomes which could have otherwise been missed and have previously been demonstration to be poorly represented in twin pregnancy clinical trials (100). In addition to this, interviews were held during the Covid-19 Pandemic so including those that had experienced twin pregnancy outside of this time may help to reduce covid-specific issues that could potentially skew the results.

Participants were recruited across the UK via the following sources: -

1. Birmingham Women's and Children's Hospital: Mothers and/or their partners attending a specialised twin pregnancy outpatient clinic or an inpatient on the postnatal ward were approached by a research midwife.
2. Twin pregnancy social media platforms and groups: Adverts were placed on twin pregnancy social media platforms and in twin pregnancy groups i.e. parent education classes, detailing the study and contact numbers were provided. Sharing the advert was encouraged to increase diversity within the sample.

3. Snowball sampling: Mothers and/ or their partners that had been recruited were asked to identify others that were eligible and interested in the study.

3.3.3 Data Collection

Interviews with mothers and their partners were held separately to allow for open discussion about their experience and priorities. Interviews were conducted by two researchers separately (NF & BC). Initially face-to-face interviews were planned, however due to the Covid-19 pandemic restrictions, interviews were held on the telephone and digitally recorded. This subsequently allowed for a wider geographical spread and the interviews were less resource and time intensive for both the researchers and participants. However, due to the restrictions consent forms were sent via the post with a prepaid envelope to return the signed consent form, which was agreed by the sponsors.

To encourage openness and trust (102), prior to recording, the researcher had a short discussion with the participant informing them of their professional background and general scope of the study. Participants were also asked to complete a short demographic questionnaire detailing such things as; their age, gender, ethnicity, type of twin pregnancy e.g DCDA, and reminded that they could stop at any point, without giving a reason and could be signposted to support networks should they require it.

All interviews were professionally transcribed intelligent verbatim and stored onto an encrypted memory sick. Participants were given the opportunity to view their transcripts and remove anything they did not want published.

3.3.4 Data analysis

Transcripts were imported into NVivo software and Reflective Thematic Analysis (RTA) was undertaken by two independent researchers (NF & BC) (11). The six steps for RTA were followed (11) and a deductive approach (12), based on the domains generated in the systematic review, was initially taken to test the existing theory and a deductive codebook was created. Through the course of their interview, participants were given the opportunity to express their opinions on the outcomes of twin pregnancy that were important to them. Participants' responses were analysed for both semantic and latent codes relating to outcomes. Each new outcome that was interpreted by the two researchers (NF and BC) not otherwise captured in the systematic review and thus not present in the initial deductive codebook was inductively coded, thereby adding to the codebook. This process was iterative and, through regular collaborative discussions between the two researchers, new inductive codes were decided (12). The final codebook therefore contained both the initial deductive codes identified via the systematic review and inductive codes that were interpreted from participant's responses during interview. This supplementary inductive approach enabled the researchers to build on existing knowledge and understand *why* an outcome was important. Any discrepancies were resolved by discussion with the project steering group (12).

3.3.5 Ethical approval

Ethical approval was sought and granted by HRA and Health and Care Research Wales (HCRW) (reference number 19/YH/0191) as well as sponsor approval from The Birmingham Women's Hospital (No. 18/BW/MAT/PO36) and the University of Birmingham.

3.4 Results

3.4.1 Overview

In total, 27 participants consented to be interviewed, 7 were lost to follow-up thus 20 participants completed interviews, of which, 18 were female mothers and 2 were their male partners. All participants resided in the UK and the majority were White British (70%), over the age of 30 (75%) and antenatal (75%). There was variation in twin pregnancy type with 80% being DCDA, 5% MCDA and 15% MCMA, of these 55% had endured complications either during their pregnancy or postnatally (Table 4). No participants withdrew or requested data be removed from their transcripts. No further outcomes were identified after interview 18 therefore interviews were stopped at 20. Interviews were held between August – September 2020 and lasted between 27 - 63 min.

Table 4: Interview participant characteristics

Participant Characteristics	*n*	%
Consented		
Interviewed	20	74
Lost to follow-up	7	26
Ethnicity		
British European	14	70
Indian	3	15
Caribbean	1	5
British European & Caribbean	1	5
Irish European	1	5
Gender		
Female	18	90
Male	2	10
Age		
16 - 29	5	25
30 - 44	15	75
Pregnancy status		
Antenatal	15	75
Postnatal	5	25
Pregnancy timeline		
Currently pregnant	15	75
Within the last 2 years	4	20
Within the last 2-10 years	1	5
Type of twin		
Non-identical	16	80
Identical	4	20
MCMA	*3*	*15*
MCDA	*1*	*5*
Complications		
Without	11	55
With	9	45
Anaemia	*4*	*20*
Pre-term birth	*2*	*10*
Short long bones	*1*	*5*
UTI	*1*	*5*
Haemorrhage	*1*	*5*
Hypertension	*1*	*5*
Selective growth restriction	*1*	*5*
Single fetal death	*1*	*5*
Preterm rupture of membranes	*1*	*5*

3.4.2 Outcome themes

Seven board themes were formed during interviews which incorporated 57 outcomes, these are:

1. Death or survival
2. Fetal wellbeing
3. Birth
4. Maternal wellbeing
5. Neonatal wellbeing
6. Infant wellbeing
7. Life impact

Each theme was well represented during interviews and discussed by no less than 16 participants and referenced at least 36 times. Table 5 provides a full breakdown of how each theme was established from the outcomes identified, how many participants discussed each outcome and how often it was referenced.

3.4.3 Theme 1: Death or Survival

The theme of Death or Survival was discussed by all participants, referenced 160 times and 9 outcomes sat within it, one of which was developed inductively: Selective Termination (Table 5).

Participants described being told from an early stage about the complications associated with twin pregnancy and the increased risk of death to the twin baby(s). However, some participants were not always able to understand the information that explained *why* there was an increased risk of death, though this did differ between participants that had experienced different twin pregnancy types. For instance, those that had experienced MCMA pregnancies found the complications specific to this pregnancy type very difficult to understand initially.

“We didn’t understand that there was no dividing membrane between the two babies and that that was a problem, and we didn’t understand the problem of them sharing the same placenta. (Participants 014).

Even those that did understand the information, often felt that they had not been given enough so relied on the internet as a source which heightened their anxieties.

‘I just became obsessed with looking it up. Week by week miscarriage rate. Statistics and trying to find out information. How it is different for twins than singletons because a lot of things highlighted you’re more likely to lose a twin or to lose both with twins but there isn’t loads of statistics around’ (Participant 19).

Initially participants were particularly worried about miscarriage as they knew they were at a much higher risk then those with a singleton pregnancy. This seemed to be greater in participants that had experienced miscarriage previously or had friends or family that had.

“Yes definitely, I do worry about that (miscarriage) because I have had a previous miscarriage. It made me feel a bit more comfortable after the 12 week scan that everything was OK. But it is always in the back of your mind once you have a miscarriage. You are a bit guarded in case something bad happens again” (Participant 12).

Participants described the most anxious time was prior to 20 weeks' gestation. This was because they were unable to feel fetal movements and therefore had no reassurance of fetal well-being. However, even when they were able to monitor fetal movements, they were aware that this only provided reassurance that one baby was well as it was difficult to determine if both babies were moving, thus for many this concern remained for the entire pregnancy.

“Movement is always something I’ve been super aware of because you feel movements you know one baby is ok but you don’t know if they’re both ok, whereas with a singleton pregnancy you feel movement and you’re like yes baby is fine whereas you can’t rely on that with twins so it’s been quite an anxiety induced pregnancy from that point of view” (Participant 20).

Most mothers felt that it was important both babies survived and were upset at the thought of going home with one baby. This was due to the bond they had created with both babies so believed that losing one twin would have just as much impact as losing both babies. In addition, participants thought that it would add greater complexities because they would need to care for the surviving twin whilst grieving the death of the other. They felt that this may hinder the bonding process with the surviving twin or felt that the surviving twin may serve as a constant reminder of the baby they lost and therefore may never fully be able to grieve which could potentially cause mental health issues such as depression or anxiety.

“It would have the same impact I think in terms of it would be life changing. It would still be devastating, and you'd be grieving but you would also have to be there for the other twin and still offer support, but I think it would be very challenging and you would always know they were a twin but because of their needs and demands you'd have to continue to support and care for them so it would be life challenging” (Participant 12).

“I think what would scare me the most if one was to survive and one wasn't, if I am going to be able bond with the one that survived because, I don't know, I feel a bit

of guilt or a sort of reminder as such, I think that it might be difficult mentally. Depression or anxiety. I think I'd be always panicking. Oh! What about the other baby, you know, what if? I think my mind would be in complete overdrive for quite a long time" (Participant 10).

This did differ somewhat from the participants that were fathers, as they felt that the death of one twin could increase the bond they have with the surviving twin. This is because they would feel an overwhelming sense of protection towards them to ensure they survived, but like mothers, could lead to heightened long-term anxiety.

"I think that would probably amplify the bond more, I think it would have a positive impact not a negative impact. Child nurturing would probably be a lot more cautious, and I would probably become very protective, I think it would be at a level that may be unhealthy because to go through the journey to where we are with two and then to lose the one. I think the reactions to that would be to protect the surviving child a lot more" (Participant 13).

Mothers explained that whilst they wouldn't want the loss of any baby the loss of a twin(s) early in the pregnancy would be much easier to deal with, both mentally and physically, then losing a baby at the later gestation. This was because, through fetal movements and feeling/ watching their body adapt to pregnancy, the bond with their unborn babies intensifies the longer the pregnancy progresses. They described how they began to imagine what life would be like with them at home and bought equipment ready for their arrival and expressed that they would

feel like they had failed as a mother if they suffered a stillbirth because their body wasn't capable of continuing the pregnancy.

"I think I would have been gutted that one hadn't survived but if it had happened quite early on, I think it would have been quite easy to deal with the fact that one had miscarried. But I think later on in the pregnancy it would have been harder to deal with and especially as you start to get used to the idea, so you feel that motherly protection before they're even born" (Participant 17).

"I think in the early part of the pregnancy when you can't see any of the movements or anything you kind of feel quite detached. I felt sort of detached but now obviously towards the end, you spend a lot more time and you're getting all the kit and all that stuff and you just, I don't know how this happens but I think it's just you can build up a sort of bond really and just that closeness and you just feel a sense of responsibility, like I've got two, I've got that responsibility, I've got to do everything I can to protect them and to just make sure that they're okay" (Participant 07)

"It makes me think about failure when you ask that question almost like you've failed" (Participant 01).

"I think that would make me feel like a failure... you know, was my body not capable of finishing this pregnancy?" (Participant 10).

Because of this undeniable bond during pregnancy, like fathers, mothers also felt a great sense of protection. However, the focus was to protect the unborn twins as they felt it was their responsibility as a mother, so much so, that the mothers did not consider their survival as important as their unborn babies and often disregarded this. For many of the mothers their absolute priority was the survival of their unborn twins even if this meant the loss of their life.

"I am not bothered about myself. I just hope they are alright. Whatever happens I just hope they are OK. I am not really bothered about me" (Participant 05).

"If it were to fall to one of us to go, I would prefer that it would be me and at least they've got their dad and they've got a chance at life. I wouldn't want that it would be one of my kids, I just believe that children shouldn't go before their parents and their babies as they're just coming into the world and life has just started for them. I've lived enough life and just the fact that I'm able to give them life and I know that they're going to be in good hands, and they'll be able to see life themselves. Yeah, I'd be alright with that" (Participant 24).

However, mothers that already had children had a different view because they believed they already had a responsibility to care for and protect their living children and so these mothers expressed that maternal survival was of equal importance to their unborn twins.

"I think, especially when you've got two other children, I really do think that maternal health is hugely important because I think you become acutely aware

that if anything happens to you, you would be leaving four children without a mum whereas I think if it's your first pregnancy it's a little bit different possibly. So, I think it's equally as important" (Participant 16)

In addition to this, fathers expressed that whilst one of their priorities was the survival of the twins, their top priority was survival of their partner (the mother) as they felt that it was their duty as a husband to protect her. Furthermore, couples were aware that they had different priorities when it came to survival and had discussed this prior to the interviews.

"It's just that he doesn't agree with that, but I've said to him Well you're going to have to do that. We see that situation very differently and I completely understand his perspective as well, but I think for myself I would just feel really selfish if it was chosen for me to survive and not for them" (Participant 07).

"So yeah, the most important, is the risk to her life. I wouldn't want her to go through childbirth and that ultimately leads to her loss of life that's the probably the most important concern" (Participant 08).

Table 5:Interview codebook for qualitative interviews with those with lived experience of a twin pregnancy

Theme	Outcomes	Description	No. of interviews	No. of references	Potential new outcome (x)
Death and survival		Related to the death or survival of one or both twins and/or of the mother.	20	160	
	Infant death or survival	The death of one or both twins aged 6 weeks to 2 years.	1	1	
	Cot death (SIDS)	Related to cot death or sudden infant death syndrome (SIDS).	1	1	
	Intrapartum death or survival	The death or survival of one or both twins during the intrapartum period (during delivery).	7	8	
	Intrauterine death or survival (inc. stillbirth)	The death of one or both twins >24 weeks gestation to birth.	12	17	
	Maternal death or survival	The death of the mother.	8	17	
	Miscarriage or early fetal survival	The death of one or both twins <24 weeks gestation.	19	43	
	Neonatal death or survival	The death of one or both twins from birth to 6 weeks old.	7	12	
	Selective termination	Related to the selective termination of one or both twins.	5	13	x
	Survival of one or both twins	Related to the preference for the survival of one or both twins.	16	47	
	Survival of both twins	Related to the preference for the survival of both twins.	14	36	
	Survival of one twin	Related to the preference for the survival of at least one twin.	6	11	

Delivery and birth	Related to the intrapartum period, especially the mother giving birth to the twin(s) and the birth of the twin(s).	20	128	
Gestation at delivery	Related to gestation at delivery (how many weeks pregnant the mother was when they gave birth).	1	1	
Mode of delivery	Related to the mode of delivery (e.g. whether the mother gave birth vaginally, via c-section, with the aid of instruments, etc.).	20	70	
C-section	Related to recovering from a C-section, including experiencing pain, reduction in mobility, scarring, etc.	18	33	
Different modes of delivery	Related to each twin having a different mode of delivery (e.g. twin 1 delivered vaginally and twin 2 delivered via c-section).	7	7	
Instrumental delivery (inc. forceps)	Giving birth with the aid of instruments (e.g. forceps).	3	4	
Vaginal delivery	Giving birth vaginally.	4	7	
Recovery from birth	Related to recovering from an instrumental delivery, including experiencing pain, reduction in mobility, scarring, etc.	10	20	x
Recovery from c-section	Related to the ability for the mother to recovery after c-section	10	19	
Recovery from instrumental	Related to the ability for the mother to recovery after an instrumental birth	1	1	
Perineal trauma	Related to perineal tears or trauma during vaginal delivery.	1	2	
Pre-term birth	Related to pre-term birth (giving birth <37 weeks gestation).	13	27	
Incompetent cervix	Related to having an incompetent cervix, specifically regarding the impact this has on pre-term birth.	1	1	
Skin-to-skin at birth	Parent(s) having skin-to-skin contact with their twin(s).	4	4	x
Fetal	Related to the fetus (one or both twins).	19	96	
Monochorionic complications	Related to twin-to-twin transfusion syndrome (TTTS).	6	9	
TTTS	Related to twin-to-twin transfusion syndrome (TTTS).	3	5	
Umbilical cord entanglement	Related to umbilical cord entanglement.	1	2	
Fetal growth or weight	Related to the growth or weight of the fetus in utero.	10	16	x
Fetal malformations	Related to one of both fetuses having a malformation.	4	16	
Achondroplasia	Related to one of both fetuses having achondroplasia.	1	1	
Down's syndrome	Related to one of both fetuses having Down's syndrome.	2	5	
Edward's syndrome	Related to one of both fetuses having Edward's syndrome.	1	1	
Skeletal malformation	Related to one of both fetuses a skeletal malformation.	1	1	
Exomphalos (omphalocele)	Related to one of both fetuses having exomphalos (omphalocele).	1	1	
Talipes	Related to either twin having talipes.	2	5	
General fetal health	The general health of one or both fetuses.	15	42	
Fetal activity	Related to 'feeling' fetal movements or seeing fetal movements during scans.	6	11	
Infant	Related to the infant (one or both twins).	16	36	
Neurodevelopmental impairment	Related to neurodevelopmental disability or impairments in general.	13	20	
Autism	Related to one or both twins having autism.	1	1	
Disabilities	Related to one or both twins having one or more disabilities.	12	14	
Cerebral palsy	Related to one or both twins having cerebral palsy.	1	2	
General infant health	Related to the general health of one or both twins as an infant.	8	11	
Infant growth	Related to the growth of one or both twins as an infant.	1	1	
Increased care or hospital appointments for infant(s)	Related to increased care or hospital appointments for one or both twins as an infant.	2	2	x
Life impact	The perceived or actual impact that having twins has, will, or might have on parent(s) and their family, specifically related to the impact on their life (broadly construed).	20	343	
Being isolated or experiencing isolation	Related to one or both parents being or feeling isolated or experiencing loneliness.	6	13	x
Effect or impact on family (inc. existing children)	Related to any actual or perceived impact on one or both parents' family (e.g. how having twins has impacted on existing children, on parents individually, on extended family, etc.).	10	27	x
Maternal antenatal quality of life	Related to the quality of life of the mother during the antenatal period.	18	51	x
Increase in maternal weight	Related to the mother putting on weight during pregnancy and/or the postnatal period.	4	5	
Heartburn	Related to the mother experiencing heartburn.	1	1	
Back pain	Related to the mother experiencing back pain during pregnancy.	3	3	
Healthy eating	Related to the mother eating 'healthy' food.	6	7	
Exercise	Related to the mother exercise during pregnancy (including the importance of it or not being able to exercise as much).	4	4	
Reassurance	Related to the mother needing reassurance during her the pregnancy	9	19	
Maternal postnatal quality of life	Related to the quality of life of the mother during the postnatal period.	10	21	
Coping or managing with twin(s)	Related to having enough time to do activities or necessary work, managing one's own and one's family's time, managing one's own and one's family's life, coping with twins, etc.	15	48	
Self-care, rest, or respite	Related to one or both parents wanting or needing respite, to engage in self-care, or having rest.	4	9	
Independence or reliance on others	Related to impact on or lack of independence or (increased) reliance on others.	4	6	
Effect or impact on work or career	Related to any actual or perceived impact on one or both parents' work or career (e.g. reducing working hours, resigning, changing career, taking a career break, etc.).	7	13	
Fear, protection, or over-protection	Related to being protective or over-protective of twin(s) or fearful of harm befalling twin(s).	3	4	
Bonding or relationship with twin(s)	Related to the bond the mother creates with the twin(s)	17	31	
Effect on 'normal' life (pre-twins)	Related to the difference in the mother's life compared before birthing twins	6	13	
Routine	Related to the mother's ability to get into a routine post birth	4	11	
Tiredness or exhaustion	Related to the mother experiencing tiredness or exhaustion during pregnancy	8	12	
Paternal quality of life	Related to the quality of life of the father.	5	9	x

Increased pressure on partner or spouse	Related to one parent being more reliant on the other parent or their partner or feeling more pressure (e.g. to do increased chores, to earn an income, etc.) due to having twins.	2	6	
Quality of life of one or both twins	Related to the quality of life of one or both twins as a neonate or infant.	9	12	
Happiness	Related to the happiness of the mother	4	4	
Parental sleep	Related to sleep(lesness) in general.	14	30	
Sleep of twins	Related to the sleep(lesness) of one or both twins.	3	7	x
Relationship health and impacts	Related to the impact of having twins on the mother's and partner's/spouse's relationship.	12	15	
Financial concerns	Related to the financial considerations or impacts of having twins.	20	71	x
Childcare costs	Related to childcare or caring costs.	8	11	
'Double the cost'	Related to having twins requiring purchasing two of certain items or twins involving' double the cost' of a singleton pregnancy.	5	6	
General financial worries or pressure	Related to general the financial worries or pressure of having twins (compared to a singleton pregnancy).	7	15	
General increased costs	Related to the general increased costs of having twins (compared to a singleton pregnancy).	7	11	
Housing or space concerns	Related to housing or space concerns, such as needing more space, requiring two separate rooms, needing to move house, etc.	6	8	
Material costs (e.g. new car, new equipment)	Related to requiring purchasing new items or equipment as a result of having twins, such as requiring a new car or new equipment.	6	9	
Child support payments	Related to the increased child support payments because of the twin(s)	1	1	
Neonatal separation from (non-twin) siblings	Related to either parent being separated from one or both twins.	3	3	x
Maternal	Related to the mother of the twins.	18	89	
Antenatal hospitalisation	Related to the mother being admitted into hospital antenatally.	4	6	
Antenatal blood loss or haemorrhage	Related to blood loss or haemorrhage of the mother in the antenatal period.	4	6	
Post-partum blood loss or haemorrhage	Related to blood loss or haemorrhage of the mother during or after delivery (in the post-partum period).	4	6	
General maternal health	Related to the mother being 'healthy'.	16	42	
High blood pressure	Related to increased blood pressure of the mother (hypertension).	4	4	
Pre-eclampsia	Related to pre-eclampsia.	3	3	
Hysterectomy	Related to the mother having a hysterectomy.	1	1	
Maternal incontinence or frequent urination	Related to maternal incontinence or frequent urination.	2	2	
Maternal infection	Related to maternal infection.	2	2	
Maternal mental health	Related to maternal mental health and wellbeing.	18	79	
Anxiety	Related to general anxiety of the mother.	9	23	
Depression	Related to depression in general, as perceived or diagnosed.	9	13	
Postnatal depression	Related to post-natal depression (either as perceived or clinically diagnosed).	8	9	
Post-traumatic stress	Related to the mother experiencing post-traumatic stress disorder (PTSD) after the birth of their twins.	1	1	
Stress	Related to general stress of the mother.	4	6	
Morning sickness or hyperemesis gravidarum	Related to severe morning sickness.	6	6	x
Postnatal maternal hospitalisation	Related to the mother having to be hospitalised after delivery.	8	9	
Maternal Separation from family	Related to the mother being separated from her family (none-twins)	2	2	
Pulmonary embolism	Blood clot in the lungs of the mother	4	4	
Neonatal	Related to one or both twins as a neonate.	20	165	
Admission to neonatal care (inc. NICU)	Related to one or both twins being admitted to the neonatal intensive care unit (NICU) or other care.	18	46	
Neonatal separation from parents		11	14	
Neonatal infection	Related to neonatal infection.	2	3	
Neonatal length of hospitalisation	The length of time one or both twins are admitted to hospital.	6	9	
Neonatal lung development	Related to the lung development of one or both twins, including requiring respiratory support after birth or the mother requiring steroids during pregnancy.	6	8	
Birthweight	Related to one or both twins being born with a 'good' weight for their gestation.	7	10	
General neonatal health	Related to the twins being 'healthy' after birth.	15	32	
Jaundice	Related to one or both twins having jaundice.	1	2	
Increased neonatal outpatient visits	Related to attending as an outpatient for treatment or investigation relating to twin(s).	2	2	x
Neonatal weight loss	Related to neonatal loss of weight (especially exceeding 10% of birthweight).	3	5	x
Twin(s) feeding well	Related to the twin(s) feeding well, i.e. getting the right nutrients.	18	52	
Lactose intolerance	Related to lactose intolerance.	1	2	
Milk supply	Related to the supply of breastmilk.	4	6	
Reflux	Related to one or both twins having reflux.	1	1	
Tongue tie	Related to one of both twins having tongue tie.	2	3	
Method of feeding	Related to the method of feeding.	18	45	
Breastfeeding	Related to breastfeeding.	11	16	
Combi feeding	Related to combi feeding, e.g. changing between breastfeeding and formula feeding one or both twins.	4	6	
Expressing milk	Related to expressing breastmilk.	5	6	
Formula feeding	Related to formula feeding.	2	3	
Separation of twins	Related to twins being separated from each other.	2	2	x

3.4.4 Theme 2: Fetal Wellbeing:

Fetal wellbeing was discussed by 19 participants, referenced 96 times and 4 outcomes sat within it, one of which was developed inductively: - Fetal growth/weight (Table 5)

Most participants expressed the importance of their unborn babies' being 'healthy' and often used this terminology throughout the interview. What was meant by 'healthy' seemed to vary significantly, with some using it in a very general sense whereas others expressed specific concerns around fetal weight, fetal abnormalities and specific complications related to twin pregnancy. Participants associated these specific concerns with an increased risk of fetal mortality and morbidity which all participants wanted to reduce. Furthermore, because twin pregnancy carries a significant increased risk of neonatal mortality and morbidity participants wanted the unborn babies to be born as healthy as possible to give them the best chance of survival afterbirth.

"Because I know that if they're growing well, they're healthy, and the placenta's working, and so the other thing is that I know if they weren't growing well that I would have to be induced early because sometimes they're safer out than in, and you wouldn't choose to keep your baby in if you knew it wasn't growing properly but then you've also got that hard decision to deliver it early and then you've got the potential risk of having a pre-mature baby, so it's just weighing what's the risks and benefits is? And seeing, are they safer out than in? If they're growing well at least you can keep them in and you can get them as healthy as possible before they're born" (Participant 17).

Participants used fetal weight as a marker of fetal health and therefore placed a great deal of emphasis around this. They were aware that irregularities in the babies' weight could potentially be caused by complications with the placenta and result in preterm birth (PTB), something that participants wanted to avoid due to the increased risk of mortality and morbidity. Participants described each scan as a milestone and often used the fetal weight results to help manage their expectations for expected delivery gestation especially those with MC twins, due to the added concern of TTTS.

"Knowing that they are growing well is important but it also helps to know if you can get to the 37 weeks and deliver then, or whether actually things might not go as well and they need to come early, so if they're going to be born pre-maturely then maybe it helps to adjust your expectations of things and how things are going to happen in the pregnancy and the delivery" (Participant 26).

The detection and management of fetal abnormalities was discussed by several participants but views in this area greatly differed. For some, because of the increased risk of miscarriage during Amniocentesis, detection wasn't important because they felt it wouldn't change their management of the pregnancy regardless of the outcome. Others voiced that whilst detection wouldn't change their management of the pregnancy, it was important because it would allow mental preparation for a child with abnormalities if the result was positive. However, other participants felt detection was important because they would potentially terminate the pregnancy, depending on the severity of the abnormality.

"It depends on the extent of the disability because say if they had a severe heart condition or a really severe condition that they don't think they will survive out of the womb. Then maybe it would be different, but a disability like Down syndrome or Edward's syndrome, stuff like that, people can live a happy life with Down Syndrome and their experience is just different" (Participant 13).

3.4.5 Theme 3: Birth.

The theme of Birth was discussed by all participants, referenced 128 times and 6 outcomes sat within it, two of which were developed inductively: - Recovery from birth and Skin-to-skin at birth (Table 5).

A great deal of emphasis was placed on the gestation at birth and not wanting to birth prematurely. Participants were aware that PTB was highly likely and expressed a desire to birth as close to 37 weeks gestation as possible as this is what is classed as full term. They associated PTB with increased risk of neonatal complications, Neonatal Unit (NNU) admission, the requirement of mechanical support such as ventilation and long-term disabilities such as neurodevelopmental impairment. In turn, they were concerned that prematurity resulting in NNU admission could affect their own mental health and may also delay bonding if they were not able to have skin-to-skin at birth or if the twin(s) were admitted for an extensive period. Therefore, PTB was only important to them because of the potential undesirable consequences.

"If they come early then it's going affect my mental health" (Participant 18).

“They said the initial bonding stage is straight after birth, you know skin-to-skin contact, but I feel like if they needed care straight away when they are born and they’re taken away from you straight away, and then bonding can't happen until a later date so I'd be worried. What if they don't know who I am? You know what if they don’t recognise me? Silly things like that because I know the skin-to-skin contact is really important” (Participant 10).

Conversely, mode of birth was discussed by all participants, but the preferred mode of birth was varied. In fact, most participants didn’t’ have a preference, they simply wanted whichever birth they had been advised was the safest option for the twin(s).

“I wasn’t really worried about me, in terms of having the c-section or a vaginal birth. I just wanted the baby to be safe. It didn’t both me either way what delivery I had” (Participant 14).

However, participants explained that due to the increased risk at birth twin pregnancy had caused them to change their preferred mode of birth. They advised that mode of birth was no longer a priority because the safety of their twin(s) superseded it. Likewise, those that expressed a desire to birth vaginally, explained that they would consent to an alternative mode of birth immediately for the wellbeing of the twin(s), but this would however upset them.

“So, I would just want to do the gas and air and just naturally let it take its course. But I do understand as well there are times where your birth plan won't be your

birth plan and other precautions do have to take place. I don't think I would be happy about it but they're the professionals and I feel safe in their hands. If it has to happen, I would allow it to happen. I think I would be upset but I would allow it to happen" (Participant 10).

Even though their twin(s) survival and health was paramount, some participants believed that they would still feel a sense of failure if their body hadn't allowed them to birth vaginally as they believed this is what you are meant to do as a woman but instead their bodies have potentially caused harm.

"That's how we are supposed to do it. We're supposed to naturally push our own babies out. So, I feel if I couldn't do that, it's that sense of failure again I suppose and also I know that a stressful birth can be stressful on the babies as well, so because I can't do things that I am supposed to am I causing harm to the babies during my birth" (Participant 10).

Participants that were postnatal saw positives from the different birth options because it gave them a sense of empowerment being able to choose what was best for their babies. Likewise, some participants felt that birthing by elective c-section provided them with a feeling of control, in a pregnancy that at times felt uncontrollable.

"I felt a sense of empowerment being able to make that decision for the babies to ensure they're safe" (Participant 26).

Although birth preference was varied, one area that was important to most participants was optimal recovery after birth. Participants expressed that, although their priority was a safe birth, this increased their likelihood of birthing by C-section and so, they felt anxious about the detrimental effects it would have on their recovery. Participants felt worried that they were going to find it extremely difficult to care for two babies especially if they already had children and because of this, was the main reason why some participants had opted for vaginal birth. Participants were particularly apprehensive about increased pain, immobility, recovery time and not being able to drive which meant they will need to rely on others which diminishes their independence.

"I think it's more about my ability to be able to care for them afterwards. I feel like if I'm in pain or not able to move as freely that's going to make it more challenging in a time where you don't want to be challenged. You're already trying to deal with a new situation, and you want to feel like yourself … It's more about caring for them, my ability to be able to move and be able to feel like myself … now I just have to sit down and feel less independence and be reliant on other people to do that. It's not really what want to kind of feel like" (Participant 12).

3.4.6 Theme 4: Maternal Wellbeing

The theme of Maternal Wellbeing was discussed by all participants, referenced 89 times and 12 outcomes sat within it, of which one was developed inductively: - Morning sickness/ Hyperemesis Gravidarum (Table 5).

Women advised that morning sickness was an undesirable outcome because of how negatively it affected them during their pregnancy. Mothers felt that the severe sickness hindered their ability to mentally prepare for the birth of the twin (s) and were only able to do so once the sickness had subsided. Those that experienced morning sickness described a sense of guilt in several areas in their life due to the exhaustion it caused. For instance, some felt guilt towards their family and current children as they were not able to complete their normal household chores or care for their current children as they normally would. Others felt guilt towards the unborn twin(s) because they were not able to eat nutritional food and was therefore in some way harming them. Lastly, others felt guilt within their career, because they were not able to perform as well or support their colleagues as they did previously which was heightened because their workplace were not aware they were pregnant. There appeared to be constant moral battle between doing what they thought was best for themselves, doing what they thought was best for the unborn twin(s) and doing what they thought was best for others i.e. family/ career.

“I was always quite healthy, plant-based diet and then I thought I was definitely going to continue that in pregnancy, if anything I would be better and only eat amazing foods and carry on exercising, but I’ve literally just been eating cracker and silly sweets. I just felt so guilty because I felt like I wasn’t giving them the best start“ (Participant 17).

"I think because I hadn't really told anyone, so I was still trying to work full time. I found that really tough, and then I started to feel a bit guilty because things at work were slipping... I felt like I wasn't really supporting my colleagues properly. It was a double edge sword, I either felt guilty that I wasn't working properly or if I was trying to work, I felt guilty that I wasn't resting and that I was pushing myself to much" (Participant 19).

Some participants expressed concerns about specific maternal complications such as PE, Pulmonary Embolism, infection, and haemorrhage. However, the emphasis was placed on fetal wellbeing rather than their own, for instance, mothers advised that they would not want to develop conditions such as PE because of the increased risk of PTB. Likewise, others were concerned about haemorrhaging or infection because it would impact on their ability to care for the twin(s) postnatally due to the increased recovery time. Thus, mothers often disregarded their own safety as the safety of the twin(s) was paramount.

"I do have those worries, but it's not really worries about myself if that makes sense, it's more about how is this going to impact on my ability to be able to look after them? It always centres around that as opposed to what I feel about myself if that makes sense" (Participant 07).

Participant fathers viewed this differently, as they believed maternal wellbeing was of equal importance to the twin(s). Instead, fathers expressed that it would be extremely upsetting if either of the twin(s) or the mother suffered complications that affected their wellbeing.

"They are all entwined together, healthy children and healthy wife. There is no great hierarchy because a failure of any of those outcomes would have been extremely sad…They're the only 3 things I cared about. I didn't massively care about one more than the other". (Participant 27).

3.4.7 Theme 5: Neonatal Wellbeing

The theme Neonatal Wellbeing was discussed by all participants, referenced 165 times and 11 outcomes sat within it, 3 of which were developed inductively: - Increased neonatal outpatient visits, Neonatal weight loss and separation of the twins (Table 5).

Some participants described specific conditions which they would not want the twin(s) to be affected by as they knew they were an indicator of their heath, such as Jaundice, infection, low birthweight, and the need to respiratory support. However, most participants used NNU admission as an indicator of their health rather than a specific condition. Admission into the NNU was an undesirable outcome for three reasons; firstly because it signified the babies were unwell which could potentially result in long-term problems and reduce their quality of life; secondly because the NNU environment was frightening to the parents due to the unfamiliar noises and neonatal invasive equipment i.e. intubation equipment or intravenous cannula's etc; and lastly because NNU admission resulted in neonatal separation from the mother or separation of the twins.

"We'd like to avoid anything like that, but I would hope that as a result of that, that eventually they'll recover and come out and it's not a long-term issue and that's

important just because I want them to have the quality of life as they're getting older as well not having to be dependent on medical intervention or throughout their life" (Participant 07).

However, participants also knew NNU admission was very likely due to the increased risk of PTB so were accepting of this. This therefore led participants to focus on the length of neonatal hospitalisation with many voicing that it was important they were not admitted for a prolonged length of time, although what they meant by 'prolonged' was not quantified.

"Just the idea of them having to be in a special baby unit for weeks and weeks and weeks on end because for me as soon as I had my first son I just wanted to get him home so we could bond with him and get to know him as soon as possible. Obviously if you've got premature babies that is a little bit more difficult if they are in hospital". (Participant 01)

Those that were mothers felt that prolonged NNU admission would delay their ability to bond with their twin(s) and cause a degree of separation anxiety or mental health problems, especially if they were discharged from hospital whilst the twin(s) remained inpatients. This was because, they felt their role as the mother was removed as they were not the primary carer. Likewise, one participant described being concerned that prolonged NNU admission would further hinder the bonding process that was already going to be difficult because of having twins.

“You don’t have the same bonding with your baby because you’re not doing its daily care. You’re just like a visitor. You’re just going in and popping in and having a little cuddle and saying hello and going. You’re not the babies’ primary carer you’re not its mother. So that would have been hard... having to be discharged from hospital and leaving the hospital without your babies must be a really hard thing. I just think you might not bond with your babies and especially because I found twin pregnancy hard. You think there could be bonding problems anyway and if you were separated from your babies that might make it even worse” (Participant 17).

This was supported by one mother that had experienced prolonged NNU admission of her twins after birth who felt that bonding was delayed due to the NNU admission as she only started to bond with her twins after they were discharged and were a few months old.

“I would say it was a couple of months after they were born that I thought, I am actually bonding with them now. But I didn’t feel that I’d bonded with them for a long time actually” (Participant 26).

Method of feeding was discussed by 18 participants but with mixed views. Some participants felt breastfeeding was important to them because it would increase their bond with the twin(s) and reduce their workload i.e. preparing and sterilise bottles, reduce the financial impact i.e. buying formula and enable them to leave the house easily as they wouldn’t need to consider taking multiple bottles with them. However, they were aware that this could potentially cause further sleep deprivation as they would be the sole ‘feeder’ which could ultimately affect their mental health.

“Breastfeeding is a good outcome. I think it’s really good for bonding. But I also think it’s easier personally for me. You haven’t got bottles to sterilise. You haven’t got to preparation. You haven’t got to think about it because you can go out the house and it doesn’t matter how long you’re out for your boobs are always there and you can always feed the baby where when you’re bottle feeding you’ve got to plan, how many hours you’re going to be out the house for, and how many bottles I need. You’ve got to think about the sterilisation, the cleaning, and it’s just easier to just breastfeed although it’s more time consuming and the emphasis is put on you as a mother” (Participant 17).

Others advised that breastfeeding was important initially, however this changed after discovering they were pregnant with twins and less emphasis was placed on their preferred method of feeding but instead on their ability to be able to manage feeding two babies and reduce their risk of readmission due to weight loss.

“Breastfeeding was always on my agenda. I was always adamant that I knew that’s what I wanted to do. But with having twins, I feel like I’m going struggle a bit more because I think breastfeeding two babies, they eat more, so for me it wasn’t a better option. So, I think bottle feeding would be a better option for me with the twins”. (Participants 13).

“The best outcome in relation to feeding would be not needing to go back into hospital” (Participant 27).

3.4.8 Theme 6: Infant Wellbeing

The theme of Infant Wellbeing was discussed by 16 participants, referenced 36 times and 4 outcomes sit within it, one of which was developed inductively: Increased care or hospital appointments (Table 5).

The outcomes within this theme are long-term outcomes as they focused on the twin(s) when they are older. The main emphasis was placed on the infants' neurodevelopmental function as participants were aware of the increased risk of neurodevelopmental impairment if they were born prematurely and often used the term 'disability' when describing this. Participants expressed that having a child with neurodevelopmental impairment was undesirable as they felt it would reduce their own quality of life because they would need to provide life-long care which could also affect other areas of their life such as their career. In addition, participants felt that it would also reduce the quality of life of the affected twin(s) which would not be kind.

"The earlier they're born the more health problems they might have which could affect everything, it could affect your future as a parent. If you've got a child that's disabled, your career's gone because you won't be able to work anymore as well. Having to look after that child is important for the future mainly" (Participant 18).

"I think I've always thought I wouldn't like to bring a child into the world if they couldn't fulfil their life. I don't think it's very nice. I wouldn't really like to have a child in the world that couldn't look after themselves physically or they were needed 24/7 care I don't think it will be nice to live at all". (Participant 19).

3.4.9 Theme 7: Life impact

The theme Life impact was discussed by 20 participants, referenced 343 times and 11 outcomes sit within it, 7 of which were developed inductively: - being isolated or experiencing isolation, effect or impact on family, maternal antenatal quality of life, paternal quality of life, sleep of twins, financial concerns, neonatal separation from (non-twin) siblings (Table 5).

Participants advised that the outcomes within this theme were not the most important to them initially because the mothers and twins' survival and health were priority. However, once their survival and health were deemed okay their priority shifted towards the impact of caring for twins would have on their quality of life and the possible long-term effects. Participants described feeling concerned out their emotional, physical, and practical ability to care for two children not only as newborns but also later in life.

Lack of sleep during the newborn phase was discussed by 14 participants and worries tended to focus on the negative effects it could have on parental mental health, relationship with their partner, and ability to care for the twin(s). Participants expressed that they often have low mood when sleep deprived and didn't want this to progress into Depression or Anxiety. Likewise, they felt that this could put strain onto their relationship with their partner and also hinder their ability to perform day to day activities. The effects of sleep deprivation were even more of a concern in those that already had children as they didn't want it to affect their relationship with their other children.

“I think when you’ve not had enough sleep, it’s really hard to function some days. Just on basic level. I think it’s important for mental health that you’re resting. I think it’s important for my other children that I am getting enough sleep so that I’m not crabby and grumpy with them” (Participant 16).

“I have been diagnosed in the past with depression and anxiety so it's a case of, if I don't get enough sleep this is going to arise” (Participant 10).

Participants were also worried about the massive financial stain having twins had put them under. They described struggling to cope with the increased financial needs as many needed to buy a larger car and/ or home to accommodate a larger family, as well as expensive twin specific items such as double pushchairs. They were also worried about the long-term financial pressures as many felt they couldn’t afford the increased childcare costs and advised it was unlikely the mother could return to work fully until the children were much older. Because of this, those that were mothers were particularly worried about the increased pressure being placed on the father and how this might affect them, as well as, how it will affect their own independence as they will need to rely on others for money which could lead to feelings of isolation, increased anxiety, and mental health issues.

“I think I probably will have to give up work for a while, but its' the pressure that I am putting my husband under financially because he's going to be the only one that's earning. I've always earned my own money and I am quite independent in that sense, so I suppose it’s just making myself a little bit more isolated and being less

independent than I was before and relying on somebody else to make sure we've got enough for everything" (Participant 01).

"I think I've been a lot more anxious because when you have twins you can't see your friends as easily and on top of that our living circumstances aren't great. We live in a small basement flat and so getting out isn't easy and I did feel like I'd spent all day indoors which is actually quite draining, and you don't have as much contact with people compared to people with single pregnancies. They're going off to do this and that, and this class and that class, and you can't necessarily manage that so it's different. You do feel a bit more isolated" (Participant 09).

The feeling of isolation seemed to be a major worry for many of the women which wasn't only due to financial concerns but also due to the practicalities of being able to leave the house on their own with two children and complete day-to-day activities. They were concerned about feeling lonely or forgotten about and often felt overwhelmed with how they were going to cope with caring for two babies on their own which could ultimately result in postnatal depression.

"Sometimes it's not even about the money. It's about having someone there, I want to feel like I'm part of the world again if that makes sense? Feel like I'm not forgotten about. Postnatal depression is serious, and I feel like with twins it's even more serious because you've not just got one crying baby. You've got two crying babies and doing that on your own when everyone's at work and in their normal life and you can't do nothing and feel isolated. Obviously, most of me is excited and looking

forward to it but in the back of my head I do think sometimes Oh. I wonder if I'm going to get postnatal depression" (Participant 18).

3.5 Discussion

The main aim of this study was to identify outcomes important to patients and their partners. The outcomes generated will be combined with outcomes identified in the systematic review of twin pregnancy research (Chapter 2) (100) to form a comprehensive outcome inventory (Chapter 4). The next stage in the COS development would be to use the Modified Delphi Method to present the comprehensive outcome inventory to three international twin pregnancy expert groups (Obstetricians/ midwives, Neonatologists/ neonatal nurses and Patients with a lived experience of twin pregnancy) and consider the outcomes for inclusion in a COS for twin pregnancy.

The COMET initiative advises the use of multiple methods to source outcomes and endorses the use of qualitative research as it minimises the risk of omitting potentially important outcomes (9). The importance of this has been highlighted in previous COS developments when Core Outcome Set's produced without qualitative research have neglected the views of stakeholders (93–95). Nevertheless, variation remains in how COS developers choose to identify outcomes with most COS developers choosing not to undertake qualitative research (19,92).

Neither of the two Core Outcome Set's in multiple pregnancy conditions previously published undertook Qualitative research during the develop of their COS and relied solely on the outcomes generated from the systematic review (41,71). Whilst many

COS developers have chosen this method (19), outcome identification may not be exhaustive and because of this, outcomes important to patients may have been missed (9). It is therefore crucial a COS, that can be utilised for research in all twin pregnancy types and has considered a patient voice is developed.

The Outcomes and Themes generated in this research highlights the extensive psychological, social, and physiological impact twin pregnancy has on mothers and/ or partners, some of which may last a lifetime, yet most twin pregnancy RCT's has focused on short-term physiological outcomes (100). Whilst patients have confirmed that many of these short-term physiological outcomes are of equal importance, it is not a true representation of the wide-ranging priorities of patients and their partners. Thus, this research highlights the differences between researchers and patients' priorities and one area that was profoundly different was the theme of Life Impact. Outcomes generated within this theme are long-term, account for 19% of all outcomes generated in this study and was the most referenced theme. This emphasises the importance of Life Impact outcomes to patients, yet the systematic review discussed in chapter 2 shown that long-term outcomes were poorly reported by RCT's, only reported after 2001, and to date only three studies have followed-up their participants for longer than 2 years (100). In addition to this, this research also suggests that the long-term outcomes that have been reported in RCT's may not be those that patients deem a priority as 44% of all the outcomes created inductively, and are therefore potentially new outcomes, sit within the Life Impact theme. Furthermore, 7 of the 11 Life Impact outcomes were generated inductively which suggests that long-term outcomes reported in previous research are not aligned to patients' long-term priorities. Conversely, when focusing on short-term outcomes,

this study suggests that researcher and patient priorities are somewhat comparable, as the systematic review shown that the three most reported domains were: Neonatal (reported in 77% of trials), Delivery (reported in 70% of trials) and Survival (reported in 67% of trials) (100). This shows significant similarities to those deemed important by patients as the only four themes discussed by all participants and the highest referenced, were: Neonatal Wellbeing, Birth, Death and Survival, and Life impact. Additionally, 68% of all outcomes generated from patient interviews were deductively created, meaning they had already been identified during the systematic review. However, all participants expressed that the theme of Death and Survival was their top priority, yet it has only been reported in 67% of RCT's (100). Likewise, although the domain 'Delivery' was reported in 70% of trials (100), all failed to report the outcome 'Recovery after birth' which was inductively created during patient interviews and overwhelming reported as one of the most important outcomes within the theme of Birth, yet it has been missed from all previous research. This therefore demonstrates that twin pregnancy research does not always reflect patient priorities. Furthermore, the noticeable differences in outcome prioritisation between researchers and patients as well as the number of inductive outcomes generated in this study highlights the importance of using a mixed-method approach when developing a COS.

3.6 Strengths and Weaknesses

To the author's knowledge, this is the first qualitative study exploring patients and partners' perspectives, experience and priorities of twin pregnancy and has led to an in-depth understanding of why certain outcomes were important to patients. The methodology for this study was developed *a priori* in a study protocol (Appendix 1)

that underwent robust peer-review. Due to the Covid- 19 Pandemic, interviews were held via telephone which meant that we were able to take a wider geographical purposive and snowball sampling approach, and potentially increase generalisability. However, all participants were UK based and required to speak and understand English. The lack of internationally based participants is a potential limitation of the study because participants from outside the UK may report different outcome priorities, especially those in low- or middle-income countries. This is because their cultural differences may shape their expectations and priorities of twin pregnancy in some way, however to date there has been no COS developers that have established a difference (19). Nevertheless, 80% of the worlds twin population birth in Africa (1) so it is essential the COS for twin pregnancy is internationally relevant including those in low- and middle-income counties as it could potentially make the greatest difference there.

To mitigate this, the RCT's eligible for the systematic review (Chapter 2) were not limited to the UK and so the outcomes gathered were from international twin pregnancy RCT's which will reflect the priorities of the researchers in that area. Likewise, the next stage planned for this research will be an international Modified Delphi Survey, whereby experts, including patients with a lived experience of twin pregnancy, will have the opportunity to suggest any important outcomes they feel have been missed. Furthermore, the participants in this study had a broad range of characteristics representative of twin pregnancy, including one participant that had undergone Selective Termination which enabled deep and rich understanding of single fetal death, which is often a taboo subject. Likewise, the participant twin type

population in this study was 70% DC and 30% MC which is representative of the general UK twin type population (26).

This study also highlights the difficulties faced when using medical terminology with patients. Participants often didn't understand the term 'outcome' or specific medical terminology and often used very general language such as 'healthy'. This study enabled participants to express and explain what they meant by these terms, which will ensure the outcomes taken through to the Delphi Survey are correctly contextualised. Likewise, the language used by participants will be utilised to create the Delphi Survey outcome lay definitions and ensure patient understanding during the next stage of this research.

Interviews and interview analysis were completed by two independent researchers, however one of the researchers was a medical professional with experience of twin pregnancy and may have resulted in a degree of observer bias. Additionally, participants were aware of the interviewers' background and potentially modified their responses. To mitigate this potential limitation, the second interviewer was not a twin pregnancy expert, and both researchers made every effect to follow the interview guide that was developed *a priori*. Ongoing regular discussions also took place with the project steering group and clear-consensus lead decisions were made to minimise this risk. Furthermore, interviews lasted between 27 and 63 minutes which shows that participants were given ample time express themselves.

Recruitment into this study stopped when no new outcomes were identified, however there is an ongoing debate whether 'data saturation' can ever be met as there is no

true way of knowing if further outcomes would have been identified (103). However, this will be mitigated during the planned Delphi Survey when patients can suggest important outcomes they feel may have been missed.

A further limitation of this is study, is that the interviews were held during the Covid-19 Pandemic. Thus, the obscure situation and uncertainties faced by participants could have impacted participants' priorities and may have skewed the results. Because of this, and to ensure important long-term outcomes were also represented, participants that had experienced twin pregnancy prior to the pandemic were eligible. Likewise, the outcomes collected during the systematic review (Chapter 2) will have been reported prior to the Covid-19 Pandemic. That said, no Covid-19 themes were generated during the data analysis.

3.7 Conclusion:

In summary, this study is the first of its kind and generated 57 outcomes that were important to patients with a lived experience of twin pregnancy, 16 of which are potentially new outcomes. Whilst there are similarities between researcher and patients' short-term physiological outcome priorities, there remains a degree of difference that needs to be addressed as many RCT's failed to report the most important theme to patients and did not address the majority of important long-term outcomes. Furthermore, those that were addressed did not match with those the patents reported as the most important.

3.8 Future research

These outcomes will be combined with the outcomes identified in the systematic review reported in Chapter 2 to form a comprehensive outcome inventory reported in Chapter 4. The comprehensive outcome inventory will be considered for consensus into the COS by twin pregnancy experts during an International Modified Delphi Survey.

Chapter 4:

The development of a Core Outcome Set for Twin pregnancy: An international consensus development study.

4.1 Introduction

The systematic review completed as part of this thesis and discussed in Chapter 2 (100), shows significant heterogeneity within outcome reporting in twin pregnancy RCT's and their follow up studies which has made data synthesis in this area almost impossible. This is because researchers often did not address the same outcomes as part of their research and instead reported 170 unique outcomes across 57 trials. Furthermore, many trials failed to define outcomes and those that did, utilised several different definitions and measures for the same outcome. In addition to this, the qualitative interviews undertaken with mothers and partners (Chapter 3) that has experienced twin pregnancy, suggested that outcomes selected by researchers historically, may not be those that are deemed important to patients, as outcomes that were expressed as the most important by patients i.e. death, had only been reported in 47% of trials. Likewise, there were several 'new' outcomes formed during interviews, which had not been identified during the systematic review, this suggests researchers have missed important outcomes in previous clinical trials in twin pregnancy. Furthermore, the majority of these were derived from the theme of Life Impact which was also shown to the poorly reported in the systematic review. This therefore shows that researchers may not be collecting and reporting outcomes that are important to patients which means twin pregnancy research is not relevant and therefore will not actually improve outcomes.

These two pieces of research highlight the urgent need to develop the COS for twin pregnancy to reduce inconsistencies in trial reporting. The COS will standardise outcome collection and reporting, including outcome definitions and measurements, across all future trials in twin pregnancy. This in turn will allow studies to compare

data and reduce research waste whilst ensuring the research remains relevant to patients which will ultimately improve outcome for those whom the research is aiming to benefit.

This study is the second and final stage of the initial development of a twin pregnancy COS as recommended by COMET (9). The outcomes identified during stage one of this research will be combined to form a comprehensive outcome inventory which will be considered for consensus into the twin pregnancy COS by key stakeholders during a Modified Delphi Survey.

4.2 Methods

This study was prospectively registered with COMET under the registration number 844 (http://www.comet-initiative.org). The development of the COS was directed by recommendations from The COMET Handbook (9), the Core Outcome Set-STAndards for Development (104), and the OMERACT handbook (105). Modifications were made to align the recommendations to the scope of this research and a protocol was developed priori (appendix 1). This study is the second stage of the COS development.

4.2.1 Comprehensive Outcome Inventory

Outcomes identified from the systematic review and interviews were combined and inputted into Microsoft EXCEL© along with the following data for each outcome; The number of clinical trials that reported the outcome, and the number of times the outcome had been discussed by participants and percentages were calculated. To avoid replication, the project steering group reviewed all outcomes and grouped

those with the same sematic meaning into unique outcomes and agreement was sought regarding outcome classification in accordance with OMERACT2.0 framework (105). To reduce the risk of response fatigue (106) and ensure consensus of the comprehensive outcome inventory was manageable, any outcomes that were only identified in the systematic review and reported in ≤5% of clinical trials or any outcomes that were only identified in the interviews and discussed by ≤5% of participants were removed from the comprehensive outcome inventory.

4.2.2 Modified Delphi Survey

The method for consensus was a two round online Modified Delphi Survey. This is considered gold standard for COS development as it facilitates a means of international consensus between expert stakeholders by using a series of sequential questionnaires to gather opinion (9). It has been utilised to development many COS, not only in women's health, but across a number of different specialities (89,107–110). The DelphiManager Software from the University of Liverpool which is established in COS research (89,91) was used to design and manage the Modified Delphi Survey.

4.2.3 Key Stakeholders

Targeted expert stakeholders were invited to take part in the Delphi Survey via national and international organisations including Twins Trust, British Maternal and Fetal Medicine Society (BMFMS) and The International Society of Twin Studies (ISTS), as well as national and international bodies for Obstetrics and Neonatology, such as the Royal College of Obstetricians and Gynaecologists (RCOG), American Congress of Obstetricians (ACOG) and Gynaecologists Federation of Obstetric and

Gynaecological Societies of India (FOGSI) and Gynaecologists and British Association of Perinatal Medicine (BAPM). In addition, adverts were placed on twin national and international social media groups promoting the survey to patient representatives. To increase diversity, snowball sampling was implemented, and participants were encouraged to share the study details with others they felt were eligible. The eligible participant population reflected a variety of twin expert stakeholders and were grouped into three panels depending on their area of expertise: -

1) Maternity employee's – Registered Obstetricians and Midwives

2) Neonatal Employee's – Registered Neonatologists, Paediatricians and Neonatal Nurse's

3) Parents with a lived experience of twin pregnancy both past (within the last 10 years) and present

Due to the high levels of attrition observed with the Delphi Method (111) a minimum target of 20 participants in each panel was set, however, as the Delphi method does not depend on statistical power we aimed to recruit as many as possible into each panel.

4.2.4 Delphi rounds

Willing experts were required to register online, and Delphi survey instructions were emailed to them. Each expert was given a unique identifier to anonymise their response and asked to complete a short demographic questionnaire. Supplementary lay descriptions based off the outcome definitions in clinical trial, as well as the language used to describe outcomes in the interviews were provided to aid understanding. To ensure ease of completion, the project steering group piloted the

demographic questionnaire and Delphi survey and sought feedback to make relevant adjustments. Each Delphi round was open for 4 weeks and participants received weekly emails reminding them to complete the survey.

4.2.4.1 Round one

During round one, experts scored outcomes using a grading system recommended by COMET (9) and devised by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) which has been widely employed for COS development (112) . This system requires experts to score each outcome on a nine-point Likert scale, scoring them between 1 (limited importance in decision making) and 9 (Critical in decision making). An option to select 'unable to score' was available if an expert felt they did not have the capability to score a particular outcome. Outcomes were presented to experts in a randomised order depending on domain category and at the end of the round, experts had the opportunity to add important outcomes they felt had been missed. Once the round had closed, scores were aggregated for each outcome within individual expert panels and percentages for each scoring (1 to 9) were calculated using Microsoft EXCEL©. The project steering group discussed all additional outcomes and those deemed relevant and were not already present were added into the inventory for round two. Experts that had failed to score all outcomes in round one was not invited to take part in round two.

4.2.4.2 Round two

During round two, experts were asked to rescore each outcome on the inventory plus the additional outcomes suggested in round one. However, this time experts

were able to view their previous grading, plus the grading of each expert panel. At the end of the round, scores were aggregated for each outcome within each expert panel and percentages were calculated for the following subdivisions of the Likert Scale Grading; - 1-3 of limited importance to decision making, 4-6 of some importance to decision making, 7-9 critical for decision making. The following criteria for consensus in/ out were applied which is supported by the COMET initiative (9) and OMERACT (105).

- Consensus in - ≥70% of all experts graded the outcome between 7-9 and ≤15% graded it between 1-3
- Consensus out - ≥70% of experts graded the outcome between 1-3 and ≤15% graded it between 7-9
- Dissensus - ≥70% of experts in one or more expert groups scored the outcome between 7-9 and less than ≤15% graded it between 1-3

Those that met ‘consensus in’ were planned to be taken through to the consensus meeting and those that met ‘dissensus’ would be discussed (105). All other results would be excluded from the consensus meeting.

4.3 Results

4.3.1 Comprehensive Outcome inventory.

Figure 6 shows the number of outcomes gathered during each phase of outcome identification and Delphi. 186 outcomes were identified during the systematic review and patient interviews, of these 117 were excluded for the following reasons: 53 outcomes were identified from the systematic review only and reported in ≤5% of trials, 49 outcomes had the same semantic meaning as another and 15 were

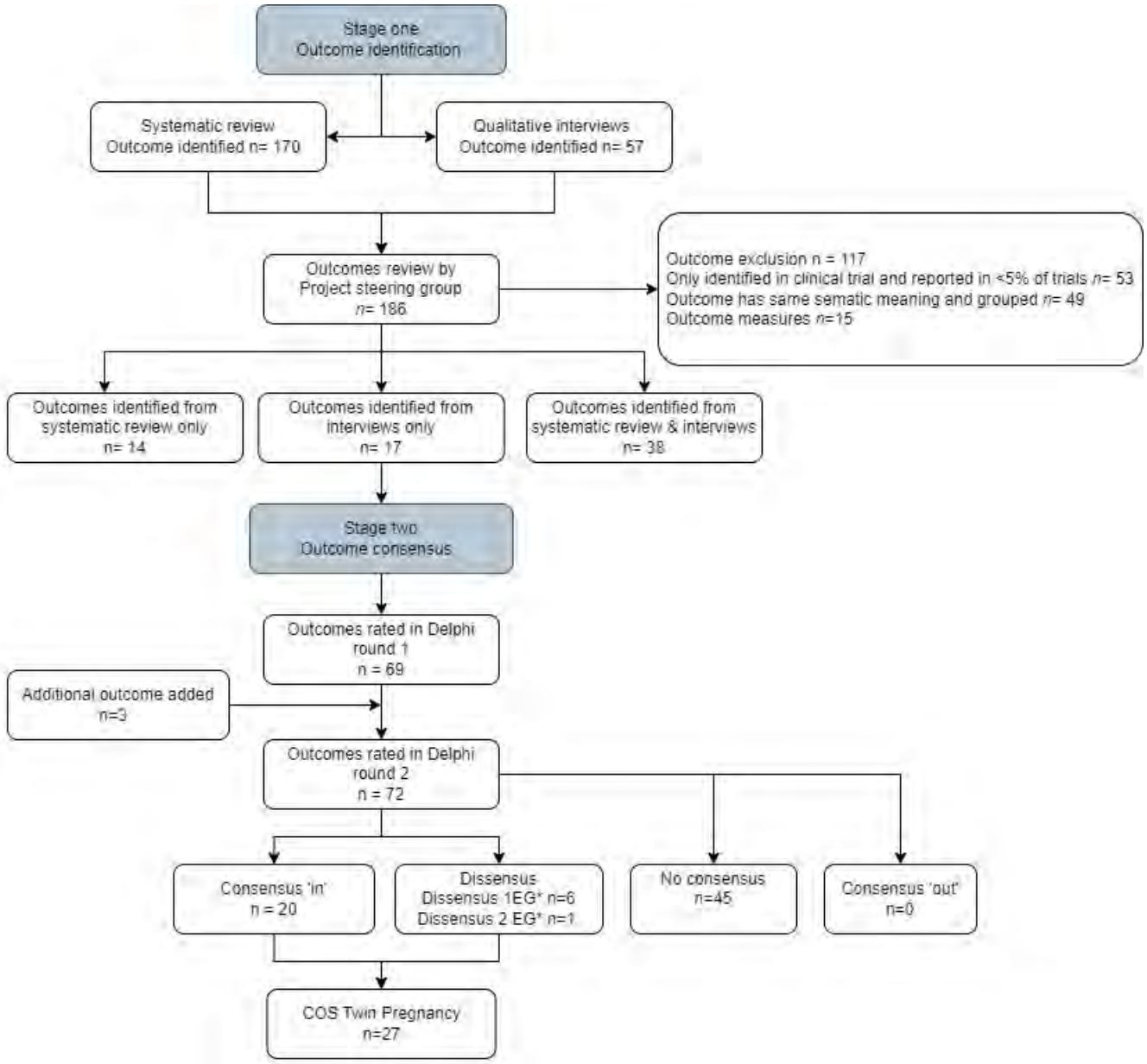
outcome measures. Appendix 9 details the full list of outcomes gather during outcome identification and how each outcome was scored and combined.

The comprehensive outcome inventory was formed of 69 unique outcomes of which, 14 were identified from the systematic review, 18 were identified from the patient interviews and 37 were identified from both sources. This outcome inventory was taken through to the Delphi Survey.

4.3.2 Delphi Survey

Recruitment into the Delphi Survey commenced on the 1st May 2021. Table 6 shows the participant demographics by Delphi round. 176 participants registered to take part in the Delphi survey from 8 countries with the majority being from the UK (82%). 40 participants were Maternity employee's, the majority of which had more than 11 years of experience (50%), 28 were Neonatal employee's, the majority of which had more than 11 years of experience (70%) and 108 participants were parents with a live experience of twin pregnancy, the majority of which were mothers (92%) or had experienced twin pregnancy in the last 2 years (58%).

Figure 6: Outcomes gathered during each phase of outcome identification and the Delphi process.



*1EG = >70% of 1 expert group scored the outcome between 7-9, 2EG = >70% of 2 expert groups scored the outcome between 7-9

Table 6: The Modified Delphi Survey Participants Characteristics

Participants Characteristics	Round 1 *n*=	Round 2 *n*=
Expert stakeholder group	176	47
Obstetricians, Midwives	40	19
Qualified 0 -5 years	7	3
Qualified 5 - 11 years	13	6
Qualified 11 + years	20	10
Neonatologists, Paediatricians, Neonatal nurses	28	6
Qualified 0 -5 years	2	1
Qualified 5 - 11 years	6	1
Qualified 11 + years	20	4
Parents with a lived experience of twin pregnancy	108	22
Mother	99	22
Partner	9	0
Currently pregnant	16	3
Pregnant within the last 2 years	63	13
Pregnant within the last 2 - 10 years	29	6
Geographical Location		
Australia	2	0
Austria	1	0
Canada	4	1
Egypt	2	1
Ireland	1	1
Netherlands	4	2
United Kingdom	145	38
Unites States of America	17	4

The first round of the Delphi Survey commenced on the 10 June 2021 and was open for 4 weeks. Table 7 shows outcome scoring by Delphi round. There were 7 outcomes in the Area of ‘Death’, 5 of which were scored as critical (between 7-9 on the Likert scale) by all three expert panels, these were: ‘Intrauterine Death’, ‘Intrapartum Stillbirth’, ‘Neonatal Death’, ‘Perinatal and Infant Death’ and ‘Maternal Mortality’. The outcome ‘Miscarriage’ was scored as critical by two expert panels. The only outcome in this area scored between 1-6 on the Likert Scale by all thee expert panels was ‘Selective Termination’.

There were 19 outcomes in the Area of ‘Life Impact’, two of which were scored as critical by all three expert panels, these were: ‘Infant Neurodevelopmental

Impairment' and 'Neonatal and Infant Quality of Life'. One other outcome in this area was scored as critical by two expert panels and this was: 'Maternal Mental Health', all other outcomes were scored between 1-6 on Likert Scale by all expert panels.
There were 30 outcomes in the Area of Pathophysiology/ Manifestations, 6 of which were scored as critical by all three expert panels, these were: 'Complications of Monochorionic Twins', 'Fetal growth Restriction', 'Gestation at Delivery', 'Neonatal Neurological Complication', 'Neonatal Respiratory Complication' and 'Pre-term Birth'. The outcomes 'Neonatal Sepsis/ Infection' was scored as critical by two expert panels and 6 other outcomes were scored as critical by one expert panel, these were: 'Fetal Abnormality', 'Necrotizing Enterocolitis', 'Need for Neonatal Resuscitation', 'Hysterectomy resulting from Birth', 'Postpartum Haemorrhage' and 'Prolonged Rupture of Membranes'. All other outcomes were scored between 1-6 of the Likert scale by all three expert panels.
There were 12 outcomes within the area of 'Resource' none of which were scored as critical by any expert panel. However, the outcome 'Need for Neonatal Respiratory Support' was deemed critical by two exerts groups and the outcomes 'Admission to Neonatal Care' and 'Maternal Corticosteroids for Lung Maturation' were deemed as critical by one expert panel. All other outcomes in their area were scored between 1-6 on the Likert Scale by all expert panels.
All outcomes regardless of scoring were taken through to the second round of the Delphi Survey along with the three additional outcomes suggested by participants (figure 1). The 3 additional outcomes were all suggested by the parent expert panel and were: 'Satisfaction with the Level of Support from Maternity Services', 'Satisfaction with the Level of Support from Neonatal Services' and 'Impact on Future Fertility'.

Round two of the Delphi Survey commenced on the 12th August 2021, was open for 4 weeks and consisted of 72 outcomes. 47 participants took part from 6 countries (Table 6), of which 19 were Maternity employee's, 6 were Neonatal employee's and 22 were parents with a lived experience of twin pregnancy. The majority of employee experts had more than 11 years of experience and the majority of the parents' expert panel had experienced twin pregnancy in the last two years (59%) and all of them were mothers. 20 outcomes met the definition for 'consensus in' (Table ??), 10 of these were within the Fetal and Neonatal Pathophysiology domain and 6 were from Fetal, Infant and Maternal Death domain. Miscarriage, which was previously scored as critical by only two expert groups met the 'consensus in' criteria during round two which meant 6 of the 7 outcomes within this domain were classified as critical by all three expert panels. There were 6 other outcomes that did not meet the criteria for 'consensus in' during round one but did meet this criteria during round two, 5 of these were within the Fetal, Neonatal and Maternal Pathophysiology domain, these were: 'Fetal Abnormality', 'Birthweight', 'Need for Neonatal Resuscitation', 'Necrotizing Enterocolitis', 'Neonatal Infection/ Sepsis' and 'Prolonged Rupture of Membranes'. Furthermore, the outcome 'Need for Neonatal Respiratory Support' in the Resource domain also met the 'consensus in' criteria this time around. There was only one outcome that met the 'Consensus in' criteria during round 1 but did not meet this criteria during round two, this was 'Neonatal and Infant Quality of Life', however it did met the criteria for 'dissensus' and will therefore be discussed during the next phase of the research. Likewise, there were 6 other outcomes that also met the dissensus criteria and will therefore also be discussed during the next phase of the research, these were: 'Neonatal length of hospitalisation', 'Post-partum Haemorrhage', Maternal Infection/ Sepsis', 'Antenatal haemorrhage', 'Skin-to-skin at

birth', 'Maternal Mental Health'. None of the additional outcomes suggested by participants during round 1 were scored at critical by any expert group and no outcomes met the 'consensus out' criteria.

Table 7: Comprehensive Outcome Inventory and Delphi scoring on outcomes stratified by domain.

Area / Domain	Outcomes	Outcome source			Delphi outcome consensus	
		SR	Qual	Delphi	Round 1**	Round 2
Death						
	Fetal					
	Selective termination		x			
	Miscarriage	x	x		Dissensus (2 EG)*	Consensus in
	Intrauterine death or survival (inc. stillbirth)	x	x		Consensus in	Consensus in
	Intrapartum stillbirth	x	x		Consensus in	Consensus in
	Infant					
	Neonatal death	x	x		Consensus in	Consensus in
	Perinatal and infant death	x	x		Consensus in	Consensus in
	Maternal					
	Maternal mortality	x	x		Consensus in	Consensus in
Life Impact						
	Neonatal					
	Separation of twins		x			
	Infant					
	Infant Growth impairment	x	x			
	Infant Neurodevelopmental impairment/morbidity	x	x		Consensus in	Consensus in
	Neonatal or infant quality of life	x	x		Consensus in	Dissensus (1 EG)*
	Parental					
	Maternal antenatal quality of life		x			
	Being isolated or experiencing isolation		x			
	Effect or impact on family		x			
	Financial impact on family		x			
	Incontinence	x	x			
	Maternal mental health	x	x		Dissensus (2 EG)*	Dissensus (1 EG)*
	Maternal postnatal quality of life	x	x			
	Method of feeding	x	x			
	Parental sleep	x	x			
	Co-parent quality of life		x			
	Recovery from birth	x	x			
	Relationship health and impacts	x	x			
	Skin-to-skin at birth		x			Dissensus (1 EG)*
	Sleep of twins		x			
	Siblings					
	Neonatal separation from (non-twin) siblings		x			
Pathophysiology/ Manifestations						
	Fetal					
	Complications of monochorionic twins	x	x		Consensus in	Consensus in
	Fetal abnormality (Chromosomal or structural)	x	x		Dissensus (1 EG)*	Consensus in
	Fetal growth restriction	x	x		Consensus in	Consensus in
	Neonatal					
	Apgar score	x				
	Birthweight	x	x			Consensus in
	Cord PH	x				

	Gestation at delivery	x	x		Consensus in	Consensus in
	Necrotizing Enterocolitis	x			Dissensus (1 EG)*	Consensus in
	Need for neonatal resuscitation	x	x		Dissensus (1 EG)*	Consensus in
	Neonatal hypoglycaemia	x				
	Neonatal jaundice	x	x			
	Neonatal neurological complication	x	x		Consensus in	Consensus in
	Neonatal respiratory complication	x	x		Consensus in	Consensus in
	Neonatal sepsis and infection	x	x		Dissensus (2 EG)*	Consensus in
	Neonatal weight loss		x			
	Patent ductus arteriosus	x				
	ROP	x				
Maternal						
	Antenatal haemorrhage or blood loss	x	x			Dissensus (1 EG)*
	Diabetes	x				
	Haematological disturbances	x				
	Hypertensive disorders	x	x			
	Hysterectomy resulting from birth	x	x		Dissensus (1 EG)*	
	Maternal infection or sepsis	x	x			Dissensus (2 EG)*
	Mode of delivery	x	x			
	Morning sickness or hyperemesis gravidarum		x			
	Perineal trauma	x	x			
	PPH	x	x		Dissensus (1 EG)*	Dissensus (1 EG)*
	PROM	x			Dissensus (1 EG)*	Consensus in
	Pre-term labour/ birth	x	x		Consensus in	Consensus in
	Spontaneous labour/ birth	x				
	Thromboembolic event	x				
Resource						
	Need for extended infant outpatient visits		x			
	Need for extended neonatal outpatient visits		x			
	Admission to neonatal care	x	x		Dissensus (1 EG)*	
	Need for Neonatal respiratory support	x	x		Dissensus (2 EG)*	Consensus in
	Maternal antenatal hospitalisation	x	x			
	Maternal cerclage placed	x				
	Maternal corticosteroids for lung maturation	x			Dissensus (1 EG)*	
	Duration of maternal hospitalisation	x				
	Induction of labour	x				
	Neonatal length of hospitalisation	x	x			Dissensus (1 EG)*
	Postnatal hospitalisation	x				
	Need for maternal Tocolytic therapy	x				
Additional outcomes added during Delphi						
	Satisfaction with the level of support from maternity services			x		
	Satisfaction with level of support from neonatal services			x		
	Impact on future fertility/ pregnancy			x		

*1EG = ≥70% of 1 expert group scored the outcome between 7-9 and ≤15% scored it between 1-3, 2EG = ≥70% of 2 expert groups scored the outcome between 7-9 and ≤15% scored it between 1-3
**All outcomes were taken through to the 2nd round of the Delphi regardless of consensus

4.4 Discussion

This international consensus study applied validated methods involving three key stakeholder panels which included Obstetricians, Midwives, Neonatologists, Neonatal Nurses and patients with a lived experience of twin pregnancy including their partners, to develop a COS for twin pregnancy as specified in stage two of COS development methodology (9). This research will help to standardise outcome reporting in future twin pregnancy research which will improve the quality of research in this field by enabling data synthesis of individual patient data and ensure outcomes reported in trials are relevant to those it seeks to help. In turn, this will reduce research waste and ultimately improve outcomes for patients. The COS generated in this study will be finalised during a consensus meeting with twin pregnancy experts whereby the definition, measure and reporting of each outcome will be agreed and standardised.

108 patients with a lived experience of twin pregnancy, 40 maternity employee's and 28 neonatal employees from eight countries registered for the Delphi Survey and considered 72 outcomes for consensus into the COS for twin pregnancy. Twenty outcomes achieved the predefined inclusion criteria for inclusion into the COS and will therefore be taken forward to the consensus meeting, these were: Miscarriage, Intrauterine Death or Survival, Intrapartum Stillbirth, Neonatal Death, Perinatal and Infant Death, Maternal Mortality, Infant Neurodevelopmental Impairment/ Morbidity, Complications of Monochorionic Twins, Fetal Abnormality, Fetal Growth Restriction, Birthweight, Gestational at Delivery, Neonatal Necrotising Enterocolitis, Need for Neonatal Resuscitation, Neonatal Neurological Complications, Neonatal Respiratory Complications, Prolonged Rupture of Membranes, Pre-term Labour/ Birth and Need for Neonatal Respiratory Support. A further seven outcomes achieved the predefined

criteria for dissensus and will therefore be discussed at the consensus meeting and considered for inclusion in the COS, these are: Neonatal or Infant Quality of Life, Maternal Mental Health, Skin-to-skin at Birth, Antenatal Blood loss or Haemorrhage, Maternal Infection or Sepsis and Neonatal Length of Hospitalisation.

Most Core Outcome Sets, once finalised, will agree on approximately 10 core outcomes to form their COS, however the increased number of outcomes within this COS highlights the diversity and complexities of twin pregnancy research due to the need to address maternal, single and double fetal outcomes as well as different types of chorionicity and amnionicity e.g. DCDA, MCDA, MCMA. Furthermore, this systematic review discussed in Chapter 2 highlighted the use of composite outcomes, which were reported in many twin pregnancy RCT's (100). A composite outcome is when researchers combine two or more singular outcomes that encapsulate a board concept and are used to increase the power of a study. The majority of composite outcomes reported in twin pregnancy RCT's were based on neonatal health outcomes and death. This aligns with this COS as 65% of the outcomes within the COS sit within the Neonatal Pathophysiology/ Manifestations and Death domain and had formed composite outcome in a number of RCT's and may reflect why experts have considered a high number of outcomes as essential for the COS in twin pregnancy. Furthermore, some RCT's reported these outcomes in singular form and others reported them as part of a composite outcome, it is therefore essential during the final consensus meeting to determine if any of the outcomes within the twin pregnancy COS should be reported as a composite outcome.

The majority of the outcomes within the agreed COS, sit within the Death and Neonatal Pathophysiology/ Manifestations domains. This is comparable to those deemed important historically by researchers, as two of the three most reported domains within RCT's are Neonatal (reported in 77% of trials) and Survival (reported by 57% of trials). However, 27-43% of trials still failed to report these themes within their research (100). Furthermore, experts have also classified the outcomes within the Fetal Pathophysiology/ Manifestation domain as critical for inclusion into the COS, along with the long-term outcome Neonatal and Infant neurodevelopmental Impairment, yet these outcomes are also significantly underrepresented in previous RCTs with <20% of trials reporting them (100). Likewise, three most commonly reported outcomes within the twin pregnancy RCT's are Birthweight, Gestation at Delivery and Neonatal Death (100) all of which have been confirmed as critical by all three expert stakeholder panels during the Delphi Survey. Whilst this does suggest that some researchers' and patients' priorities may be aligned, massive inconsistencies remain as 50-53% of trials did not report these within their research. Furthermore, those that did report these outcomes did not define them clearly or used different outcome definitions. For instance, of the 27 trials that reported Neonatal Death, 13 studies did not define the outcome and those that did define it used 12 different outcome measures e.g. one study defined it as death before 24 hours and another study defined it as death between 2-7 days. This ultimately eliminated the ability to synthesis this data and show treatment and effect on this important outcome. Furthermore, given that many trials failed to report outcomes that have been deemed as critical for inclusion within the COS, even if a treatment had shown effect, it may not have 'improved' outcomes for patients if the outcome was not relevant to them. The COS developed in this study, is aligned to the twin

pregnancy patient priorities that were expressed during patient interviews as women and their partners expressed that the most important outcomes were death (of any sort, including the mother) closely followed by fetal and neonatal health outcomes. This strongly matches the twin pregnancy COS as 80% of outcomes sit within the themes of Death and Fetal/ Neonatal Pathophysiology. Furthermore, during interviews women often disregarded their own health because they prioritised the health of their twins. This is also represented in this COS as the only two outcomes related to the mother are prolonged rupture of membranes (PROM) and Pre-term Birth. Whilst PROM was not discussed in the interviews, Pre-term Birth was discussed extensively and prioritised highly due to the significantly increased risk of twin morbidity and mortality. In addition, patients also explained that whilst they wouldn't want their twins to be admitted onto the Neonatal Unit (NNU), they knew this was highly likely and therefore placed a great deal of emphasis on the length of time the twins were admitted onto the NNU instead. Mothers described concerns about prolonged NNU admission as they associated increased length of time with neonatal illness and believed it could delay bonding, hinder breastfeeding, and cause separation anxiety and mental health problems. The twin pregnancy COS is also aligned to this, as experts did not score NNU admission as critical, however 'Neonatal Length of Hospitalisation' has been classified as critical by the patient expert panel. Thus, although this does not meet the criteria for inclusion into the COS, it does meet the inclusion criteria for dissensus which means it will be discussed as a potential outcome during the consensus meeting. It may be that once other expert groups understand the narrative as to why this outcome is important to patients an agreement may be made to include it into the COS. Conversely, the majority of 'new' outcomes created during patient interviews were in the theme of

Life Impact. This suggests that the long-term outcomes within this theme are not only important to patients but underreported in previous twin pregnancy research, yet experts only classified one outcome within this domain as critical. However, even though patients advised that a number of long-term outcomes were important to them during interviews, they also explained that the health of twins was paramount which is supports this COS as the long-term outcome deemed as critical was Infant Neurodevelopmental Impairment/ Morbidity. Thus, going forward the use of this COS in future twin pregnancy research will ensure reported outcomes remain clinically relevant to patients. Furthermore, all but two outcomes that form this COS were identified from both the systematic review and qualitative interviews. This triangulation of outcome selection within each phase of COS development shows that the outcomes within the COS are truly those that are the most important to all key stakeholders, including researchers and clinicians.

4.5 Strength and weaknesses

The strengthens of this research lies within the rigorous research methodology followed during every stage of COS development and set out by the COMET initiative (9). The study protocol, which was developed priori and went through robust peer review, retrospectively met the standards set out by The Core Outcome Set-STAndardies Protocol Items (COS-STAP) which were published after the development of the protocol utilised within this research (113). This study met the 11 minimum standards recommended by Core Outcome Set-Standards for Development (COS-STAD) which ensures the design of the COS is relevant and has been developed using a reasonable approach, including standard number 8 which states that outcome identification must include ‘patient views’ (114) which many COS

developers have failed to achieve. Likewise, both the systematic review and qualitative interviews utilised for outcome identification were performed according to recommended methods set out by PRISMA (10) and Braun (11) . Furthermore, this study ensured patient representation was embedded throughout the entire process as a PPI formed part of the project steering group and therefore assisted with the design and implementation of the study during all phases of COS development. Likewise, in order to ensure the COS remained relevant to patients, interviews were completed during outcome identification which provided a true understanding of their perspectives, experiences and priorities of twin pregnancy and was the first of its kind. However, all outcomes selected for inclusion into the COS were also identified from the systematic review which does pose the question if patient interviews are needed for COS development if they do not enhance the COS especially given the increased resources, time and cost needed to undertake this type of research. However, unless qualitative research is completed researchers can never be certain that all outcomes important to patients have been collected. Likewise, it is important to understand why these outcomes are important as it gives research more meaning and could potently help to shape what research is undertaken in the future.

All stakeholders' panels were broadly represented within the Delphi Survey and included Obstetricians, Midwives, Neonatologists, Neonatal Nurses, and people with a live experience of twin pregnancy. There was international stakeholder representation from 8 different countries with the greatest representation from within the patient expert panel. Given that is the population which will be most affected by this research it is a strength of this study and also shows that it is important to patients that research in this area is improved. Furthermore, the majority of medical experts had more than 11 years of clinical experience which meant that the Delphi

Survey was prioritised by those that are likely to be the most knowledgeable and skilled in twin pregnancy. However, this study also had potential bias within stakeholder representation as the majority of stakeholders resided in the UK or America and were limited to those that spoke and understood English and had access to a computer and internet. These limitations could have impacted outcome prioritisation and skewed the results especially as there was minimal input from low- and middle-income countries. However, outcomes were identified for inclusion into the Delphi from international literature that was not restricted by country. Therefore, outcomes considered during consensus included those deemed important in these countries. Furthermore, during the next phase of the research experts will be purposively recruited from low- and middle-income countries into the consensus meeting to ensure there is fair representation and may address this limitation somewhat.

The attrition rate between the first and second round of the Delph Survey was between 52% for maternity employee's, 79% for neonatal employee's and 80% for patients. Although, these figures seem high, it is comparable with other Delphi's where attrition rates have been shown to be as high as 92% (115) and is an inherit limitation of using this methodology however it is also unclear why there is a variation in attrition rates between stakeholder panels in this research. Nevertheless, high attrition could potentially cause response bias within this study as participants with opposing views may omit subsequent Delphi rounds and create a false sense of consensus (116). Researchers can potentially reduce attrition by ensuring the comprehensive outcome inventory presented during the Delphi survey is manageable and not too lengthy. Thus, the high attrition observed in this study supports the decision to remove outcomes from the outcome inventory prior to

consensus, that had only been identified from one source and had been reported/discussed by <5% of trials/participants. 53 outcomes were removed from the outcome inventory, which if kept may have resulted in Delphi Survey being unmanageable and potentially increased attrition rates further. This did however need to be carefully balanced with the requirement to provide a comprehensive outcome list that was exhaustive. This decision was supported by all members of the project steering group, including the PPI who did not feel any of the outcomes removed were a priority. Furthermore, experts also had the opportunity to suggest any outcomes they feel may have been missed off the outcome inventory during the first round of the Delphi Survey which potentially mitigated this because if any removed outcome were truly a priority, they would be suggested during round one. However, none of the additional outcomes suggested aligned to any of the outcomes that were removed which provides further support for this decision.

Finally, the study protocol that was developed a priori applied the 'consensus in' recommended OMERACT (105) and used in the development of multiple Core Outcome Sets (71,89,91). 'Consensus in' was reached if ≥70% of all experts panels scored the outcome between 7-9 (critical for decision making) and ≤15% scored the outcome between 1-3 (of limited importance). However, this is a potential limitation as this definition is not based upon research and is subjective, thus there is still uncertainty regarding what constitutes as 'consensus' which raises questions over the consensus-building methodology. Furthermore, the definition for 'consensus out' may not be appropriate for COS development as it is defined as ≥70% of all stakeholders have scored the outcome between 1 -3 (of limited importance) and ≤15% have scored the outcome between 7- 9 (critical for decision making). None of the outcomes considered for consensus during this study met these criteria or came

near to the pre-defined percentages. However, given that all outcomes within the inventory have been deemed important by researchers and/or patients prior to inclusion into the inventory, it is unlikely any outcome will be classified ‘of limited importance’ and therefore removed from subsequent Delphi rounds which may increase attrition rates if multiple Delphi rounds were to be completed.

4.6 Conclusion

This study is the second phase in the development of a COS for twin pregnancy and the final phase in this thesis. The COS developed in this research will help to standardise outcome selection, collection and reporting in twin pregnancy trials. Which in turn, will allow meta-analysis of twin pregnancy research data and improve the quality of research whilst ensuring outcomes that are reported are those that are deem the most important and relevant those experiencing a twin pregnancy.

4.7 Recommendations for future research

The initial COS created in this research will be taken to a consensus meeting attended by multiple twin pregnancy experts and finalised. Each outcome within in the COS will be defined and the most appropriate measurement tool will be assigned.

Chapter 5:

Conclusion

5.1 Introduction

This thesis achieves the aim specified in Chapter 1 as it has completed stage one and stage two of COS development as defined by The COMET initiative (1) and an initial COS for twin pregnancy has been developed which has laid the foundation for the final COS for twin pregnancy.

The three pieces of research incorporated within this thesis were utilised to complete stages one and two of the COS development. Stage one of COS development focuses on outcome identification and should include multiple sources to ensure all possible outcomes have been identified prior to consensus, including those important to patients (1). This was achieved by undertaking two pieces of research. Firstly, a systematic review of published twin pregnancy RCT's and their follow up studies was completed to identify outcomes important to researchers and clinicians. Thereafter, Qualitative interviews with parents within a lived experience of twin pregnancy were undertaken to identify outcomes important to patients. Stage two of COS development focuses on outcome consensus and was achieved by undertaking an International Modified Delphi Survey with three twin pregnancy expert panels that consisted of Obstetricians and Midwives, Neonatologists and Neonatal Nurses and parents with a lived experience of twin pregnancy.

The previous chapters provide detailed discussions of the above pieces of research including their strengths and limitations. This chapter will discuss the main findings of the work that has been undertaken and discusses its overall strength and weaknesses leading to recommendations for future research.

5.2 Summary of main findings

5.2.1 Systematic review key points

- 1113 citations found in literature, 452 articles were screened, and 108 articles were read in full of which 57 trials were deemed eligible for inclusion (48 RCT's and 9 follow-up studies)
- 1257 verbatim outcomes were reported which were categorised into 170 unique outcomes.
- The three domains most reported by trials were 'Neonatal', 'Delivery' and 'Death', and the outcomes most reported by trials were 'birthweight', gestation at birth' and 'neonatal death'. However, long-term outcomes especially those related to the parent were greatly underrepresented.
- The systematic review highlighted massive heterogeneity within outcome selection with a clear lack of standardisation within all areas. This was further compounded by the use of composite outcome reporting and inconsistencies in outcome definitions, measurements tools and the denominator chosen to be reported, which is a problem unique to twin pregnancy research.

5.2.2 Qualitative interview key points

- 20 parents with a lived experience of twin pregnancy were interviewed by two independent researchers.
- 57 outcomes important the patients were generated, 16 of which were potentially 'new' outcomes. The outcomes generated were wide-ranging highlighting the extensive psychological, social and physiological impact twin pregnancy has on mothers and/ or partners.

- The majority of outcomes that were important to patients aligned to those deemed important by researchers (68%). Likewise, there were similarities between patient-researcher priorities with regards to outcome themes/domains as the three most important themes as described by patients were Neonatal Wellbeing, Birth, and Death and Survival, which matched the three most reported domains in RCT's which were Neonatal, Delivery and Survival.
- Most outcomes that were aligned between patients and researchers were short-term physiological outcomes.
- The domain/theme of 'Death', which was described as the most important theme to all patients and was one of the most reported domains in RCT's was still only reported in half of the RCT's thus highlighting that not all researchers' priorities are aligned, and major inconsistencies remain.
- Long-term outcomes are important to patients as 19% of all outcomes generated, sat within the Life Impact theme. However, most of these were 'new' outcomes which suggests that important long-term outcomes have previously been missed from research. Likewise, the long-term outcomes that have been reported by researchers do not match the priorities of patients.

5.2.3 The Modified Delphi Survey

- The comprehensive outcome inventory consisted of 72 unique outcomes, 17 were identified from the systematic review, 14 were identified from the Qualitative interviews, 38 were identified from both sources and a further 3 outcomes were suggested by experts during round one of the Delphi Survey and considered for consensus during round two.

- 176 twin pregnancy experts commenced the Delphi Survey from 8 different countries, 108 of these were parents with a lived experienced of twin pregnancy.
- 20 outcomes met the pre-defined criteria for ‘consensus in’ and will therefore form the initial COS for twin pregnancy and be taken through to the consensus meeting. A further 7 outcomes met the pre-defined criteria for ‘dissensus’ and will be discussed as optional during the consensus meeting.
- The majority of outcomes within the initial COS sit within the domain of death, and fetal and neonatal pathophysiology and are mostly short-term outcomes. This aligns with the outcomes that were deemed the most important by researchers and patients during the systematic review and Qualitative interviews.
- The high number of outcomes scored as crucial for the COS highlights the complexities of twin pregnancy research due to the need to address maternal, single and double fetal outcomes as well as the different twin types i.e. DCDA, MCDA, MCMA.

5.3 Strengths and limitations of the thesis

5.3.1 Systematic review

- This review followed robust systematic review methodology throughout the entire process to ensure a rigorous approach was taken which will instil confidence in the final COS.
- Previous COS developers have chosen to collect primary outcomes only. If this approach was taken during the systematic review in Chapter 2, 80% of outcomes would have been missed. Thus, researchers utilising the final COS

for twin pregnancy can be confident that outcome identification during the systematic review (chapter 2) was comprehensive.

- The RCT's and follow-up studies included in the systematic review in Chapter 2 were from multiple different countries and continents, including those from low-, middle-, and high-income countries. This will increase the international generalisability of the COS as outcomes important to stakeholders in these areas were considered for consensus into the COS.
- Observational studies were excluded from the review which may be a limitation of this study as it may have identified important long-term outcomes which were shown to be lacking in the RCT's. However, undertaking qualitative interviews mitigated this as long-term outcomes important to patients were inductively created and included within the comprehensive outcome inventory. Likewise, key stakeholders had the option to suggest long-term outcomes they felt had been missed during the Delphi Survey.
- Another limitation of this review, which was also noted during the combining of both sets of unique outcomes when forming the comprehensive outcome inventory, was the degree of subjectively when categorising outcomes into unique outcomes as many were poorly defined or closely interrelated. However, to overcome this consensus-led clear decisions were made which incorporated all members of the project steering groups.

5.3.2 Qualitative interviews

- This is the first qualitative study exploring patients and partner's perspective, experience and priorities of twin pregnancy which has given an in-depth understanding of why certain outcomes are important to them.

- Qualitative methodology was followed throughout the study along with the protocol that was developed *priori.*
- The participant twin type population was representative of the UK population and had a broad range of characteristics that were also representative of twin pregnancy which enabled a deep and rich understanding of twin pregnancy.
- The study highlighted the difficulties faced when using medical terminology with patients as they struggled to understand the term 'outcome' and specific medical terminology. This study allowed them to express themselves fully and explain what they meant by certain terms which ensured the correct context was taken forward to the Delphi Survey.
- All participants resided within the UK and required access to a telephone which is a limitation to this study as outcomes important to patients in other countries especially those from low- and middle-income countries may have been missed. However, the systematic review gathered outcomes from international RCT's including those from low- and middle- class countries which may mitigate this somewhat.
- The interviews were held during the Covid-19 pandemic which may have skewed the results as patients' priorities may be different at this time. However, to mitigate this, patients that had experienced twin pregnancy prior to the Covid-19 pandemic were eligible and included in the study.
-

5.3.3 Delphi Survey

- The comprehensive outcome inventory was exhaustive as outcomes were identified from multiple sources as suggested by COMET (1), including

qualitative interviews. This will give future researchers confidence in the final COS as all important outcomes will have been considered for consensus.

- The language used by participants during the interviews was used to inform the Delphi Survey outcome lay definitions which ensured patient understanding during the Delphi Survey.
- All stakeholder panels were broadly represented within the Delphi Survey and included Obstetricians, Midwives, Neonatologists, Neonatal Nurses, and people with a live experience of twin pregnancy. Furthermore, the majority of medical experts had more than 11 years of experience within their field which meant they were the most highly knowledgeable and skilled in twin pregnancy.
- The majority of participants resided in the UK and USA and was limited to those that could read and understand English and had access to computer which is a limitation of this study. This is because it may have impacted outcome prioritisation and skewed the results as expert priorities may be different in other countries, especially those from low- and middle-income countries. However, this is mitigated somewhat as the outcomes included for consensus were those deemed important by international experts as the systematic review was not limited by country.
- A further limitation is the high attrition rate observed between Delphi rounds; however, this is comparable to other Delphi surveys and is an inherit limitation of using this methodology.

5.3.4 Strength and limitations of the COS

- The strength of this body of research lies within the rigorous methodology followed during every stage of the COS.
- PPI involvement was seen throughout this COS development which will ensure the final COS remains relevant to patients. This is because, not only did patients identify outcomes to be considered for consensus by all stakeholders during the Delphi Survey, but they also prioritised all the outcomes within the initial COS for twin pregnancy during the Delphi Survey. Likewise, the project steering group included two PPI members that helped shape this research during every phase.
- Outcome identification was exhaustive as three different sources were utilised to identify outcomes (Systematic review, Qualitative Interview, Delphi Survey) thus researchers can be confident that all outcomes have been considered for consensus.
- The high number of outcomes within the COS should give researchers confidence that the COS is inclusive of all the possible and complex variables reported in twin pregnancy research i.e. maternal, fetal and twin type outcomes. This will reduce the risk of multiple researchers adding similar outcomes when reporting future research which could potentially reduce confidence in the final COS for twin pregnancy.
- A limitation of this COS was the minimal input from participants from low- and middle-income countries however this will be mitigated during the consensus meeting as participants from these countries will be purposely recruited.

5.4 Recommendations for future research

The COS determined in this study will be finalised during a consensus meeting with key stakeholders, including people with a lived experience of twin pregnancy. Furthermore, experts from low-, middle- and high-income countries will be purposively recruited to ensure the finial COS has international generalisability. Following the recommendations set out by The Consensus-Based Standards for the Selection of Health Measurements Instruments (COSMIN) initiative (2), experts will systematically and objectively determine each outcomes' definition and measurement instruments as well as how each outcome should be reported, specifically which common denominator to report i.e. number of mothers or the number of babies that were affected by the outcome and the use of composite outcomes. Potential definitions and measurements will be sought from national and international guidelines as well as each definition and measurement identified during the systematic review reported in Chapter 2. These will be reviewed and assessed for quality using the COSMIN framework (2). Once the definition and measures have been confirmed by consensus the twin pregnancy COS will be submitted for publication and disseminated to twin pregnancy experts and researchers to ensure it is utilised in all future twin pregnancy trials. Only once all areas of the COS I.e. outcome, definition, measure and common dominator, has been standardised, will data synthesis be possible.

5.5 Recommendations for practise

The final COS for twin pregnancy should be reported in all future trials within twin pregnancy. The utilisation of this COS will standardise outcome reporting in future twin pregnancy research. This in turn will allow data synthesis, reducing research waste both in terms of cost and time, and provide stronger evidence to support the clinical guidance for patients with a twin pregnancy. The COS will also ensure that future twin pregnancy research remains relevant to patients as the outcomes being reported will be those that are meaningful to them and so the COS for twin pregnancy will ultimately improve outcomes for mothers and twins.

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Appendices

Appendix 1: *A Core outcome set for Clinical trials in twin pregnancy – A study Protocol.*

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1. Background

The prevalence of multiple pregnancy varies significantly, affecting between 0.7% - 3.34% of women worldwide (1–4) Currently, 1.54% of women in England and Wales have a twin pregnancy (5) whereas in the United States it is more than double, at 3.34% (6). Monozygotic twins have remained at a constant rate globally; however, the increased use of assisted reproductive techniques (ART), maternal age and parity has resulted in a rise in dizygotic (and a less extent monozygotic) twinning and is the main cause of the variation in prevalence worldwide. Following the introduction of ovulation induction and multiple embryo transfer fertility therapies, twin pregnancy rates increased by 50% between 1975 to 2002 in England and Wales (7). This was not only observed in the UK but worldwide with countries such as the Netherlands recording a 90% increase (7). Reassuringly, a change in policy advising single-

embryo transfer (8) has resulted in twin pregnancy rates stabilising (9). Although zygosity is important, clinical relevance and risk is inferred by chorionicity and amnionicity (10–16).

Nevertheless, twin pregnancy is still a common occurrence with an increased risk of adverse outcomes for mother and baby(s). Excess maternal risks include anaemia, urinary tract infection, hypertension, gestational diabetes, haemorrhage and maternal mortality and as such require closer and more frequent monitoring compared to low-risk singleton pregnancies (10–13). The fetuses are also at risk, but it is important to differentiate the type of twin e.g. dichorionic/diamniotic (DCDA), monochorionic/diamniotic (MCDA), monochorionic/monoamniotic MCMA) as complications can be unique to each. DCDA twins are considered to have the lowest risk of complications, however when compared to a singleton pregnancy DCDA twins still have a higher risk of pre-term birth, fetal growth restriction, morbidity, stillbirth and neonatal death (10–12). In addition, 20% of dichorionic twins are monozygotic. Monochorionic twins are at higher fetal risk than their dichorionic counterparts and monoamnionicity carries additional higher risks of fetal loss from complex congenital malformations and umbilical cord entanglement. The prime and common risks are secondary to placental vascular anastomoses and/or unequal placental sharing. These unique complications include selective growth restriction (sIGR), twin reverse arterial perfusion sequence (TRAP), twin-to-twin transfusion syndrome (TTTS) and twin anaemia-polycythaemia sequence (TAPS) (10,13,14). These complications significantly increase the risk of fetal morbidity and mortality (15,16) and make research in twins difficult as there is a large variation in reported

outcomes. It is thus vital that RCTs use outcomes that are relevant to the chronicity of included pregnancies and to any interventions performed.

The heterogeneity in outcome reporting makes analysis of observational studies and randomised control trials (RCT's) of interventions for effectiveness particularly difficult causing major barriers for international data-analysis. This is further hampered using different methods of measurement or definitions for an outcome. This in turn limits the precision and applicability of findings for clinical guidance. Whilst there has been a substantial amount of attention towards standardising RCT's methods, the selection, collection and reporting of outcomes has been overlooked (17). Consequently, there is no consensus regarding the minimum that should be collected and reported. Selecting appropriate outcomes that not only capture the efficacy and safety of potential interventions but also includes outcomes that are important to patients as well as health care professionals is crucial. Therefore, to improve the quality of research a standardised core outcome set (COS) for twin pregnancy is vital. Core outcome sets are agreed, clearly defined outcomes that are measured in a standardised manner and reported consistently as a minimum in all research trials within a specific discipline (18) and are advocated by relevant UK institution (19,20).

The demand for COS development has increased over recent years and the importance has been acknowledged by several key national and international organisations including The National Institute for Health and Care Excellence (NICE) and the National Institute of Health Research (NIHR). Initiatives such as The Core Outcome Measures in Effectiveness Trials (COMET) (19) have been set up to

promote the development of core outcome sets throughout multiple disciplines and provide support to researchers. In addition to this, 78 speciality journals of women's health have formed The Core Outcomes in Women's Health (CROWN) initiative (20) which advocates COS development specifically in women health and facilitates effective distribution of manuscripts. Furthermore, the Cochrane Pregnancy and Childbirth group, who form part of the CROWN initiative, have specified that authors will be expected to report core outcome sets and conclusions will only be drawn if core outcomes sets have been utilised within their research (20). Thus, our objective is to produce, disseminate and implement a COS that should be reported as a minimum in all clinical trials regarding twin pregnancy.

2. Methods

2.1. Prospective registration

This study has been prospectively registered with COMET and the International Prospective register of Systematic Reviews (PROSERO), registration number (CRD42019133805). We will follow guidelines set out by the Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (21–23) statement and the COMET initiative (18).

2.2. Study funding

The study is funded by British Maternal and Fetal medicine Society (BMFMS) and the Twins and Multiple Births Association (TAMBA). The funder has no role in the design or conduct of the study, the collection, management, analysis or interpretation of data or manuscript preparation.

2.3. Steering committee and study management group:

A steering committee, including healthcare professionals from multiple disciplines with twin expertise and patient representatives will be formed to oversee and guide the COS development. Further stakeholders will be involved in the COS consensus-forming process.

2.4. Scope of this outcome set

The twin COS will be applicable to all clinical trials investigating a therapeutic intervention on a current twin pregnancy.

2.5. Study overview

There will be three distinct stages in the COS development:

1) Identifying all possible twin outcomes.

2) Determining which of those outcomes should form the COS.

3) Deciding how each core outcome within the COS should be defined and measured.

2.5.1. Stage one: Identifying the potential core outcomes.

2.5.1.1. Systematic review

We will conduct a systematic review to identify outcomes that have previously been reported in clinical studies. Electronic database searches will be executed in The

Cochrane library, MEDLINE, CINHAL and EMBASE using a pre-defined search strategy. RCT's reporting an outcome following a therapeutic intervention on a current twin pregnancy will be included. However, only trials whose entire participant population has a current twin pregnancy or there is a sub-group analysis based on twins will be included. Furthermore, all three variations of twins will be incorporated i.e. monochorionic diamniotic, monochorionic monoamniotic, dichorionic diamniotic and all therapeutic interventions will be considered regardless of type, setting or mode of administration. No date, country of origin or language restrictions will apply, and an English translation will be sought for any non-English language studies. Case reports (N=<3), narrative reviews, letters to the editor and studies that do not fit the PICO, detailed below, will be excluded:

P Participants in an RCT, in which 100% of the participant population has a current twin pregnancy or there is a sub-group analysis based on twins.

I Any therapeutic intervention

C Any comparison

O All outcomes

Two review authors will independently screen the title and abstracts for eligible studies using the PICO above. Full text manuscripts will be obtained and independently reviewed by each review author for all studies deemed eligible. Data will be extracted in duplicate using a standardised and piloted data extraction proforma recording the study and outcome characteristics. Disagreements will be resolved by discussion with a third review author.

2.5.1.2. Qualitative focus groups/patient interviews

Parents with a lived experience of twin pregnancy will be invited to take part in qualitative interviews as they can often identify potential outcomes unique to their 'disorder' (18). To increase participant diversity the qualitative interviews will be performed in one of two ways, the participant can choose their preferred method, they can either: attend a focus group that will be held in Birmingham or complete the interview via telephone. Participants will be recruited through National Health Service (NHS) clinic's, focused twin parent/toddler support groups and social media platforms.

The following participant inclusion/ exclusions criteria will apply: -

Inclusion criteria

- Parents with a lived experience of twin pregnancy past or present.
- 18 years of age or above
- Must be able to read, understand and speak English.
- Able to give informed consent.

Exclusion criteria

- Unable to give informed consent.
- Unable to read, understand and speak English.

Each participant will receive two reminder emails, one email will be sent seven days prior to the focus group/telephone interview and another email will be sent the day

before. They will be required to provide informed written consent and complete a recruitment questionnaire recording their demographic details and twin pregnancy experience. The systematic review will aid the question development for the qualitative interviews, with assistance from the steering committee. The focus group and telephone interviews will be executed by an experienced qualitative researcher and be audio recorded and transcribed verbatim. Two experienced qualitative researchers will collect and analyse the data which will establish outcomes that are important to parents with a lived experience of twin pregnancy. These outcomes will be added to the outcome inventory previously formed from the systematic review. The wording of the outcomes will be taken from the qualitative data with input from the patient representative within the steering committee.

2.5.1.3. *Outcome inventory*

Outcomes identified in the systematic review and qualitative interviews will be combined to form a comprehensive outcome inventory for the modified Delphi survey. Advice from the steering committee will be sought if there is any uncertainty regarding an outcome classification and an agreement will be made.

2.5.2. Stage two: Determining core outcomes.

2.5.2.1. The Delphi method:

The core outcome sets will be determined using the modified Delphi method. The Delphi method is a long-established tool used to facilitate a means of international consensus between expert stakeholders and has previously been used in COS

development (18)(19). It allows for consensus-building by using a series of sequential questionnaires to gather opinion from experts within the chosen topic.

The target population will reflect a variety of expert twin international stakeholders including obstetricians, paediatricians, neonatologists, midwives/ obstetric nurses, neonatal nurses and parents with a lived experience of twin pregnancy. The stakeholders will be grouped into three panels depending on their area of expertise as this will ensure each expert group has equal consideration. If a single heterogeneous panel was used, the results would favour whichever field of expertise has most participants, especially if opinions differed between experts i.e. obstetricians and parents, which would result in outcomes important to the smallest expert group being excluded.

The experts will be grouped into the three panels as follows: -

Panel 1 Maternity employee's – Obstetricians and Midwives

Panel 2 Neonatal employee's – Neonatologists, Paediatricians and Neonatal nurses.

Panel 3 Parents with a lived experience of twin pregnancy

A minimum of 20 participants will be recruited into each panel. If this target is not achieved the steering committee will review the recruitment process and re-recruit before commencing the Delphi survey. Recruitment will be facilitated by national and international organisations including TAMBA, BMFMS and national and international

professional bodies, such as the Royal College of Obstetricians and Gynaecologists (RCOG), The International Society of Twins Studies (ISTS) and advertised through social media platforms.

The following participant inclusion/exclusion criteria will apply: -

Inclusion criteria

- Participants must be either an obstetrician, neonatologist, paediatrician, midwife, neo-natal nurse or a parent with a lived experience of twin pregnancy past or present.
- Can read, understand and write English.

Exclusion criteria

- Unable to read, understand and write English.

Willing experts will be required to register online, and Delphi survey instructions written in plain language will be emailed to them. A unique identifier to anonymise their response will also be provided, along with a short questionnaire recording their demographic details. To ensure ease of completion, the steering committee will pilot the recruitment process and Delphi survey beforehand.

2.5.2.1.1. Round one

Using the Likert Scale expert stakeholders will be asked individually to score each outcome within the inventory. This grading system has been recommended by COMET and was devised by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to facilitate the ranking of outcomes (24). Each outcome will be scored between 1 (limited importance in decision making) and 9 (critical in making a decision) and a supplementary lay definition will be provided to aid understanding. If an expert believes that they do not have the expertise to score an outcome, an 'unable to score' option will be available. Furthermore, if an expert feels that a crucial outcome has been missed off the initial outcome inventory, they will have the opportunity to add additional new outcomes to the inventory. These outcomes will be reviewed by the steering committee and included within the outcome inventory during round two of the Delphi survey. Experts will only have the option to add 'new' outcomes during the first round of the Delphi survey.

Experts will have approximately four weeks to complete the Delphi survey, responses will be monitored and up to three reminders will be sent. Attrition rates will be recorded and those that fail to complete the Delphi survey within the specified time will not be invited into successive rounds. Once all experts have responded or four weeks has elapsed, the outcome scores will be collated and analysed prior to round two of the Delphi survey.

2.5.2.1.2. Round Two

Like round one, experts will be asked to score each outcome on the outcome inventory using the Likert Scale. However, during this round the inventory will also include any 'new' outcomes that were suggested during round one and they will also be able to view their own results from the previous round together with the scores from each expert panel before they rescore the outcome again.

A standardised definition will be applied during this round to enable core outcomes to be established: -

<u>Consensus in</u>

- Over 70% of participants in each stakeholder panel have scored the outcome between 7 - 9 (critical for decision making) on the Likert scale.

  And

- Less than 15% of participants in each stakeholder panel have scored the outcome between 1 - 3 (of limited importance in decision making) on the Likert scale.

<u>Consensus out</u>

- Over 70% of participants in each stakeholder panel score outcome between 1 - 3 'of limited importance' on the Likert scale

And

- Less than 15% of participants in each stakeholder panel have scored the outcome between 7 – 9 ‘critical for decision making’ on the Likert scale.

Dissensus

- Over 70% of experts in one or more expert group scored the outcome between 7-9.

Those that met ‘consensus in’ will be taken through to the consensus meeting and those that met ‘dissensus’ will be discussed as optional (117). All other results will be excluded from the consensus meeting.

2.5.3. Stage three: Outcome finalisation

2.5.3.1. Consensus meeting

The aim of the consensus meeting is to discuss the results from the Delphi survey including any outcomes that did not meet a consensus and to formalise the twin COS.

To ensure unbiased consensus development, a heterogeneous group of experts purposely sampled to include a minimum of three experts from each expert panel i.e. maternity, neonatal/paediatric and parents with a lived experience of twin pregnancy, will be invited to the consensus meeting. Furthermore, only experts that completed all rounds of the Delphi survey will be considered. Any materials that may be used

during the consensus meeting will be distributed prior to the meeting so experts can consider them individually. To achieve effective and efficient consensus formation, the facilitator will ensure that the meeting is collaborative, cooperative and non-competitive and inclusive with equal input from all experts. Outcomes will be discussed to ensure the core outcome set contains no more than ten outcomes and covers all domains. Each outcome will be scored ‘yes’ or ‘no’ and the top ten items, based on percentage of ‘yes’ votes by panel members, will be included.

2.5.3.2. Determining how each outcome is measured.

Once the COS has been established it is vital that each outcome within it has an agreed definition and form of measurement. Currently, there are no current guidelines to facilitate the measurement of outcomes; however, The Core Outcome Measurement Instrument Selection (COMIS) project is in the process of developing standards for assessing the methodological quality of studies exploring the measurement properties of instrument (25). Thus, once this has been published, we will evaluate possible tools using the framework developed. The assessment will be undertaken in duplicate and any disagreements will be resolved by discussion with the steering committee. High quality outcome measures will be associated with each outcome.

3. Conclusion

The development of a twin COS will ensure homogeneity across clinical trials by reducing the need for research duplication, aiding evidence synthesis and promoting international data collaboration. COS development will improve the quality of evidence-based clinical care which will ultimately enhance patient experience. The implementation of core outcome sets has been promoted by The COMIT initiative, the CROWN initiative as well as national organisations such as NICE and NIHR thus the demand for COS development is only set to increase. Currently, there is an extensive list of core outcome sets that have been planned, being developed or have been completed within the COMET initiative, however a twin COS has not been established so to improve the quality of care for this high-risk group of patients a twin COS is essential.

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Appendix 2: *PRISMA Checklist*

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Appendix 3: *Systematic review search strategy*

Athens search strategy

HDAS - Export
Date run: 25 Jan 18 - 13:11

#	Database	Search term	Results
1	CINAHL	exp "PREGNANCY, TWIN"/	680
2	CINAHL	((monochorionic OR dichorionic OR monoamniotic OR diamniotic) AND (pregnancy OR pregnancies OR birth)).ti,ab	828
3	CINAHL	(1 OR 2)	1297
4	CINAHL	3 [Publication types Clinical Trial OR Randomized Controlled Trial]	22
5	Medline	exp "PREGNANCY, TWIN"/	1835
6	Medline	((monochorionic OR dichorionic OR monoamniotic OR diamniotic) AND (pregnancy OR pregnancies OR birth)).ti,ab	2331
7	Medline	(5 OR 6)	3642
8	Medline	7 [Document type Clinical Trial OR Controlled Clinical Trial OR Randomized Controlled Trial] [Humans]	71
9	EMBASE	exp "TWIN PREGNANCY"/	10737
10	EMBASE	((monochorionic OR dichorionic OR monoamniotic OR diamniotic) AND (pregnancy OR pregnancies OR birth)).ti,ab	3511
11	EMBASE	(9 OR 10)	12155
12	EMBASE	11 [Humans] [Clinical trials Clinical Trial OR Randomized Controlled Trial OR Controlled Clinical Trial]	521

Cochrane database search

Search Name: Cochrane search
Date Run: 02/02/2019 12:54:52

ID	Search	Hits
#1	twin pregnancy in Trials	494
#2	monochorionic in Trials	35
#3	dichorionic in Trials	22
#4	monoamniotic in Trials	9
#5	diamniotic in Trials	16
#6	#1 OR #2 OR #3 OR #4 OR #5	499

Appendix 4: *Detailed Study Characteristics per trial*

First Author	Year of Publication	Study Type	Type of RCT	Type of intervention	Sample size (n)	Country of Origin	Multi-Continent	Twin Type	Topic	Interventions
Marivate	1977	RCT	Intervention	Medical	46	South Africa	No	All Twin Types	Preterm labour	Fenterol
O'Connor	1979	RCT	Intervention	Medical	49	Ireland	?	All Twin Types	pregnancy prolongation	Ritodrine
Skjaerris	1983	RCT	Intervention	Medical	50	Sweden	No	All Twin Types	Preterm birth	Turbutaline
Saunders	1985	RCT	Intervention	Medical	212	Zimbabwe	Yes	All Twin Types	pregnancy prolongation	Hospital admission
Rabinovici	1987	RCT	Intervention	Surgical	33	Israel	No	All Twin Types	poor outcomes	Cesarean section
Crowther	1990	RCT	Intervention	Medical	118	Zimbabwe	No	All Twin Types	Pregnancy duration	Hospital admission
MacLennan	1990	RCT	Intervention	Medical	141	Australia	Yes	All Twin Types	Preterm birth	Hospital admission
Knuppel	1990	RCT	Prediction/ Prognosis	n/a	58	America	Yes	All Twin Types	Preterm labour detection	Home uterine activity monitoring
Saari-Kemppainen, A	1990	RCT	Prediction/ prognosis	n/a	148	Finland	Yes	All Twin Types	Poor outcomes	UUS
Ashworth	1990	RCT	Intervention	Medical	160	United Kingdom	No	All Twin Types	Preterm birth	Salbutamol
Italian Study of Aspirin in Pregnancy	1993	RCT	Intervention	Medical	1106	Italy	Yes	All Twin Types	PIH/IUGR	Aspirin
Caspi	1994	RCT	Intervention	Medical	47	Israel	No	All Twin Types	PIH/IUGR	Aspirin
Suzuki	1999	RCT	Intervention	Medical	36	Japan	No	All Twin Types	Birth outcomes	Induction of Labour
Giles	2003	RCT	Prediction/ Prognosis	n/a	539	Multiple Countries		All Twin Types	Poor outcomes	Doppler USS
Senat	2004	RCT	Intervention	Surgical	142	Multiple Countries		MCMA or MCDA	TTTS	Laser coagulation VS Amnioreduction
Moise	2005	RCT	Intervention	Surgical	73	America	Yes	MCMA or MCDA	TTTS	Amnioreduction VS Septostomy
Crombleholme	2007	RCT	Intervention	Surgical	42	America	Yes	MCMA or MCDA	TTTS	Amnioreduction VS Laser coagulation

Olsen	2007	RCT	Intervention	Medical	367	Multiple Countries		All Twin Types	Pregnancy duration	Fish oil
Norman	2009	RCT Follow up study	Intervention	Medical	500	United Kingdom	Yes	All Twin Types	Preterm birth	Progesterone
Briery	2009	RCT	Intervention	Medical	30	America	No	All Twin Types	Preterm birth	Progesterone
Eddama	2010	RCT Follow up study	Intervention	Medical	500	United Kingdom	Yes	All Twin Types	Cost effectiveness	Progesterone
Elsheikhah	2010	RCT	Intervention	Medical	100	Egypt	?	All Twin Types	Preterm birth	Progesterone
Cetingoz	2011	RCT	Intervention	Medical	150	Turkey	No	All Twin Types	Preterm birth	Progesterone
Coombs	2011	RCT	Intervention	Medical	240	America	Yes	DCDA	Preterm birth	Progesterone
Lim	2011	RCT	Intervention	Medical	671	Netherlands	Yes	All Twin Types	Preterm birth	Progesterone
Rode	2011	RCT	Intervention	Medical	677	Multiple Countries		DCDA	Preterm birth	Progesterone
Dodd	2012	RCT	Intervention	Surgical	235	Multiple Countries		All Twin Types	Poor outcomes	Elective birth
Aboulghar	2012	RCT	Intervention	Medical	313	Egypt	No	DCDA	Preterm birth	Progesterone
Serra	2012	RCT	Intervention	Medical	290	Spain	Yes	DCDA	Preterm birth	Progesterone
Barrett	2013	RCT	Intervention	Surgical	2804	Multiple Countries		DCDA or MCDA	Poor outcomes	Cesarean section
Liem	2013	RCT	Intervention	Medical	813	Netherlands	Yes	All Twin Types	Poor outcomes	Pessary
Senat	2013	RCT	Intervention	Medical	165	France	Yes	DCDA or MCDA	Pregnancy duration	Progesterone
Priyadarshini	2013	RCT	Intervention	Medical	12	India	No	All Twin Types	Preterm labour	Ritodrine VS Nifedipine
Carrick-Sen	2014	RCT	Intervention	Medical	162	United Kingdom	Yes	All Twin Types	Depression	Parent Education Classes
Awwad	2014	RCT	Intervention	Medical	293	America	No	All Twin Types	Preterm birth	Progesterone
Slaghekke	2014	RCT	Intervention	Surgical	274	Multiple Countries		MCDA	TTTS	Soloman technique VS Laser coagulation
Fahmy	2015	RCT	Intervention	Medical	60	Egypt	No	All Twin Types	PPH	Carbetocin
Hutton	2015	RCT Follow up study	Intervention	Surgical	2570	Multiple Countries		DCDA	Long-term outcomes	Cesarean section

Gliozheni	2015	RCT	Intervention	Medical	218	?	?	All Twin Types	Preterm birth	Pessary
Brizot	2015	RCT	Intervention	Medical	390	America	No	DCDA or MCDA	Preterm birth	Progesterone
McNamara	2015	RCT Follow up study	Intervention	Medical	?	United Kingdom	Yes	All Twin Types	Long-term outcomes	Progesterone
Asztalos	2016	RCT Follow up study	Intervention	Surgical	4603	Multiple Countries		DCDA or MCDA	Long-term outcomes	Cesarean section
Gordon	2016	RCT	Prediction/ Prognosis	n/a	125	America	Yes	DCDA or MCDA	Pregnancy duration	TV cervical length scan
Goya	2016	RCT	Intervention	Medical	137	Spain	Yes	All Twin Types	Preterm birth	Pessary
Nicolaides	2016	RCT	Intervention	Medical	1180	Multiple Countries		All Twin Types	Preterm birth	Pessary
El-Refaie	2016	RCT	Intervention	Medical	322	Egypt	No	DCDA or MCDA	Preterm birth	Progesterone
Vedel	2016	RCT Follow up study	Intervention	Medical	498	Danish	Yes	DCDA	Preterm birth	Progesterone
Van Klink	2016	RCT Follow up study	Intervention	Surgical	216	Multiple Countries		MCDA	Long-term outcomes	Soloman technique VS Laser coagulation
Shinar	2017	RCT	Intervention	Medical	87	Israel	No	All Twin Types	Anaemia	Iron
Ali	2017	RCT	Intervention	Medical	120	Egypt	No	All Twin Types	Anemia	Iron
Quintero	2017	RCT	Intervention	Surgical	20	America	?	MCMA or MCDA	long term outcomes	Laser coagulation
Berghella	2017	RCT	Intervention	Medical	46	America	Yes	DCDA or MCDA	Preterm birth	Pessary
Mikami	2017	RCT	Intervention	Medical	171	Brazil	No	All Twin Types	Breastfeeding	Prenatal breastfeeding counselling
Dang	2018	RCT	Intervention	Medical	300	Vietnam	No	All Twin Types	Preterm birth	Cervical pessary VS Vaginal progesterone
Brocklehurst	2018	RCT	Prediction/ Prognosis	n/a	?	United Kingdom	Yes	All Twin Types	Poor outcomes	Computerised CTG interpretation
Hutton	2018	RCT Follow up study	Intervention	Surgical	2305	Multiple Countries		DCDA	Urinary incontinence	Cesarean section
Van ‘t Hooft	2018	RCT Follow up study	Intervention	Medical	133	Netherlands	Yes	All Twin Types	Long-term outcomes	Pessary

Appendix 5: *Outcome classified according to OMERACT 2.0, their characteristics and reported percentages.*

			Reporting Frequency				Definition Reporting			Outcome Classification		
Area	Domain	Outcome	No. of trials that reported the outcome (n=57)	%	No. of times the outcome was reported (n=1257)	%	No. of outcomes that were defined	No. of different definitions used	No. of outcomes that were not defined	Primary	Secondary	Not stated
Pathophysiology /Manifestations	**Delivery**	Preterm delivery	26	45.6	77	6.1	77	18	0	12	58	7
		Mode of delivery	24	42.1	54	4.3	54	16	0	2	46	7
		Preterm prolonged rupture of membranes	11	19.3	11	0.9	1	1	10	0	11	0
		Spontaneous preterm delivery	9	15.8	16	1.3	16	12	0	4	12	0
		Induction of labour	8	14.0	16	1.3	9	5	7	0	7	1
		Duration of treatment	6	10.5	7	0.6	7	7	0	2	3	2
		Elective preterm delivery	5	8.8	6	0.5	6	4	0	2	4	0
		Postpartum Haemorrhage	5	8.8	8	0.6	7	5	1	2	6	0
		Spontaneous labour	5	8.8	6	0.5	2	2	4	0	4	2
		Preterm labour	4	7.0	5	0.4	4	4	1	1	4	0
		Spontaneous delivery	4	7.0	4	0.3	3	3	1	1	2	1
		Duration of labour	3	5.3	9	0.7	9	9	0	0	7	2
		Blood loss	2	3.5	3	0.2	2	2	1	0	0	2
		Genital tract injury	2	3.5	9	0.7	9	9	0	0	9	0
		Intraoperative damage to the bladder, ureter or bowel	2	3.5	4	0.3	4	4	0	0	4	0
		Meconium at delivery	2	3.5	2	0.2	0	0	2	0	1	1
		Spontaneous rupture of membranes	2	3.5	2	0.2	2	2	0	0	2	0
		Amniotic fluid embolism	1	1.8	1	0.1	0	0	1	0	1	0

	Cardiotocogram abnormality during labour	1	1.8	1	0.1	1	1	0	0	1	0
	Duration of induction	1	1.8	2	0.2	2	2	0	0	0	2
	Epidural	1	1.8	1	0.1	0	0	1	0	1	0
	Hysterectomy resulting from birth	1	1.8	1	0.1	1	1	0	0	1	0
	Placental weight	1	1.8	1	0.1	0	0	1	0	0	1
	Prolonged rupture of membranes	1	1.8	1	0.1	0	0	1	0	0	1
	Reduced isoflurane concentration	1	1.8	1	0.1	0	0	1	0	0	1
	Required methergine	1	1.8	1	0.1	0	0	1	0	0	1
	Uterine hyperactivity	1	1.8	1	0.1	0	0	1	0	0	1
	Uterine rupture	1	1.8	1	0.1	1	1	0	0	0	1
	Uterine tone after delivery	1	1.8	2	0.2	2	2	0	0	0	2
Neonatal	Birthweight	29	50.9	42	3.3	21	6	21	3	24	29
	Gestation at delivery	29	50.9	34	2.7	7	6	27	5	19	10
	Admission to higher level of care	27	47.4	37	2.9	37	14	0	7	24	6
	Respiratory distress syndrome	19	33.3	22	1.8	5	5	17	6	13	3
	Intraventricular haemorrhage	17	29.8	20	1.6	15	10	5	8	12	0
	Low Apgar score	16	28.1	26	2.1	25	16	1	3	16	7
	Low birthweight	16	28.1	43	3.4	43	13	0	1	29	13
	Necrotizing Enterocolitis	16	28.1	17	1.4	8	8	9	6	11	0
	Sepsis	15	26.3	16	1.3	10	7	6	5	11	0
	Intrauterine growth restriction	11	19.3	14	1.1	13	9	1	4	7	3
	Retinopathy of prematurity	11	19.3	12	1.0	2	2	10	2	10	0
	Bronchopulmonary dysplasia	8	14.0	8	0.6	4	4	4	4	5	0
	Duration of admission to higher level of care	8	14.0	10	0.8	10	6	0	1	9	0

Intubation and mechanical ventilation	7	12.3	8	0.6	8	7	0	4	4	0
Patent ductus arteriosus	7	12.3	7	0.6	1	1	6	1	6	0
Apgar	6	10.5	10	0.8	10	7	0	0	2	8
Pneumonia	6	10.5	6	0.5	1	1	5	2	4	0
Respiratory support	5	8.8	6	0.5	3	3	3	1	5	0
Seizures	5	8.8	5	0.4	2	2	3	2	3	0
Assisted ventilation	4	7.0	7	0.6	4	4	3	4	3	0
Jaundice	4	7.0	5	0.4	3	3	2	0	5	0
Periventricular leukomalacia	4	7.0	6	0.5	1	1	5	2	4	0
Poor cord gas results	4	7.0	5	0.4	5	5	0	3	2	0
Chronic lung disease	3	5.3	3	0.2	2	2	1	2	1	0
Cystic periventricular leukomalacia	3	5.3	4	0.3	2	2	2	4	0	0
Hypoglycaemia	3	5.3	3	0.2	0	0	3	0	2	1
Resuscitation	3	5.3	4	0.3	3	3	1	2	2	0
Ischemic injury	2	3.5	2	0.2	1	1	1	2	0	0
Neonatal encephalopathy	2	3.5	2	0.2	2	2	0	2	0	0
Neonatal treatments	2	3.5	4	0.3	4	4	0	2	2	0
Severe birth trauma	2	3.5	10	0.8	10	9	0	10	0	0
Transient tachypnoea	2	3.5	2	0.2	0	0	2	1	0	1
Abnormal consciousness level	1	1.8	2	0.2	2	2	0	2	0	0
Anaemia	1	1.8	1	0.1	1	1	0	0	1	0
Blood transfusion	1	1.8	2	0.2	2	2	0	0	2	0
Congenital abnormalities at birth	1	1.8	4	0.3	4	3	0	0	4	0
Head circumference	1	1.8	1	0.1	1	1	0	0	1	0

	Hemodynamic instability	1	1.8	1	0.1	1	1	0	0	1	0
	Hyperbilirubinemia	1	1.8	1	0.1	0	0	1	0	1	0
	Infection	1	1.8	1	0.1	1	1	0	0	1	0
	Life threatening events	1	1.8	1	0.1	0	0	1	0	1	0
	Meconium aspiration	1	1.8	1	0.1	0	0	1	1	0	0
	Meningitis	1	1.8	1	0.1	1	1	0	1	0	0
	Metabolic acidosis	1	1.8	1	0.1	0	0	1	0	1	0
	Neonatal morbidity	1	1.8	1	0.1	0	0	1	0	0	1
	Pneumothorax	1	1.8	1	0.1	0	0	1	1	0	0
	Porencephalic or parenchymal cyst	1	1.8	1	0.1	1	1	0	1	0	0
	Secondary apnoea	1	1.8	1	0.1	0	0	1	0	0	1
	Stroke	1	1.8	1	0.1	0	0	1	1	0	0
	Ventricular dilatation	1	1.8	1	0.1	1	1	0	1	0	0
Fetal	Fetal malformations	7	12.3	14	1.1	11	10	3	0	13	1
	Fetal complications	2	3.5	2	0.2	0	0	2	0	0	2
	Abnormal umbilical artery Doppler	1	1.8	1	0.1	1	1	0	0	1	0
	Amniondelhiscence (membrane separation)	1	1.8	1	0.1	0	0	1	0	1	0
	Amniotic band injury	1	1.8	1	0.1	0	0	1	1	0	0
	Arterial infarction	1	1.8	1	0.1	1	1	0	1	0	0
	Bizygotic	1	1.8	1	0.1	0	0	1	0	0	1
	Gestation age at treatment	1	1.8	1	0.1	1	1	0	0	0	1
	Iatrogenic monoamnioticity	1	1.8	1	0.1	0	0	1	0	1	0
	Monozygotic	1	1.8	1	0.1	0	0	1	0	0	1
	Twin-to-Twin Transfusion Syndrome (TTTS)	1	1.8	1	0.1	1	1	0	1	0	0

	Twin Anemia Polycythaemia Sequence (TAPS)	1	1.8	1	0.1	1	1	0	1	0	0
Maternal Morbidity	Hypertensive disorders	13	22.8	16	1.3	8	7	8	1	14	1
	Side effects from intervention	12	21.1	85	6.8	85	72	0	0	85	0
	Diabetes	7	12.3	7	0.6	6	5	1	0	7	0
	Intrauterine infection	7	12.3	10	0.8	1	1	9	0	10	0
	Thromboembolic event	6	10.5	10	0.8	6	6	4	3	7	0
	Haematological disturbances	5	8.8	7	0.6	7	6	0	0	6	1
	Genitourinary infection	3	5.3	4	0.3	2	2	2	0	4	0
	Antepartum haemorrhage	2	3.5	2	0.2	1	1	1	0	2	0
	Bowel obstruction after delivery	2	3.5	2	0.2	2	2	0	0	2	0
	Obstetric Cholestasis	2	3.5	2	0.2	1	1	1	0	2	0
	Paralytic ileus	2	3.5	2	0.2	1	1	1	0	2	0
	Pneumonia	2	3.5	2	0.2	1	1	1	1	1	0
	Primary pulmonary hypertension	2	3.5	2	0.2	0	0	2	1	1	0
	Sepsis	2	3.5	3	0.2	2	2	1	2	1	0
	Wound infection	2	3.5	8	0.6	8	6	0	4	4	0
	Urinary, faecal or flatal incontinence	2	3.5	2	0.2	2	2	0	0	1	1
	Acute respiratory distress	1	1.8	1	0.1	0	0	1	1	0	0
	Bleeding at placental surface	1	1.8	1	0.1	0	0	1	0	1	0
	Liver disease	1	1.8	1	0.1	1	1	0	0	0	1
	Maternal complications	1	1.8	1	0.1	1	1	0	0	0	1
	Maternal morbidity	1	1.8	1	0.1	0	0	1	0	0	1
	Neurological disturbances	1	1.8	1	0.1	1	1	0	0	1	0
	Polyhydramnios	1	1.8	1	0.1	0	0	1	0	1	0

		Pulmonary oedema	1	1.8	1	0.1	0	0	1	0	1	0
		Renal insufficiency	1	1.8	1	0.1	1	1	0	0	1	0
		Respiratory arrest	1	1.8	1	0.1	0	0	1	0	1	0
		Respiratory depression syndrome	1	1.8	1	0.1	0	0	1	0	1	0
		Maternal disability or incapacity	1	1.8	1	0.1	0	0	1	0	1	0
		Stroke	1	1.8	1	0.1	1	1	0	0	1	0
	Maternal Investigations	Cervical measurement	4	7.0	11	0.9	10	10	1	0	3	8
		Ferritin	2	3.5	3	0.2	3	3	0	0	3	0
		Haemoglobin	2	3.5	7	0.6	7	7	0	2	5	0
		Increased liver enzymes	2	3.5	2	0.2	0	0	2	0	2	0
		Haematocrit	1	1.8	2	0.2	2	2	0	1	1	0
		Maternal weight gain during pregnancy	1	1.8	1	0.1	0	0	1	0	0	1
		Mean arterial blood pressure at delivery	1	1.8	11	0.9	11	11	0	0	0	11
		Mean heartrate value at delivery	1	1.8	11	0.9	11	11	0	0	0	11
		Number of observations	1	1.8	1	0.1	1	1	0	0	0	1
Death		Neonatal death	27	47.4	36	2.9	23	12	13	8	27	1
		Intrauterine death	24	42.1	33	2.6	16	12	17	9	21	3
		Perinatal death	13	22.8	14	1.1	6	5	8	3	7	4
		Live births	10	17.5	16	1.3	15	11	1	0	15	1
		Infant death	4	7.0	4	0.3	3	3	1	2	2	0
		Intrapartum death	4	7.0	5	0.4	5	5	0	1	4	0
		Maternal death	4	7.0	4	0.3	4	4	0	0	3	1
		Neonatal survival	4	7.0	11	0.9	11	11	0	7	4	0
		Infant survival	2	3.5	7	0.6	7	7	0	6	1	0

		Miscarriage	2	3.5	2	0.2	1	1	1	0	0	2
		Death or survival with neurodevelopmental disability	1	1.8	1	0.1	0	0	1	1	0	0
		Perinatal and infant death	1	1.8	1	0.1	0	0	1	0	1	0
		Sudden infant death syndrome	1	1.8	1	0.1	0	0	1	0	1	0
Life Impact	**Parental**	Breastfeeding	4	7.0	10	0.8	10	10	0	4	5	1
		Psychological health	2	3.5	22	1.8	22	22	0	1	19	2
		Relationship health	2	3.5	5	0.4	3	3	2	0	3	2
		Satisfaction with motherhood	2	3.5	4	0.3	4	4	0	0	3	1
		Paternal psychological health	1	1.8	2	0.2	2	2	0	0	2	0
		Quality of life	1	1.8	2	0.2	2	2	0	0	0	2
		Satisfaction with method of delivery	1	1.8	1	0.1	1	1	0	0	0	1
		Sleep	1	1.8	3	0.2	3	3	0	0	3	0
	Infant	Neurodevelopmental impairment	10	17.5	37	2.9	37	36	0	28	4	5
		Poor health	3	5.3	20	1.6	20	17	0	9	0	11
		Cerebral palsy	2	3.5	4	0.3	4	4	0	4	0	0
		Hearing impairment	2	3.5	2	0.2	2	2	0	1	0	1
		Growth impairment	1	1.8	5	0.4	5	5	0	0	0	5
		Physiological impairment	1	1.8	9	0.7	9	9	0	9	0	0
		Visual impairment	1	1.8	1	0.1	1	1	0	0	0	1
Resource Use/Economical		Corticosteroids for lung maturation	11	19.3	11	0.9	11	11	0	0	11	0
		Tocolytic therapy	11	19.3	12	1.0	12	2	0	0	12	0
		Antenatal hospitalisation	10	17.5	14	1.1	14	11	0	1	6	7
		Duration of hospitalisation	8	14.0	4	0.3	4	4	0	0	4	0
		Cerclage placed	4	7.0	4	0.3	1	1	3	0	4	0

Blood transfusion	3	5.3	3	0.2	0	0	3	0	2	2
Hospitalisation	2	3.5	2	0.2	0	0	2	0	2	0
Activity restriction	1	1.8	2	0.2	1	1	1	0	2	0
Laparotomy	1	1.8	1	0.1	1	1	0	0	1	0
Magnesium sulphate for neuro protection	1	1.8	1	0.1	1	1	0	0	1	0
Postnatal hospitalisation	1	1.8	5	0.4	5	4	0	0	0	5
Intervention cost difference	1	1.8	8	0.6	8	8	0	8	0	0

Appendix 6: *Outcome measures used to evaluate the three most frequently reported outcomes.*

1. Side effects of intervention

Outcome measure (n= 72)	No. times reported (n)
Abdomen pain at 24 weeks gestation	1
Abdomen pain at 36 weeks gestation	1
Black staining to stool at 24 weeks gestation	1
Black staining to stool at 36 weeks gestation	1
Diarrhoea at 24 weeks gestation	1
Diarrhoea at 36 weeks gestation	1
Loss of appetite at 24 weeks gestation	1
Loss of appetite at 36 weeks gestation	1
Metallic taste in the mouth at 24 weeks gestation	1
Metallic taste in the mouth at 36 weeks gestation	1
Nausea and vomiting at 24 weeks gestation	1
Nausea and vomiting at 36 weeks gestation	1
No side effects at 24 weeks gestation	1
No side effects at 36 weeks gestation	1
Acne	1
Allergic reactions	1
Any side effects	1
Bloating	1
Breast tenderness	1
Bruising	1
Cervical tear from pessary	1
Delay in labour	1
Depression	1
Difficulty sleeping	1
Discharge and pain	1
Discomfort	1
Leading to discontinuation of study drug	1
Dizziness	1
Drowsiness	1
Excessive hair growth	1
Excessive weight gain	1
Fever	1
Fever or signs of infections	1
Fluid retention	1
Gastrointestinal upset	1
Gastrointestinal side effect	2
Generalised pruritus	1
Hair loss	1

Headache	3
Heavy bleeding from pessary	1
Injection site bruising	1
Injection site itching	1
Injection site pruritus	1
Injection site soreness	1
Itching	2
Jaundice	1
Joint pain	1
Nausea	1
Nausea, vomiting, and diarrhoea	1
Necrosis	1
Pain	2
Pelvic discomfort	1
Pessary replacement	1
Pessary repositing	1
Pessary repositioning without removal	1
Pruritus	1
Pubic pain	1
Rash	1
Reproductive system and breasts side effects	1
Rupture of the cervix	1
Skin rashes	1
Skin side effects	1
Soreness	1
Suspected fetal distress	1
Swelling	1
Systemic reaction	1
Uterine rupture	1
Virginal discharge	7
Vaginal discomfort	1
Vaginal infection	1
Vaginal irritation	1
Vaginal itching	3

2. Preterm delivery

Outcome measure (n= 18)	No. times reported (n)
Delivered <22 weeks of gestation	1
Delivered <24 weeks of gestation	3
Delivered <27 weeks of gestation	1
Delivered <28 weeks of gestation	9
Delivered <30 weeks of gestation	3
Delivered <31 weeks of gestation	1
Delivered <32 weeks of gestation	14
Delivered <33 weeks of gestation	1

Delivered <34 weeks of gestation	15
Delivered <34 weeks of gestation(gestational age calculated before 20/40 at USS)	1
Delivered <35 weeks of gestation	4
Delivered <37 weeks of gestation	17
Spontaneous delivery <37 weeks of gestation (Gestational age calculated based on last menstrual period)	1
Spontaneous or induced delivery <37 weeks of gestation spontaneous or induced (Gestational age calculated based Dodowitz score)	2
Delivered between 30-34 weeks of gestation	1
Delivered between 34-35 weeks of gestation	1
Delivered between 34-37 weeks of gestation	1
Preterm delivery after failed tocolysis	1

3. Mode of delivery

Outcome measure (n= 16)	**No. times reported (n)**
Delivered by cesarean section	18
Instrumental delivery or cesarean section	1
Delivered by elective cesarean section	7
Delivered by emergency cesarean section	7
Breech delivery	1
Instrumental delivery	5
Vaginal delivery	5
Vontouse delivery	2
Forceps delivery	1
Lower segment cesarean section	1
Cesarean section of the second twin	1
Labouring cesarean section	1
Emergency cesarean section for the second twin	1
Cesarean section for arrest in labour - 2 hours with no cervical change and arrest of descent as 1 hour without fetal decent despite ARM or antenatal oxytocin	1
Delivered by cesarean section for fetal distress	1
Cesarean section for maternal infection - maternal temperature of ≥38C, white blood count of ≥20,000/mm3 and C-reactive protein of ≥2	1

Appendix 7: *Outcome measures used to evaluate the three outcomes reported most by trials.*

1. Birthweight

Outcome measure (n = 6)	No. times reported (n)
Birthweight of both twins	4
Birthweight of twin 1	7
Birthweight of twin 2	7
Birthweight of twins >38/40	1
Birthweight of recipient twin up to 30 days	1
Birthweight of donor twin	1
Not defined	21

2. Gestation at birth

Outcome measure (n = 6)	No. times reported (n)
Last menstrual period, ovulation or ovum picked up in IVF cases and confirmed by 1st or 2nd trimester USS	1
USS or last menstrual period using Naegeles rule	1
Maternal menstrual history, confirmed by USS - fetal crown rump length at 9-11 weeks	1
Menstrual history and confirmed by USS - crown-rump measurement of the bigger fetus at 11-13 weeks	1
Dubowitz scoring	2
Last menstrual period	1
Not defined	27

3. Neonatal Death

Outcome measure (n = 12)	No. times reported (n)
Death <24 hours	1
Death before discharge	4
Death between 2-7 days	1
Death between 8-28 days	1
Death <27 days	1
Death <28 days after delivery	5
Death <28 days after delivery excluding abnormalities	1
< 6 weeks after expected term date	1
Early neonatal death	2
Early neonatal death excluding abnormalities	1
Death of the donor twin	1
Death of the recipient twin	1
Not defined	13

Appendix 8: *Interview Discussion Guide*

Introduction

1. Thank the participant for agreeing to take part.
2. Confirm that they have read and understood the PIL.
3. Ensure that we have received their completed consent form and that this has been recorded on the spreadsheet and saved to the research folder.
4. Complete the medical questionnaire.
5. Remind participants of the statement on confidentiality, their right to withdraw consent, and that the interview will be recorded.
6. Review the purpose of the study in general.
7. Emphasise the value of their views and opinions – there are no right or wrong answers.
8. Ask if they have any questions before starting the interview (if asked about COS, read the COS statement in Appendix 1).
9. Turn on the audio recorder and:
    i. state the date and time of interview.
    ii. state the name of the interviewer and the participant ID of the participant (not their name);
    iii. ask the participant to re-confirm consent for the recording.

Research Objective	Research Question	Objectives
N/A	What type of **experience** have they had?	Explore current pregnancy and background: - Confirm their gestation or no. of weeks postnatal for current/recent pregnancy. - Identify no. of previous pregnancies and children - Explore the type of twin pregnancy: DCDA (non-identical), MCDA (identical), or MCMA (identical, high risk) Explore support and any changes in support: - What support will/do they have (or have they had) around them? - How has the support they have received changed?
Identify potential outcomes unique to their disorder	What were their **initial thoughts** about having twins?	Explore their initial thoughts about having twins: - Explore initial feelings and emotions: *How did you feel when you found out you were having twins?* - Explore concerns, worries, hopes, benefits, etc.: *What were your initial thoughts, hopes, and worries?* *What positive or negative challenges do/did you think you might face?* - Explore why they had these thoughts: *Why are/were these a concern, worry, hope, or benefit, etc.?* - Explore why they are/were important to them. *Why are/were these important to you?* - Explore the potential impacts/consequences. *What do you think are the potential impacts or consequences of these challenges?* Explore any other thoughts/feelings and important domains.

Identify all possible twin pregnancy outcomes via qualitative interviews.	What **outcomes have they experienced** during pregnancy?	Explore what positive challenges or outcomes have they have experienced because they are having (or have had) twins: what problems, difficulties, etc. they have faced (or think they might face) in relation to their pregnancy: - Explore what problems have they have faced (experiential): *Thinking about your experiences so far, what has been important to you and why?* - Explore what challenges they think they might face (hypothetical): *Thinking about the birth and beyond, what is going to be important to you and why?* - Explore why they perceive these to be challenges. - Explore whether and why these are/were important to them. - Explore the (actual or possible) consequences (for mother, father, twins, and family) Explore any other outcomes that are important to them (other challenges, etc.) in other domains (see Appendix 2 for a list of example domains). Explore what (outcome) matters to them the most: *Thinking about what you've discussed, what is most important to you?*

Conclusion

1. State time that the interview ended and stop the recording.
2. Thank them for participating.
3. Ask if they have any questions.
4. Remind them that they can contact us if they have any questions.
5. Statement on COS:

When we talk about ‘outcomes’, we are referring to the different consequences of having a certain condition that is measured during research studies by using questionnaires, physical tests, and other instruments to determine the extent to which an intervention or treatment was effective. These outcomes can include things like changes in a persons’ health, financial considerations, and clinical interventions. In these interviews, we are particularly interested in hearing about outcomes that are important to you – these are often known as ‘patient reported outcomes’. A core outcome set is a list of the most essential outcomes that researchers should measure and report when undertaking research in a particular area. So, we are interested in finding out what minimum set of outcomes should be reported during research involving twin pregnancy, and we will use the outcomes that are important to you to help us construct this list. This will help researchers to standardise outcome reporting across studies, and to better compare the effectiveness of interventions or treatment

Appendix 9: *Outcomes identified from systematic review and qualitative interviews combined.*

				Quantitative Reporting Frequency		Qualitative reporting frequency	
Area	**Domain**	**Systematic review outcomes**	**Qualitative Interview Outcome**	No. of trials that reported in *n*=57	%	No. of participants that discussed by *n*=20	%
Death	**Maternal**	Maternal death	Maternal death or survival				
	Fetal	Miscarriage	Miscarriage or early fetal survival	2	3.5	19	95
		Intrauterine death	Intrauterine death or survival (inc. stillbirth)	24	42.1	17	85
		Intrapartum death	Intrapartum death or survival	4	7.0	7	35
	Neonatal/ Infant	Neonatal death	Neonatal death or survival	27	47.4	7	35
		Neonatal survival	Survival of one or both twins	4	7.0	16	80
			Selective termination			5	25
		Infant death	Infant death or survival	4	7.0		
		Infant survival		2	3.5		
		Perinatal death		13	22.8		
		Perinatal and infant death		1	1		
		Death or survival with neurodevelopmental disability		1	1.8		
		Sudden infant death syndrome	Cot death (SIDS)	1	1.8	1	5
Life Impact	**Infant**	Neurodevelopmental impairment	Neurodevelopmental impairment	10	17.5	18	90
		Cerebral palsy		2	3.5		
		Death or survival with neurodevelopmental disability		1	1.8		
		Growth impairment	Infant growth	1	1.8	1	5
			Increased care or hospital appointments for infant(s)			2	10
		Poor health	Quality of life of one or both twins	3	5.3	9	45
		Neonatal morbidity	General neonatal health	1	1.8	15	75
			Separation of twins			2	10
		Hearing impairment		2	3.5		
		Physiological impairment		1	1.8		
		Visual impairment		1	1.8		
	Parental	Psychological health	Maternal mental health	2	3.5	18	90
		Relationship health	Relationship health and impacts	2	3.5	14	70
		Breastfeeding	Method of feeding	4	7.0	16	80
			Maternal antenatal quality of life			10	50
		Quality of life	Maternal postnatal quality of life	1	1.8	16	80
		Paternal psychological health	Paternal quality of life	1	1.8	5	25
			Being isolated or experiencing isolation			6	30
			Effect or impact on family (inc. existing children)			10	50
		Urinary, faecal of flatal incontinence	Maternal incontinence or frequent urination	2	3.5	2	10
			Financial concerns of parent(s)			20	100
			Sleep of twins			3	15
		Sleep	Parental sleep	1	1.8	14	70
			Recovery from birth			10	50
			Skin-to-skin at birth			4	20
		Satisfaction with motherhood		2	3.5		
		Satisfaction with method of delivery		1	1.8		
	Siblings	Neonatal separation from (non-twin) siblings				3	15
Pathophysiology/ Manifestations	**Fetal**	Complications of monochorionic twins (TAPS, TTTS)	Complications of monochorionic twins (TTTS, cord entanglement)	2	3.5	4	20
		Fetal malformations	Fetal malformations	7	12.3	5	25
		Congenital abnormalities at birth		1	1.8		
		Intrauterine growth restriction	Fetal growth or weight	11	19.3	10	50
			General fetal health			15	75
		Fetal complications		2	3.5		
		Amniondelhiscence (membrane separation)		1	1.8		
		Amniotic band injury		1	1.8		
		Arterial infarction		1	1.8		
		Bizygotic		1	1.8		
		Iatrogenic monoamnioticity		1	1.8		
		Cardiotocogram abnormality during labour		1	1.8		
		Abnormal umbilical artery Doppler		1	1.8		
		Gestation age at treatment		1	1.8		
		Monozygotic		1	1.8		
	Maternal	Antepartum haemorrhage	Antenatal blood loss or haemorrhage	2	3.5	4	20

		Sepsis	Maternal infection	2	3.5	2	10
		Pneumonia		2	3.5		
		Wound infection		2	3.5		
		Intrauterine infection		7	12.3		
		Hypertensive disorders	High blood pressure	13	22.8	4	20
		Primary pulmonary hypertension		2	3.5		
		Diabetes		7	12.3		
		Thromboembolic event	Pulmonary embolism	6	10.5	4	20
			Morning sickness or hyperemesis gravidarum			6	30
		Maternal morbidity	General maternal health	1	1.8	16	80
		Maternal disability or incapacity		1	1.8		
		Hysterectomy resulting from birth	Hysterectomy	1	1.8	1	5
		Mode of delivery	Mode of delivery	24	42.1	20	100
		Preterm prolonged rupture of membranes		11	19.3		
		Prolonged rupture of membranes		1	1.8		
		Postpartum Haemorrhage	Post-partum blood loss or haemorrhage	5	8.8	4	20
		Blood loss		2	3.5		
		Bleeding at placental surface		1	1.8		
		Haematological disturbances		5	8.8		
		Blood transfusion		3	5.3		
		Preterm delivery	Pre-term birth	26	45.6	13	65
		Spontaneous preterm delivery		9	15.8		
		Elective preterm delivery		5	8.8		
		Preterm labour		4	7.0		
		Spontaneous labour		5	8.8		
		Spontaneous delivery		4	7.0		
		Spontaneous rupture of membranes		2	3.5		
		Genital tract injury	Perineal trauma	2	3.5	1	5
		Genitourinary infection		3	5.3		
		Obstetric Cholestasis		2	3.5		
		Liver disease		1	1.8		
		Neurological disturbances		1	1.8		
		Polyhydramnios		1	1.8		
		Pulmonary oedema		1	1.8		
		Renal insufficiency		1	1.8		
		Respiratory depression syndrome		1	1.8		
		Duration of induction		1	1.8		
		Intraoperative damage to the bladder, ureter or bowel		2	3.5		
		Meconium at delivery		2	3.5		
		Amniotic fluid embolism		1	1.8		
		Epidural		1	1.8		
		Placental weight		1	1.8		
		Uterine hyperactivity		1	1.8		
		Uterine tone after delivery		1	1.8		
		Duration of labour		2	3.5		
		Uterine rupture		1	1.8		
		Bowel obstruction after delivery		2	3.5		
		Paralytic ileus		2	3.5		
		Acute respiratory distress		1	1.8		
		Maternal complications		1	1.8		
		Respiratory arrest		1	1.8		
		Maternal weight gain during pregnancy		1	1.8		
		Stroke		1	1.8		
		Side effects from intervention		12	21.1		
		Duration of treatment		6	10.5		
		Ferritin		2	3.5		
		Haemoglobin		2	3.5		
		Increased liver enzymes		2	3.5		
		Haematocrit		1	1.8		
		Mean arterial blood pressure at delivery		1	1.8		
		Mean heartrate value at delivery		1	1.8		
		Number of observations		1	1.8		
		Cervical measurement		4	7.0		
	Neonatal/ Infant	Birthweight	Birthweight	29	50.9	7	35
		Low birthweight		16	28.1		
		Gestation at delivery	Gestation at delivery	29	50.9	1	5
		Respiratory distress syndrome	Neonatal lung development	19	33.3	6	30
		Secondary apnoea		1	1.8		
		Meconium aspiration		1	1.8		

		Transient tachypnoea		2	3.5		
		Bronchopulmonary dysplasia		8	14.0		
		Chronic lung disease		3	5.3		
		Pneumothorax		1	1.8		
		Necrotizing Enterocolitis		16	28.1		
		Sepsis	Neonatal infection	15	26.3	2	10
		Infection		1	1.8		
		Meningitis		1	1.8		
		Pneumonia		6	10.5		
		Retinopathy of prematurity		11	19.3		
		Patent ductus arteriosus		7	12.3		
		Apgar		6	10.5		
		Low Apgar score		16	28.1		
		Jaundice	Jaundice	4	7.0	1	5
		Poor cord gas results		4	7.0		
		Cystic periventricular leukomalacia		3	5.3		
		Periventricular leukomalacia		4	7.0		
		Intraventricular haemorrhage		17	29.8		
		Stroke		1	1.8		
		Seizures		5	8.8		
		Ischemic injury		2	3.5		
		Abnormal consciousness level		1	1.8		
		Hypoglycaemia		3	5.3		
		Resuscitation		3	5.3		
			Neonatal weight loss			15	75
			Neonatal lung development			6	30
			Increased neonatal outpatient visits			2	10
		Porencephalic or parenchymal cyst		1	1.8		
		Ventricular dilatation		1	1.8		
		Severe birth trauma		2	3.5		
		Life threatening events		1	1.8		
		Neonatal encephalopathy		2	3.5		
		Hemodynamic instability		1	1.8		
		Blood transfusion		1	1.8		
		Anemia		1	1.8		
		Head circumference		1	1.8		
		Hyperbilirubinemia		1	1.8		
		Neonatal treatments		2	3.5		
		Metabolic acidosis		1	1.8		
Resource		Corticosteroids for lung maturation		11	19.3		
		Tocolytic therapy		11	19.3		
		Antenatal hospitalisation	Antenatal hospitalisation	10	17.5	3	15
		Hospitalisation		2	3.5		
		Duration of hospitalisation		8	14.0		
		Cerclage placed		4	7.0		
		Postnatal hospitalisation	Postnatal maternal hospitalisation	1	1.8	8	40
		Induction of labour		8	14.0		
		Admission to higher level of care	Admission to neonatal care (inc. NICU)	27	47.4	18	90
		Respiratory support		5	8.8		
		Intubation and mechanical ventilation		7	12.3		
		Assisted ventilation		4	7.0		
		Duration of admission to higher level of care	Neonatal length of hospitalisation	8	14.0	6	30
		Intervention cost difference		1	1.8		
		Activity restriction		1	1.8		
		Laparotomy		1	1.8		
		Magnesium sulphate for neuro protection		1	1.8		
		Reduced isoflurane concentration		1	1.8		
		Required methergine		1	1.8		

Key

	Unique Outcome
	<5% of trials of trials reported it or <5% of participants discussed it
	Outcome Measure
Red	Outcome with the same semantic meaning as another from the same source