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A core outcome set for studies investigating the management of selective fetal growth restriction in twins

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ABSTRACT

Background

Selective fetal growth restriction occurs in monochorionic twin pregnancies where unequal placental sharing leads to restriction in the growth of just one twin. The management options include laser separation of the fetal circulations, selective reduction or expectant management, but the best treatment is not yet known.

New trials in this area are urgently needed, but in this rare and complex group maximising the relevance and utility of clinical research design and outputs is paramount. A core outcome set ensures standardised outcome collection and reporting in future research.

The objective of this study was to develop a core outcome set for studies evaluating treatments for selective fetal growth restriction in monochorionic twins.

Methods

We established an international steering group of clinicians, researchers and patients to oversee the process of core outcome set development. Outcomes reported in the literature were identified through a systematic review and informed the design of a three round Delphi survey. Clinicians, researchers and patients and family representatives participated in the survey. An international meeting of stakeholders used the modified Nominal Group Technique to consider the consensus outcomes and agree a final core outcome set.

Results

Ninety-six outcomes were identified from 39 studies in the systematic review. One hundred and two participants from 23 countries completed the first round of the Delphi survey. Eighty-eight completed all three rounds. Twenty-nine outcomes met the a priori criteria for consensus and

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were prioritised using the modified nominal group technique. Participants included researchers (n=3), fetal medicine specialists (n=3), obstetricians (n=2), neonatologists (n=3), midwives (n=4), parents and families (n=6), patient group representatives (n=3) and a sonographer. 11 core outcomes were agreed. These were live birth, gestational age at birth, birth weight, inter-twin birthweight discordance, death of surviving twin after death of co-twin, loss during pregnancy or before final hospital discharge, parental stress, procedure-related adverse maternal outcome, offspring length of stay in hospital, neurological abnormalities on postnatal imaging and childhood disability.

Conclusions

This core outcome set represents the consensus of a large and diverse group of international collaborators. Use of these outcomes in future trials will help to increase the clinical relevance of the research. Consensus agreement on core outcome definitions and measures are now required.

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Introduction

Clinical uncertainty regarding the optimal management strategy of selective fetal growth restriction (sFGR) in monochorionic twin pregnancies persists, particularly for cases presenting at very early gestations. Intrauterine demise in sFGR (with a shared placenta) seems less predictable than in fetal growth restriction (FGR) associated with placental insufficiency of an individual placenta in dichorionic twins or singletons, and additionally carries the unique additional risk of acute feto-fetal transfusion after the death of one twin that may cause death or neurological injury in the co-twin.[1] Available options include expectant monitoring or active fetal intervention including selective termination with a variety of techniques, fetoscopic laser treatment or termination of the whole pregnancy.[2] A recent systematic review and meta-analysis reported data from over 700 pregnancies affected by sFGR comparing these management options.[3] Many studies were excluded because of variation in case definition and classification, and meta-analysis of several key outcomes, for example, neurological morbidity, intrauterine death and preterm birth, was limited by variation in outcome reporting and measurement in the included studies.[3,4] Such variation in outcome selection, collection, and reporting has been observed across women's health.[5,6]

Given the high potential for morbidity and mortality in sFGR there is a need for robust guidance and given the rarity of this condition, it is critical that diagnostic criteria and reported outcomes are consistent across trials. Consensus in diagnosis, classification and outcomes is key to the generation of high-quality studies amenable to comparison and meta-analysis.[4,7] Incorporating agreed variables helps to avoid wasted effort and equally importantly, needless exposure to trial participation for women and babies affected by sFGR.

Core outcome sets are groups of outcomes that can be collected and reported consistently, selected by consensus.[6] The development of a core outcome set requires taking into account the perspective of all relevant stakeholders.[8,9] Core outcome sets should include outcomes relevant to clinical practice and the outcomes in the set should also reflect both harmful and beneficial aspects of a treatment, especially in the case of twins where a benefit to one twin may often be associated with a harm to the other. Additionally, components of a core outcome set

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should be clearly defined and amenable to standardised measurement. The aim of this study was to develop a core outcome set for sFGR.

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Methods

The development of this core outcome set was planned in accordance with the methodology recommended in the Core Outcomes Measures in Effectiveness Trials (COMET) handbook 1.0,[8] the International Consortium for Health Outcomes Measurement methods,[10] and drawing upon the experience of the steering group of developing other core outcome sets in women's health.[11–14] The detailed protocol has been published.[15] Details of this core outcome set have been included in the COMET database (registration number 998) and further details are available at www.comet-initiative.org. The guidelines of the National Research Ethics Service have established that ethical approval is not required for this project.

Steering Group

An international steering group of key experts in the fields of fetal medicine, management of multiple pregnancies and fetal growth restriction, paediatricians, neonatologists and midwives was established to guide the development of the core outcome set. Parents and non-clinical stakeholders were included through the participation of the Twin and Multiple Birth Association (TAMBA). The steering group determined the scope of the core outcome set and defined the methodology and recruitment strategies.

Definition of terms

In the development of this core outcome set the steering group agreed to use the recently published consensus diagnostic criteria for sFGR.[2] This requires either the solitary finding of an estimated fetal weight (EFW) below the third centile in one of the twins or at least two out of four of the following: (1) EFW below the 10th centile in one of the twins, (2) an abdominal circumference (AC) below the 10th centile in one of the twins, (3) EFW discordance ≥25%, and (4) UA Doppler pulsatility index (PI) >95th centile in the smaller twin.

Systematic review of variation in outcome reporting in sFGR

In order to establish outcomes reported in the existing literature and investigate the degree of variation in outcome reporting, a systematic review of published trials of interventions for sFGR was performed. The protocol for the systematic review was prospectively registered on

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PROSPERO (International Prospective Register of Systematic Reviews), registration number: CRD42018092697. The methodology followed the reporting guidelines for meta-analyses and systematic reviews of randomised controlled trials, as outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16]

The Cochrane Central Register of Controlled Trials, EMBASE, and Medline from inception to February 2018 were searched for randomised controlled trials, non-randomised studies, and observational studies evaluating any potential intervention for monochorionic twin pregnancies affected by sFGR. Abstracts and full texts were screened by two reviewers (RT and FS) and studies meeting the inclusion criteria were assessed using a purposively constructed data extraction form.

The population was all monochorionic twin pregnancies complicated by sFGR. For this initial review, we accepted the authors' definition of sFGR given that the consensus diagnostic criteria have only been recently published. The interventions included any intervention used for the treatment of sFGR. The comparator included any comparator treatment used for the interventions of sFGR. The outcome was all outcomes reported in the included studies investigating sFGR. A comprehensive inventory of these outcomes was developed with outcomes initially organised into seven broad categories: offspring mortality, pregnancy outcomes, procedure-related outcomes, fetal outcomes, neonatal outcomes, childhood outcomes. We used descriptive statistics to characterise included studies, mapping the reporting of maternal, fetal, neonatal, and childhood outcomes across the included studies.

Consensus development using the Delphi technique

The outcomes identified in the systematic review were taken into consideration by the steering group in designing a Delphi survey in order to achieve convergence of opinion on the key outcomes to be included in the core outcome set. After reviewing these outcomes, the steering group were invited to add any outcomes that they felt were potentially relevant but had not been reported in previously published studies. Outcomes were defined in lay terms for the Delphi questionnaire, in keeping with prior COS development or existing published patient information.

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The survey was developed using established online software (DelphiManager, University of Liverpool) appropriate for the delivery of online Delphi surveys relating to core outcome set development.[17,18] The survey invited participants to score each outcome using the scale developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group and commonly used in core outcome set development, a nine-point Likert scale from 1 ('of limited importance for making a decision') to 9 ('critical for making a decision').

Key stakeholder groups identified by the steering committee included clinicians (obstetricians, fetal medicine specialists, neonatologists, and midwives), researchers, and parents or patients who had been affected by sFGR. Potential participants from these stakeholder groups were identified from the researchers and clinicians whose studies were identified during the systematic review, professional networks, for example, the Royal College of Obstetricians and Gynaecologists and the International Society for Twin Studies, personal contacts of the steering group and via TAMBA. Participants were invited by email to respond to the web-based Delphi survey. Each participant was allocated a unique identifier to anonymise their responses.

The survey was first piloted with representatives of the key stakeholder groups and then disseminated to all invited participants. Participants were asked to provide demographic data before commencing the survey and self-identified as either healthcare professionals, researchers or parents and family. The first and second rounds were open for responses for two weeks and the third and final round was open for three weeks. Personalised reminders were sent to participants to prompt completion of data entry during each round. During the first round, participants were invited to suggest additional outcomes to be considered for inclusion in the subsequent round of the survey. After the first round, any additional outcomes suggested were included in the subsequent survey round. Participants received feedback on their own responses and the overall responses of the group in the previous round (Figure 1).

Analysis of Delphi survey results

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The Delphi survey response results and demographic details were analysed using spreadsheet software. (Excel 16.13.1, Microsoft Inc., Seattle, USA) Consensus was defined according to pragmatic criteria by the steering group, as described in the study protocol, as any outcome achieving a median score of eight after the third round. Results after the third round were reported as the number of outcomes meeting the a priori definition for consensus. All outcomes meeting this criterion were taken forwards as potential core outcomes for discussion.

Face-to-face stakeholder consensus development meeting

A modified Nominal Group Technique was used in the final stage of achieving consensus on core outcomes for use in studies of interventions in sFGR.[19] This structured discussion technique allows all opinions to be considered from the start, encourages equal participation and allows the identification of divergence in opinion between different groups in a safe way.[20] This technique has been successfully used in the development of a number of core outcome sets.[11,21] Those who had participated in the initial Delphi survey were invited to attend a half day face-to-face consensus development meeting, held in the United Kingdom. Participants unable to attend in person or via teleconference were invited to contribute their views through structured interviews prior to the consensus meeting. Parents and non-clinical participants were offered the opportunity to clarify the study background and purpose, the Delphi results and the outcome terms used.

The meeting was chaired by an experienced facilitator. The meeting opened with an initial briefing on the purpose and scope of the meeting and the results of the systematic review and Delphi survey were presented. Participants were asked to engage in an initial period of idea generation in small groups or pairs before moving on to a 'round robin' sharing their priority outcomes.[22] Participants were able to suggest additional potential core outcomes. Participants were asked to identify both the most and least important outcomes for inclusion in the final core outcome set. During this discussion, outcomes were separated into three categories: (1) outcomes that should be included in the final core outcome set; (2) outcomes where opinion was divided; and (3) outcomes that should not be included in the final core outcome set.

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Participants were asked to discuss outcome terminology, simplify the similar or poorly worded outcomes and remove duplicates.

In considering the outcomes where opinion was divided, participants were asked to consider the relative importance of different outcomes in relation to each other, the overall balance between common and rare outcomes, the breadth of the outcome set and the feasibility of measurement and reporting of the outcomes. Specifying measurement and reporting tools for the included outcomes was beyond the scope of this meeting. After discussion, consensus was ultimately reached on a group of core outcomes.

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Results

Systematic review of variation in outcome reporting

The literature search yielded 1,859 records. Two independent reviewers (FS, RT) evaluated 61 potentially relevant studies and identified 39 studies that met our inclusion criteria. Thirty studies (77%) evaluated a single intervention: expectant management (20 studies; 51%), selective reduction (8 studies; 21%), and fetoscopic laser surgery (2 studies; 5%). Eight studies (20%) evaluated two different interventions in the same study. A single study (3%) evaluated all three interventions.

Included trials reported 96 different outcomes which were organised into 6 domains: fetal, neonatal, and perinatal mortality (12 outcomes), pregnancy and childbirth (15 outcomes), procedure-related (seven outcomes), fetal (13 outcomes), neonatal (36 outcomes), and childhood (13 outcomes) (Table 1).

Delphi survey results

One hundred and two participants from 23 countries completed the first round of the Delphi survey. Ninety-two completed the second round, and 88 completed the final round (Tables 2). All participants in the survey were invited to attend a face to face consensus meeting in London either in person or via teleconference. There were seven women who had experienced sFGR in pregnancy, eight relatives of people affected by sFGR, 51 fetal medicine specialists, 18 obstetricians, eight midwives, four neonatologists or paediatricians and five researchers (Table 3). Fifty-six discrete outcomes identified from the systematic review and steering committee were included in the first round and a further seven outcomes were added after participants' suggestions to the second and third rounds. After the third round, 29 outcomes met the a priori definition for consensus.

Face-to-face consensus development meeting

Nineteen people participated directly in the consensus development meeting, with another four participants contributing via teleconference. Two people with experience of sFGR took part in

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structured interviews prior to the meeting and their input was presented to the meeting by the researcher who interviewed them. Participants included three researchers, three fetal medicine specialists, two obstetricians, three neonatologists, four midwives, six parents and twins, and three patient group representatives, and a sonographer. Twenty-nine consensus and six additional outcomes were discussed in the meeting. Three outcomes were reformulated or condensed from other outcomes. The group agreed 11 core outcomes (Figure 2). The meeting additionally agreed that where relevant, each outcome should be reported for each baby (smaller and larger).

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Discussion

Summary of study findings

A group of 102 multi-disciplinary stakeholders from 23 countries have developed a core outcome set for selective fetal growth restriction in monochorionic twin pregnancies. Ninety-six outcomes identified from a systematic review of existing literature were reduced to 29 consensus outcomes using a modified Delphi method. Using the modified Nominal Group Technique, a consensus development meeting prioritised 11 core outcomes across five domains – mortality, pregnancy, procedure, neonatal and childhood outcomes (Figure 2).

There is significant variation in outcome reporting in the published literature relating to sFGR. Although most studies reported gestational age at delivery and birth weight, only 22/39 studies (56%) reported live birth. Few studies reported neonatal and childhood morbidity. During core outcome set development parents in highlighted the importance of these outcomes to them. No study reported on measures of parental stress or childhood disability as defined by the World Health Organization, new outcomes included in this set.

Strengths and limitations

The strengths of this study include the use of validated consensus building methodology, incorporating Delphi and nominal group techniques to converge many potential outcomes into a focused, clinically important set of core outcomes. The participants in this study were international, from 23 countries . Although participants were classified according to their self reported identities, many participants had multiple perspectives which informed the discussion, with several clinicians having interest in research, many participants having experience of pregnancy and parenting beyond their professional roles, several parents having previously engaged with research and one of the clinicians being a twin themselves. The key to reducing research waste and answering the most important clinical questions is to centre the end users of research – families needing care in complicated pregnancies – in the design and development of new research.(23) We have adhered to this principle in development of this core outcome set; patients and patient representative groups, notably TAMBA and the Multiple Births

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Foundation (MBF) were involved throughout the design, conduct, and dissemination of this study.

Although international and multidisciplinary, the collaborating group was limited by being dominated by professionals from Europe and North America. The survey was not available in other languages or in an offline format, and some potential participants may have been unable to take part. Balancing the widest possible participation against what is feasible with available resources, we feel the collaborators group included a broad range of perspectives. The bias relating to the large number of healthcare professionals primarily applies to the Delphi rounds, since the participants in the final meeting were proportionately more balanced between professionals, researchers and parent and family representatives, reducing the possible bias in the final core outcome set.

In developing this core outcome set we adopted a simple and pragmatic definition of consensus *a priori.* There are no accepted optimal criteria for consensus in Delphi surveys, so we have reported our results according to this definition.

Clinical and research implications

Although this core outcome set will form the basis of future research in sFGR, clear definitions and measurement instruments need to be provided for each outcome. For example, the outcome "neurological abnormalities on postnatal imaging" should be clearly specified. The measurement instrument (ultrasound and/or MRI) is understood, but the outcome definition must specify the timing of imaging and the findings of significance. The intention was to include all findings associated with increased risk of long term sequelae, but it was beyond the scope of this meeting to precisely define this outcome. Equally, the outcome of parental stress was considered by both clinicians and families to be particularly relevant in sFGR where management options include difficult choices that can prioritise one twin over the other. Assessment of parental stress should be considered by researchers but the choice of measurement instrument must maximise the utility of this outcome within the research setting. There are established tools that have been used to investigate parental psychological effects in

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similar situations – e.g a survey administered to parents after fetoscopic surgery for congenital diaphragmatic hernia(24) or after laser for twin-to-twin transfusion syndrome. (25)

Agreeing the measurement instruments for use with this core outcome set will follow the recommendations of the Consensus-based standards for the selection of health measurement instruments (COSMIN) initiative.(27) A literature search will examine formal definition development studies, guidelines, systematic reviews and trials for existing definitions and measurement instruments. These will then be quality assessed using the COSMIN criteria. A panel of healthcare professionals, researchers and parents and families with experience of sFGR will review existing definitions and measures identified and agree those that should be used in the reporting of these core outcomes in future research.

Use of this core outcome set in the future will help focus sFGR research on outcomes of importance to all stakeholders, prevent selective outcome reporting and facilitate high quality evidence synthesis.(28) Over eighty journals in the field of women's health have joined the Core Outcomes in Women's and Newborn's Health (CROWN) initiative to promote the implementation of core outcome sets. Researchers will need to meet core outcome reporting requirements in order to publish their work in these key journals, which will motivate the rapid adoption of core outcome sets across the field of women's health.(29)

The existence of a core outcome set does not limit researchers to reporting only these outcomes. It may be appropriate to collect and report others related to the specific scope of a study. We have included neonatal and childhood outcomes in the set because of the strong interest from many relevant stakeholders, and a clear deficiency in this area in published literature, but it might be necessary that a study initially reports short term outcomes while awaiting longer term data.

Conclusion

This core outcome set for studies reporting the management of selective fetal growth restriction in monochorionic pregnancies has been developed using a rigorous systematic review of the

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existing literature and robust consensus development study. This core outcome set will inform the design and reporting of future studies in sFGR and promote high quality evidence synthesis.

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Figure legends

Figure 1. Illustrative example of an outcome presented in round two.

Figure 2. Agreed core outcome set

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Table 1. Variation in outcome reporting across research studies on selective fetal growth restriction.

	Studies (*n*)
Fetal, neonatal, and perinatal mortality	
Miscarriage	6
Termination of pregnancy	10
Intrauterine fetal death overall	27
Intrauterine fetal death reported per twin	21
Double intrauterine fetal loss	13
Live birth overall	22
Live birth per twin	10
Neonatal mortality overall	26
Neonatal mortality per twin	9
Perinatal mortality	8
Perinatal mortality per twin	8
Perinatal survival	19
Fetal outcomes	
Middle Cerebral Artery Doppler	4
Ductus Venosus Doppler	5
Umbilical Artery Doppler	8
Neurological morbidity in the surviving twin following cord occlusion	4
Other fetal outcomes	7
Pregnancy and childbirth outcomes	
Premature preterm rupture of membranes	11
Mode of delivery	12
Gestational age at delivery	39
Preterm delivery	14
Procedure to delivery time interval	3
Other pregnancy and childbirth outcomes	8
Procedure related outcomes	

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Membrane septostomy	3
Intrauterine infections	5
Other procedure related outcomes	7
Neonatal outcomes	
Birth weight	35
Apgar score	7
Inter-twin birth weight discordance	14
Intraventricular haemorrhage	20
Periventricular leukomalacia	18
Retinopathy of prematurity	2
Hypertrophic cardiomyopathy	2
Respiratory distress syndrome	8
Intubation and mechanical ventilation	3
Necrotising enterocolitis	8
Sepsis	6
Neonatal intensive care unit admission	6
Other neonatal outcomes	12
Childhood outcomes	
Cognitive impairment	6
Motor impairment	6
Visual impairment	3
Hearing impairment	3
Behavioural disorders	4
Blood pressure	1
Other childhood outcomes	1

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Table 2. Results of the Delphi Survey

Outcome	Round 1		Round 2		Round 3	
	No. of responses	**Median score**	**No. of responses**	**Median score**	**No. of responses**	**Median Score**
Live birth	103	9	92	9	88	9
Miscarriage	103	8	92	8	88	9
Intrauterine death/Stillbirth	103	9	92	9	88	9
Death within the first 28 days of life (Neonatal death)	103	9	92	9	88	9
Death in the pregnancy or first 7 days of life (Perinatal death)	103	9	92	9	88	9
Termination of Pregnancy	103	7	92	7	88	7.5
Infant Death	103	9	92	9	88	9
Disease Progression	103	8	92	9	88	9
Fetal Neurological Morbidities	103	9	92	9	88	9
Fetal Heart Abnormalities	103	7	92	7	88	7
Delivery of the growth restricted twin indicated where there is no indication for delivery of the other.	0		92	8	88	7
Gestational Age at Birth	102	9	91	9	88	9
Mode of Delivery	102	6	91	6	88	6
Birth weight	102	7	91	8	88	9
Inter-twin Birthweight Discordance	102	7	91	8	88	8
Apgar Scores	102	6	91	6	88	6
Admission to the neonatal unit	102	7	91	7	88	7
Length of Stay in the neonatal unit	102	7	91	7	88	7
Intraventricular Haemorrhage	102	8	91	9	88	9
Periventricular Leukomalacia	102	8	91	9	88	9
Ventriculomegaly	102	7	91	7	88	7
Cystic Lesions	102	8	91	9	88	8
Any other neurological imaging abnormalities	102	7.5	91	8	88	8
Retinopathy of prematurity	102	7	91	7	88	6

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Hypertrophic cardiomyopathy	102	7	91	6	88	6
Persistent Pulmonary Hypertension of the Newborn	102	7	91	7	88	7
Congenital heart disease	102	7	91	7	88	6
Anaemia at birth	102	6	91	6	88	6
Anaemia-Polycythaemia at birth	102	7	91	7	88	7
Respiratory Distress Syndrome	102	7	91	7	88	7
Chronic lung disease/Bronchopulmonary Dysplasia	102	8	91	8	88	7
Intubation and Mechanical Ventilation	102	7	91	7	88	6
Pneumonia	102	6	91	6	88	6
Pulmonary Hypoplasia	102	7	91	7	88	7
Necrotising enterocolitis (NEC)	102	8	91	8	88	7
Sepsis (Severe Infection)	102	7	91	8	88	7
Feeding Difficulties	0		91	6	88	6
Histopathological evidence of sFGR	0		91	5	88	6
Neonatal Renal Failure	0		91	7	88	7
Motor impairment	101	8	91	9	88	9
Behavioural disorders	101	7	91	7	88	8
Hearing impairment	101	7	91	7	88	8
Visual impairment	101	7	91	8	88	8
Cerebral Palsy	101	9	91	9	88	9
Neurocognitive Developmental Impairment	101	8	91	9	88	9
Hypertension	101	6	91	6	88	6
Cardiovascular Disorders	101	7	91	7	88	7
Autism Spectrum Disease	0		91	6	88	6
Receptive and Expressive Language Disorders	0		91	7	88	6
Premature rupture of membranes	101	7	91	6	88	6
Chorioamnionitis	101	7	91	7	88	6

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Preterm birth	101	8	91	9	88	9
Gestational Diabetes or Pre-eclampsia complications	101	6	91	6	88	6
Maternal death	101	9	91	9	88	9
Placental abruption	101	8	91	8	88	8
Life-threatening bleeding (Haemorrhage)	101	9	91	9	88	9
Unintentional membrane separation	101	7	91	6	88	6
Unintentional septostomy	101	7	91	6	88	6
Maternal Length of Stay	101	6	91	6	88	6
Failure of procedure/treatment	101	8	91	8	88	8
Procedure/Treatment to delivery interval	101	7	91	8	88	8
Admission to an Intensive Care Unit			91	8	88	8
Postpartum Depression	101	6	91	6	88	6

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Table 3. Delphi results by stakeholder group

Outcome	Healthcare Professionals (n=81)	Researchers (n=5)	Parents and family (n=15)
Live birth	9	9	9
Miscarriage	8	9	9
Intrauterine death/Stillbirth	9	9	9
Death within the first 28 days of life (Neonatal death)	9	9	9
Death in the pregnancy or first 7 days of life (Perinatal death)	9	9	9
Termination of Pregnancy	7	9	9
Infant Death	9	9	9
Disease Progression	9	9	7
Fetal Neurological Morbidities	9	9	9
Fetal Heart Abnormalities	7	8	8
Delivery of the growth restricted (smaller) twin indicated where there is no indication for delivery of the other twin.	7	7	7
Gestational Age at Birth	9	9	9
Mode of Delivery	6	6	6
Birth weight	9	7	9
Inter-twin Birthweight Discordance	8	6	8
Apgar Scores	6	7	4
Admission to the neonatal unit	7	7	5
Length of Stay in the neonatal unit	7	7	5
Intraventricular Haemorrhage	9	9	6
Periventricular Leukomalacia	9	9	6
Ventriculomegaly	7	9	6

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Cystic Lesions	8	9	6
Any other neurological imaging abnormalities	7	9	7
Retinopathy of prematurity	6	7	6
Hypertrophic cardiomyopathy	6	7	6
Persistent Pulmonary Hypertension of the Newborn	6	8	6
Congenital heart disease	6	8	6
Anaemia at birth	6	6	6
Anaemia-Polycythaemia at birth	7	6	6
Respiratory Distress Syndrome	7	8	6
Chronic lung disease/Bronchopulmonary Dysplasia	7	9	6
Intubation and Mechanical Ventilation	6	8	6
Pneumonia	6	7	6
Pulmonary Hypoplasia	7	8	6
Necrotising enterocolitis (NEC)	7	9	6
Sepsis (Severe Infection)	7	9	6
Feeding Difficulties	6	7	6
Histopathological evidence of sFGR	5	7	6
Neonatal Renal Failure	7	9	6
Motor impairment	9	9	9
Behavioural disorders	8	7	6
Hearing impairment	8	9	9
Visual impairment	8	9	9
Cerebral Palsy	9	9	9
Neurocognitive Developmental Impairment	9	9	9
Hypertension	6	6	6
Cardiovascular Disorders	7	7	6
Autism Spectrum Disease	6	7	6

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Receptive and Expressive Language Disorders	6	7	7
Premature rupture of membranes	6	6	6
Chorioamnionitis	6	8	6
Preterm birth	9	9	7
Gestational Diabetes or Pre-eclampsia complications	6	6	6
Maternal death	9	9	9
Placental abruption	8	8	7
Life-threatening bleeding (Haemorrhage)	9	9	7
Unintentional membrane separation	6	9	6
Unintentional septostomy	6	9	6
Maternal Length of Stay	6	6	5
Failure of procedure/treatment	8	8	6
Procedure/Treatment to delivery interval	8	7	6
Admission to an Intensive Care Unit	8	8	8
Postpartum Depression	6	6	6

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Figure 1. Illustrative example of an outcome presented in round two

Outcome 52. Preterm Birth

A baby born before 37 weeks of pregnancy.

		Not important (%)			Important but not critical (%)			Critical (%)		
Stakeholder	**Number**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Healthcare professionals	57	0	0	4	13	0	56	21	3	3
Researchers	18	0	0	0	0	8	67	18	2	5
Parent or Carer	28	0	0	0	4	14	48	30	4	0
→ **Please rescore**		□	□	□	□	□	□	□	□	□

The percentage of participants scoring the outcome from every possible response from one to nine was presented. The orange column highlights the participant's score from the previous round.

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Figure 2. Agreed core outcome set

Consensus core outcomes for sFGR

1. **Live birth**
2. **Gestational age at birth**
3. **Birth weight**
4. **Inter-twin birthweight discordance**
5. **Death of surviving twin after death of co-twin**
6. **Loss during pregnancy or before final hospital discharge** ***(miscarriage, stillbirth, termination of the pregnancy, neonatal death, perinatal death)***
7. **Parental stress**
8. **Procedure-related adverse outcome** ***(failure of procedure, procedure to delivery interval, placenta abruption, life threatening haemorrhage, sepsis, maternal death)***
9. **Length of stay in hospital** ***(neonatal)***
10. **Neurological abnormalities on postnatal imaging**
11. **Childhood disability** ***(as described in the WHO International Classification of Functioning, Disability and Health (ICF): Disabilities is an umbrella term, covering impairments, activity limitations, and participation restrictions. An impairment is a problem in body function or structure; an activity limitation is a difficulty encountered by an individual in executing a task or action; while a participation restriction is a problem experienced by an individual in involvement in life situations. WHO 2001)*** (30)

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