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Research priorities for the future health of multiples and their families:

The Global Twins and Multiples Priority Setting Partnership

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Abstract

Objectives: The Global Twins and Multiples Priority Setting Partnership (PSP) sought to identify the top ten research priorities (unanswered research questions) to reduce twins and multiples' mortality and morbidity and, over the long-term, to improve health outcomes for families of multiples.

Methods: The PSP followed the James Lind Alliance method, which was overseen by a global steering group of multiple parent group representatives, clinicians and, researchers. An initial survey identified unanswered research questions for the health of multiples and their families; these questions were then verified as true unanswered research questions by a lack of existing evidence. Indicative questions requiring qualitative evidence will be analysed at a later stage. A second survey prioritised the unanswered quantitative research questions; these results created a short-list of unanswered research questions for final prioritisation at a face-to-face workshop.

Results: A sample of 1120 multiples, parents, clinicians and, researchers from 31 countries suggested 2891 research questions. There were 235 indicative questions answerable by quantitative evidence and 455 questions answerable by qualitative research. Of the questions answerable by quantitative research, 89 were deemed

unanswered after verification by absence of existing evidence. A final workshop of 23 parents of multiple, clinician, and researcher participants determined ten of these research questions to be a priority for multiple health across five categories: Antenatal Care, Intrapartum and Postpartum Care, Neonatal and Paediatric Health, Child Psychiatry and Development, Parental, and Family Health.

Conclusion: Despite evidence that multiples are at increased risk of premature mortality and morbidities, and that there is additional psychological and economic burden on the families of multiples, research and clinical attention to address these issues is lacking. We believe these priorities, derived from a collaborative participatory and multidisciplinary approach provide credible direction for those driving research forward for the health of multiples, families, and communities around the world.

Introduction

Over the last 40 years, the incidence of multiple pregnancies has risen dramatically[1] due mainly to the increasingly widespread use of assisted reproduction techniques and advanced maternal age at conception. For the purposes of the project, the term 'multiple' included twins and higher order multiples. The term 'multiple pregnancy' describes twins and higher order multiples in one pregnancy. Multiples bring many positive outcomes, but also unique challenges, for families, health care professionals, and wider society. Multiple pregnancies are disproportionately represented in stillbirths[2,3], neonatal deaths[4], and cerebral palsy[5]. Furthermore, it has been well established that parents of multiples are at risk for mental health issues postpartum and in early parenting[6-8]. Raising multiple infants of the same age also puts parents at an economic disadvantage[9-11].

Unfortunately, national audits have not yet focused on multiple pregnancies. Moreover, targeted steps to reducing perinatal deaths among multiple pregnancies have been absent from service reviews, commissioning documents, inspection frameworks, including the earlier versions of the United Kingdom's (UK) stillbirth care bundle[12]. Of note, none of the top 11 research priorities identified by the UK Stillbirth Priority Setting Partnership (PSP), target multiple pregnancies[13]. Although several studies have addressed developmental delay in multiples and the mental impact on their parents, research on modifiable risk factors, protective factors, interventions, and health professionals' expertise is lacking[14,15]. It is clear, that in striving to improve multiple

pregnancies' outcomes, there must be increased focus on specific needs of multiples, their parents, and health professionals who work with them.

Setting research priorities for the health of multiples

In November 2017, the PSP was formed at the International Society for Twin Studies Congress, Madrid. The PSP sought to bring multiples, parents, carers, clinicians, and researchers together, from around the world, to identify the top ten unanswered research questions for multiple health research. The overall long-term intention was to reduce multiple mortality and morbidity and to improve long-term health outcomes for families of multiples. Priority setting initiatives are potentially powerful and useful, as they guide national and international research funding policies[16]. They also give more credibility to research questions, as they take into account the views of multiples parents, carers, clinicians, and researchers.

The priority-setting process

The PSP was collaboratively led by a working group which comprised: Twins and Multiples Birth Association (TAMBA UK), Twins Research Australia and St George's University (working group members have been listed below). This project followed the James Lind Alliance method[16]. The process is detailed below (Figure 1).

Ethics

Priority setting partnerships do not require ethical approval as they are audits of research questions deemed important through consultation, rather than projects conducting research. However, due diligence was performed to assess the need for ethics by consulting The Melbourne School of Population and Global Health Human Ethics Advisory Group and St George's University of London Research Governance and Delivery at the Joint Research and Enterprise Office. In addition, the project followed the ethical guidelines of Australia's National Health and Medical Research Council and the European Union's General Data Protection Regulation's principles. This included requesting consent from participants and advising that their participation was completely voluntary and that personal data would be kept confidential and stored securely. Personal data would be stored for the life of the project. Demographic data collected described the sample in a non-identifiable format and we advised participants that their information provided by them would be used for the purpose of publication.

Initiation

A steering group was formed from representatives of multiples or parents of multiples organisations, clinicians (obstetricians, neonatologists, etc.), and researchers. This included 32 members from 23 institutions and 13 countries to achieve as much diversity in geographic and expertise related to multiples as possible. (Steering group members and their institutions are listed below).

Consultation

The steering group developed an initial online survey to identify priority unanswered research questions for the health of multiples and their families. The survey was

designed so that respondents would be able to suggest up to three important unanswered research questions covering topics of importance to multiples' health including: development, health, disease, emotional and mental wellbeing, etc. The survey also requested basic demographic data to describe the responding sample including their: gender, age, country of residence, and their participant role in multiple health (ie. multiple, parent, clinician, or researcher). The survey design was refined through feedback from a pilot with a small group of parent, clinician, and researcher representatives. The steering group publicised the survey through a PSP webpage, their own organisations' websites, social media, and email. The survey was open to all multiples, families of multiples, and those with experience in treating or caring for multiples and their families. Participants were able to access the survey between 16 October and 21 December 2018.

In addition, further unanswered research questions were identified by J.L. from a search of guidelines relevant to the health of multiples, from around the world. The search involved 28 bibliographic databases and searchable websites relevant for topics spanning child development. Research questions were collected from guidelines dated 2011-2017 to capture the most recent sources and were limited to the English language. The search terms used were: "twin", "triplet", "multiple", "multiple births", "multiple pregnancy", "research", and "guidelines".

Collation

The survey results were then downloaded to Microsoft Excel (Microsoft Corp., Redmond, Washington, USA) for analysis. Criteria for excluding questions were

determined *a priori*: those that were not specific to multiples, too broad (relating to the health of multiples in general, rather than a specific topic area), or incomplete. Questions were also excluded when they were translational, i.e. there was existing evidence indicating the questions had been answered, but the evidence had not been communicated adequately to stakeholder groups or implemented to improve health outcomes.

Following the removal of identifiable information, questions were categorised into the five categories listed below and duplicates removed by three working group members (J.L., B.L., and R.B.) under an agreed process. If disagreement arose it was resolved by consensus. The following five categories were used:

- Antenatal Care
- Intrapartum and Postpartum Care
- Neonatal and Paediatric Health
- Child Psychiatry and Development
- Parental and Family Health

Questions were then grouped by similarity to form 'indicative summary questions'. Indicative questions clarify the precise question at hand, omitting any narrative text, to ensure consistency in language and enable it to be checked against the evidence base[16]. When forming indicative questions, the aim was to retain the meaning intended by participants, but to shape the question into a researchable format.

Given the large number of submissions made and the resource required to assess questions requiring qualitative evidence to be answered, a decision was made to continue analysis only with indicative questions requiring quantitative evidence. Indicative questions requiring qualitative evidence would be analysed at a later date when further resourcing was available.

Indicative questions requiring quantitative evidence were then reviewed and verified by 11 steering group experts according to their areas of expertise. These indicative questions were checked against the below sources for evidence that may have already answered these questions:

- The Cochrane Database of Systematic Reviews
- National Institute for Health and Care Excellence guidelines
- Scottish Intercollegiate Guidelines Network clinical guidelines
- Relevant Royal Colleges' guidance
- Randomised controlled trials and other studies resulting in statistically significant results
- Ongoing trials and studies

Questions were deemed answered if a definitive answer was found by the above sources of evidence.

Prioritisation

Verified unanswered indicative questions and research recommendations from the guidelines search formed a list of 89 questions for a second survey. The results of this

survey were to short-list indicative questions for final prioritisation at a face-to-face workshop. Multiples, parents of multiples, clinicians, and researchers from around the world were asked to select the two questions they thought were most important from each of the five established categories (Antenatal Care, Intrapartum and Postpartum Care, Neonatal and Paediatric Health, Child Psychiatry and Development, and Parental and Family Health). The survey then asked participants to order their selected 10 questions in order of importance to them ('1' being most important and '10' being least important). To prevent bias in the selection of questions, the survey presented each new participant with a different randomised list of the questions. As in the case of the initial survey, this second survey also requested participants' demographic data. Promotion was through the same means as the initial survey. The survey was open for participation between 14 May and 9 June 2019. Once the survey closed, raw rankings were de-identified and reverse scoring was applied with Stata 15.0 (Stata Corp., College Station, Texas, USA) so that non-responses (counted as '0') would not create bias in the total scores for each question. An aggregate ranking of the indicative questions was determined for multiples and parents of multiples, and clinicians and researchers separately. Aggregate rankings for multiples and parents of multiples, and aggregate rankings for clinicians and researchers were then combined to ensure multiple and parent of multiples responses were weighted equally against clinician and researcher responses.

The three indicative questions ranked as most important in each of the five categories were presented at a workshop on 16th June 2019 at St George's Hospital, London. Participants from the second survey, steering group members, and other parents of

multiples and clinician representatives were invited to attend the meeting by the working group. At the workshop, two small groups were formed, comprising equal numbers of parents of multiples, clinicians, or researchers. Each group was asked to prioritise the 15 indicative questions as a set. To assist decision-making, aggregate rankings of the indicative questions from the second survey were provided for multiples/ parents of multiples and clinician/ researcher groups. Examples of the original questions from the first survey were also provided to give participants a sense of the alternative perspectives of the indicative questions. After each small group ranked all 15 questions, their rankings were combined into an aggregate ranking for the small groups to consider as a large group.

This process was repeated with a different assortment of parents of multiples and clinicians in each small group. A different facilitator chaired each large group session.

Outcome of the Global Twins and Multiples Priority Setting Partnership

Consultation

The response to the initial survey comprised a sample of 1120 multiples, parents of multiples, clinicians, and researchers from 31 countries (see Table 1) who suggested 2891 research questions. The sample was made up of 84% multiples or parents of multiples. Clinicians and researchers from a range of disciplines participated, with obstetricians (3.1%) and midwives (2.6%) comprising the largest professional groups.

Collation

During analysis, a total of 1744 duplicate questions were identified and 494 questions were considered out of scope as they were not specific to multiples, too broad, or were incomplete. A further 37 unanswered research questions were identified from ten guidelines on multiple health and wellbeing (see Supplementary Table).

The working group determined that 455 indicative questions were answerable by qualitative evidence and 235 indicative questions answerable by quantitative evidence. The steering group reviewed and verified the indicative questions answerable by quantitative evidence, leaving 89 indicative questions remaining as unanswered (see Supplementary material).

Prioritisation

The second survey was completed by a total of 528 multiples, parents of multiples, clinicians, and researchers from 24 countries. Multiples or parents of multiples

represented 82% of the sample. Again, a range of professionals participated, with researchers and obstetricians representing the largest professional groups (both 3.8%) (see Table 1 for a demographic summary). There were 528 submissions which ranked the list of 89 questions. The top 15 questions (the three most highly ranked questions from each of the five categories) were presented at a workshop for final prioritisation.

Of the 23 participants who attended the workshop to determine the top ten questions for the health of multiples and their families, 13 individuals identified as parents of multiples or parent representatives and 13 identified as clinicians or researchers. Seven countries were represented (Australia, Austria, Belgium, England, Germany, Netherlands, and Nigeria). The majority of professionals were obstetricians (26.1%) or fetal medicine experts (17.4%), although there were representatives from neonatology and midwifery as well.

The workshop prioritisation process resulted in ten prioritised questions, with each of the five categories represented. The workshop participants agreed that the order of questions did not reflect the relative importance of each question in the list, given they were from the five different categories. The final list of ten priority research questions answerable by quantitative evidence for the health of multiples and their families are shown in Figure 2. The questions covered the themes of:

- Specialist training to improve pregnancy outcomes.
- Reducing admissions to the neonatal unit.
- Preventing and supporting postnatal mental health problems in parents.
- Preventing maternal complications of pregnancies.

- Assessing the short- and long-term outcomes in pregnancies and how they are affected by antenatal events and medical interventions.
- Managing higher order multiple pregnancies.
- Assessing and supporting a satisfactory growth trajectory for small-for-gestational-age infants.
- Improving developmental outcomes.
- Determining the short- and long-term maternal health risks following pregnancy.
- Examining prenatal factors and supports to benefit birth and ongoing health outcomes for both parents and children.

Concluding Statements

This article provides an academic summary of the priority setting process for The Global Twins and Multiples Priority Setting Partnership. A lay report is also planned for parents of multiples and policy-makers and will be distributed to key stakeholders concerned with the health of multiples. The results of this project represent a range of health research concerns as viewed by multiples, parents of multiples, clinicians and researchers. Many clinician or researcher participants were also multiples themselves or parents of multiples, which brought unique and valuable contributions to the process. These include clinical topics such as the improvement of multiple pregnancy outcomes through training and medical interventions, maternal complications in multiple pregnancy and the growth trajectories of multiples. Key topics also included those of a psychosocial nature such as: parental postnatal mental health, community support for families of multiples and the development of multiples.

This PSP was unique, as the questions involved addressed the health and wellbeing of multiples specifically. Therefore, the range of topics extended from clinical to psycho-social domains. A few themes overlapped with previous PSPs within the antenatal period. The role of antenatal care interventions in pregnancy outcomes has also been prioritised in the stillbirth and preterm birth PSPs. This highlights the persisting gaps in antenatal interventions for complex pregnancies overall. Moreover, whilst the stillbirth PSP asked how modifiable lifestyle factors contributed to stillbirth risk[13], the global PSP prioritises the benefit of prenatal factors to parental and child outcomes. Thus, whilst there has been some overlap between pregnancy-related PSPs, this PSP supports

research specifically for the benefit of multiples, and with a more holistic focus on health.

This study encompassed a broad scope of research areas that were evaluated and a broader scope of participants than is typically found in studies involving questionnaires. This is likely to provide a more balanced representation of issues for research concerning the health of multiples. The high engagement from communities of multiples was a marker of the project's success as a participatory PSP. Combined with the use of existing evidence, this degree of stakeholder engagement produced a credible outcome.

Despite its strengths, the limitations of the PSP approach also require discussion. Given the participant makeup was not equally weighted amongst multiples and parents of multiples, and clinicians and researchers there is a potential for bias. However, when prioritising questions we attempted to mitigate this bias by using aggregate ranking to evenly weight contributions from multiples and parents of multiples, and clinicians and researchers. In addition, due to the global nature of the project, not all steering group members were able to attend the final workshop, which may have contributed to bias at the latter end of the project.

Furthermore, due to the participatory and collaborative nature of PSPs, the list of prioritised questions is broad. Each question was formed to capture the meaning intended by participants and remain accessible not only to clinicians and researchers,

but also to the multiple community. Thus, researchers will be required to refine and format the questions prior to conducting research.

We sought global representation of parents of multiples, multiples and clinicians in this PSP. However, the surveys were in English and online. Therefore, this process excluded those who did not understand English, without internet access, and may have excluded those living in remote areas. One way of addressing this issue, would be to work with community organisations to hold locally-based focus groups to prioritise the indicative questions.

Furthermore, PSPs generally require a high standard of evidence for a research question to be considered 'answered' (for example evidence from systematic reviews or randomised controlled trials). Therefore, there may be some evidence available for some of the prioritised questions, but this evidence was not deemed sufficient by the experts verifying these questions in this process. Moreover, some of the suggested questions were of more relevance to translation – reflecting the need for researchers to communicate existing evidence more effectively to stakeholder groups, rather than indicating that researchers need to conduct more research in these areas.

The results of this PSP clearly point to the top priorities for further quantitative research in clinical care and psycho-social health for multiples and their families. This includes care before, during, and beyond pregnancy for the short- and long-term wellbeing of multiples and parents of multiples. Although only ten questions were prioritised in the final list, we acknowledge that many of the other verified 89 questions (see

Supplementary material) were closely ranked and are also of importance to improve the health of multiples. We believe these priorities, derived from a collaborative participatory and multidisciplinary approach provide credible direction for those driving research forward for the health of multiples, families and communities around the world.

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Figure legends

Figure 1 Flowchart of the priority setting process for global twin and multiple health research

Figure 2 Top 10 areas for research focus

Table 1 Demographic characteristics of respondents to survey one and two to identify and prioritise unanswered research questions concerning twins and multiples

Stakeholder group, n	**Survey 1 (n=1,120)**	**Survey 2 (n=528)**
Multiples or parents of multiples*	942	434
Healthcare professionals†		
Dietitian	5	0
Educationalist	9	1
Fertility specialist	1	1
Fetal medicine expert	26	12
General Practitioner/ family doctor	6	1
Midwife	29	15
Neonatal nurse	4	1
Neonatologists or Paediatricians	8	3
Nurse (public health/ maternal child health/ community)	7	1
Nurse (other)	6	2
Obstetricians	35	18
Paediatric nurse	2	1
Physician/ medical doctor (general)	3	3
Psychologist	5	3
Researchers/ Scientists	24	20
Other	10	5

Prefer not to say	1	1
Missing	6	6
Gender, n		
Male	62	46
Female	1055	473
Transgender woman	1	1
Non-binary	0	2
Other	0	1
Prefer not to say	2	1
Missing	0	4
Age (years), n		
Less than 20 years old	4	1
20-29 years old	77	30
30-39 years old	499	213
40-49 years old	371	165
50-59 years old	133	69
Over 60 years old	30	21
Prefer not to answer	6	5
Missing	0	24
Geographical location, n		

Africa; 2 countries	7	5
Asia; 2 countries	12	2
Australia & NZ; 2 countries	594	220
Europe[‡]	190	210
Middle East[‡]	5	2
North America; 2 countries	306	83
Central & South America[‡]	4	2
Prefer not to say	2	1
Missing	0	3

*Multiples/ parents of multiples/ carers of multiples/ parent group representatives who do not identify as clinicians as well. This group includes parent representatives.

[ł]Healthcare professionals may also identify as multiples/ parents of multiples/carers of multiples. Some healthcare professionals have multiple clinical roles.

[‡]Europe: 15 countries (1st survey) 12 countries (2nd survey)

Middle East: 4 countries (1st survey) 2 countries (2nd survey)

Central and South America: 4 countries (1st survey) 2 countries (2nd survey)

SUPPLEMENTARY MATERIAL

All 89 Questions Verified for Consideration in Survey 2

In each category, questions are ordered from the most highly ranked questions at the top of the list through to low ranked questions at the bottom of the list. The term 'multiple' has been used to represent all types of multiples, except where specifically defined.

Antenatal Care

1. Would staff with specialist training in multiple pregnancies improve outcomes in these pregnancies?
2. How are higher order multiple pregnancies best managed? And what are the long-term effects to the mother and the babies?
3. What causes an embryo to split to produce identical twins?
4. How can the health of mothers pregnant with multiples be prevented from deteriorating during late pregnancy, onwards?
5. What effects do fertility drugs have on multiples' overall health and wellness, growth and development or their own fertility?
6. What treatment modalities can be used to manage and reduce pre-eclampsia in multiple pregnancies?
7. Is the incidence of preterm delivery related to overt pregnancy monitoring and misconceived risks?

8. In settings where prophylactic antenatal corticosteroids are being used in women with a multiple pregnancy, with no other identified risk of preterm birth, there is a need for a randomised trial.

9. What are the best management strategies for gestational diabetes in multiple pregnancies, and what different dietary measures can be taken to reduce need for medication?

10. How do opposite sex twins influence each other hormonally in utero?

11. What role does the mother's gut health have in multiple pregnancies and how do we optimise this to ensure a healthy pregnancy outcome?

12. What are the effects and accuracy of symphysis fundal height measurement to detect abnormal fetal growth and other risk factors for perinatal morbidity (e.g. multiple pregnancy, polyhydramnios) in settings without routine ultrasound?

13. How can multiple pregnancies be predicted and possibly reduced in both natural and assisted reproduction?

14. What is the increased chance of readmittance to hospital after discharge for premature twins?

15. What methods can be used to predict fetal feeding issues?

16. How can multiple births help us to understand reproduction and failing to reproduce?

17. Conduct a decision analysis / economic analysis for antenatal corticosteroids.

18. What impact does multiple pregnancy have on mothers' dental health?

19. What are the nutritional needs of mothers pregnant with twins when they have a history of bariatric surgery? (Including supplementation).

20. Do fertility drugs influence multiples' sexual orientation?

21. Does a history of bariatric surgery have more significant nutritional implications in twin pregnancies?

Intrapartum and Postpartum Care

1. How can we reduce multiples' stay in the neonatal intensive care unit during the postnatal period?
2. What health risks are the mother and babies at risk of following a multiple pregnancy?
3. What supports and changes to the lifestyle of the mother carrying twins/ multiples have the most benefit on the birth and ongoing health outcomes?
4. What future health risks should physicians be looking for in mothers after the birth of multiples?
5. What are the risks vs benefits of epidural in labour for multiples, and does this increase the risk for intervention?
6. What effect does giving birth to multiples have on the female brain (including central pontine myelinolysis in mothers who have had caeserean sections)?
7. What added complications are involved in the recovery following caeserean sections or vaginal deliveries in mothers of multiples?
8. Do delivery circumstances affect the cardiovascular health of twins later in life?
9. What is the optimal cord clamping time for monochorionic diamniotic twins?
10. What interventions assist a mother in recovering from a multiple birth delivery?

11. Why do mothers of multiples have lowered basal metabolic rate after birthing multiples? Is it a genetic trait and does this cause mothers of multiples to live longer?

12. Are there lingering side effects from the hormone lift and drop post-partum with twins?

13. Should timing of delivery be offered earlier to post preimplantation genetic diagnosis multiple pregnancies?

Neonatal and Paediatric Health

1. What are the long-term outcomes in twin pregnancies, and how is this effected by early medical interventions and antenatal events?

2. Are multiples more likely to experience developmental delays, based on gestational age?

3. What are the health benefits and disadvantages of being a twin?

4. What are the expected growth patterns for small-for-gestational-age multiples? And how can we ensure that they follow a satisfactory growth trajectory?

5. What medical conditions should be regularly screened for in multiples?

6. What can we do to reduce the health implications of being born a multiple?

7. Does the smaller twin always have a greater chance of health issues?

8. What nutritional support is best for preterm multiples, and how can their growth be best monitored (through customised growth charts)?

9. What is the optimum gestation to deliver multiples with twin anemia polycythemia sequence? And how does this impact the outcome of prematurely born multiples?

10. What are the differing nutritional needs between twins (term and preterm) and singletons, and are multiples at higher risk of feeding difficulties?

11. Is there a higher occurrence of Mild Intellectual Disabilities in identical multiple births?

12. What are the long-term health outcomes in preterm triplets?

13. What is the average life expectancy of multiples compared to singletons?

14. What is the incidence of a difference in handedness between twins in a pair?

15. How can we prevent family conditions affecting our multiples?

16. Is it common amongst identical twins to have identical dental records/ health?

17. What is the incidence of home oxygen therapy for twins following delivery, and what is the mean duration?

18. Do multiples begin menstruating at the same time?

Child Psychiatry & Development

1. Do interactions between twin and multiple babies help with early brain development (including mental/ motor skills) (during the first three years of life) in the same way that infant-parent interactions do?

2. What are the long-term neurological outcomes for identical twins?

3. What parenting techniques are most effective for improving educational outcomes (for identical and non-identical twins)?

4. What are the speech and language developmental trajectories of twins?

5. What can parents do from day one to reduce the chances of language delays in twins/ multiples?

6. What can be done to prevent attention deficit hyperactivity disorder/ autism in twins?

7. How does birth order correlate to developmental issues in multiples?

8. How quickly should interventions be applied if a multiple child is showing some delay?

9. What is the likelihood of all children in a multiple birth having special needs?

10. Do multiple children get to spend more time in play than singletons? If so, what are the outcomes?

11. How big is the academic gap between identical twins and is it common for them to show different academic profiles?

12. What is the relationship between higher order multiple gender and birth order and the development of mental health issues, such anxiety and depression?

13. How do genes, environment and epigenetics influence differences in identical twin girls' temperament and personality in a triplet cohort?

14. What percentage of multiples experience speech delays?

15. What difference in grades or athletic ability exist for high school age multiples? How is this difference best dealt with?

16. What preventative measures can be taken prior to birth or in infancy to minimise attention deficit hyperactivity disorder in male twins in opposite sex twin pairs?

17. What is the incidence of twins expressing their emotions differently or the same?

18. Does each triplet have the same chance of suffering from depression/ anxiety? Does birth order play a role?

19. How is the rising use of electronics impacting twins' development?

20. Can one multiple in a group be at greater risk of experiencing learning disabilities than the other multiples in the same group?

21. Does concordance and mutual reinforcement of cognitions and symptomatic behaviours compound mental illness amongst twins? E.g. How does obsessive compulsive disorder differ amongst mono and dizygotic twins?

Parental & Family Health

1. What interventions provide the best postpartum and mental health support for families of multiples?
2. What interventions prevent or minimise the impact of postpartum depression in parents/ families of multiples (including twins)?
3. At what age do twins benefit from one-on-one time from the main caregiver and how much is adequate?
4. Which prenatal factors (eg. life style, health history, personality characteristics etc.) are associated with the most positive outcomes in a multiple pregnancy and in the first years of parenting multiples for women and for men?
5. How does long-term lack of sleep/ continual sleep interruption impact the physical and mental health of parents or single parents with multiples?
6. How can we predict and ameliorate the risk of postnatal mental health problems?
7. What is the timing of the occurrence of postpartum depression in birth mothers of multiples?
8. What are the protective and risk factors for family unity in multiple birth families?
9. Does attending multiple specific antenatal classes improve parenting resilience and reduce postnatal depression for families?
10. What role does parent education play in reducing parental stress in the early years?

11. Are mental health issues greater among parents of adolescent multiples in comparison with the general population?

12. How does breastfeeding triplets affect the bone density of the mother?

13. How many people are involved in the upbringing of multiples in the first 5 years of life? What is their relationship with the multiples?

14. What can be done to prevent severe stretching of stomach skin in multiple pregnancies?

15. How should parents' knowledge of their triplets' zygosity (with an identical and fraternal combination) make decisions about their triplets' health conditions?

Supplementary Table. Thirty-seven research questions identified from guidelines collated for priority questions for the health of multiples. The majority of the questions dealing with antenatal administration of corticosteroids were not specific to multiples, and were filtered out by the PSP process.

Source	Year	Research Question
WHO – Recommendations for Induction of Labour	2011	Should induction of labour be offered to women with an uncomplicated twin pregnancy at or near term?
WHO – Recommendations on Antenatal Care for a Positive Pregnancy Experience	2016	What are the effects and accuracy of symphysis fundal height measurement to detect abnormal fetal growth and other risk factors for perinatal morbidity (e.g. multiple pregnancy, polyhydramnios) in settings without routine ultrasound?
ACOG – Delayed Umbilical Cord Clamping after Birth. Committee Opinion, No. 684	2017	The optimal timing of uterotonic agents after birth in relation to umbilical cord clamping needs further study, as does the optimal practice in multiple gestations and pregnancies with risk factors for neonatal polycythemia.
BJOG Green-top Guideline No. 51 – Management of Monochorionic Twin Pregnancy	2016	Further prospective research evaluating the role of undertaking middle cerebral artery peak systolic velocity screening in monochorionic twin pregnancies routinely to detect twin anaemia-polycythaemia sequence and to improve pregnancy outcome is required.

		The use of serial middle cerebral artery peak systolic velocity in screening for twin anaemia-polycythaemia sequence in women with monochorionic twins and its evaluation in a diagnostic accuracy study, with relevance to pregnancy outcomes.
		Research evaluating early versus late treatment for monochorionic twins complicated by twin reversed arterial perfusion sequence and its assessment in terms of pregnancy outcomes.
ICOMBO – Declaration of Rights and Statement of Needs of Twins and Higher Order Multiples	2014	Benchmarks of healthy psychological development, and relevant therapeutic interventions for multiples of all ages and at the death of a co-multiple.
		Norms for developmental processes which are affected by multiple birth such as: individuation, socialization, and language acquisition.
		Strategies and interventions that are effective in promoting the health of multiple birth families during the parenting period such as: breastfeeding, employment

		policies, prevention of postpartum mood disorders.
		Management of ethical issues by health professionals and multiple birth families such as: assisted reproduction, multifetal and selective pregnancy reduction.
		Benchmarks of healthy psychological development, and relevant therapeutic interventions for multiples of all ages and at the death of a co-multiple.
		The optimal management of plural pregnancies.
		Medical, developmental and educational assessment/treatment respectful of the relationships between co-multiples.
ISUOG – Consensus Statement on The Impact Of Non-Invasive Prenatal Testing on Prenatal Ultrasound Practice	2014	Accuracy of non-invasive prenatal testing in twin pregnancies should be investigated further.
ISUOG – Practice Guidelines: Role of Ultrasound in Twin Pregnancy	2016	Moreover, there is no effective strategy to prevent preterm birth in these women. Bed rest, progesterone therapy, Arabin cervical pessary or oral tocolytics do not reduce the risk of preterm delivery in these women. However, progesterone therapy might reduce the risk of

		neonatal morbidity and mortality. Ongoing research may clarify management in this area in due course.
Liggins Institute, The University of Auckland – Antenatal Corticosteroids Given to Women prior to Birth to Improve Fetal, Infant, Child and Adult Health	2015	There is a need to better assess the impact, if any, of in utero exposure to a single course of antenatal corticosteroids on: • The hypothalamic-pituitary adrenal axis of the infant, child and adult; • The glucose-insulin axis in childhood; • The later risk of the infant developing diabetes in adulthood.
		Future research that investigates the use of a single course of antenatal corticosteroids should include: • Outcomes on maternal quality of life; • Report on the risk factors for preterm birth of the included participants; • An assessment of the degree and health impact, if any, of changes in maternal blood glucose control.
		Randomised trials are needed to: • Compare betamethasone and dexamethasone to assess the effect on the short-term and long-term outcomes for the infant;

		• Investigate the optimal timing for antenatal corticosteroids where preterm birth is planned (e.g. maternal medical indications or fetal compromise) and women can be randomised to administration of antenatal corticosteroids at different time intervals prior to birth; • Investigate the neonatal benefits of antenatal corticosteroids administered to women at less than 24 weeks' gestation; • Investigate if smaller doses are needed at lower gestational ages; • Investigate the neonatal benefits of antenatal corticosteroids administered late preterm (34 weeks' and 6 days to <37 weeks' gestation); • Review the effect of a single course of antenatal corticosteroids on women with systemic infection at risk of preterm birth; • Evaluate the use of antenatal corticosteroids in settings where a single course of prophylactic antenatal corticosteroids is being used for women with a multiple pregnancy and no other identified risk of preterm birth.

		To maximise benefit and minimise harm to the mother and infant there is a need to establish: • The minimally effective dose per course of both betamethasone and dexamethasone; • The optimal timing interval per course between doses for both betamethasone and dexamethasone; • The optimal number of doses per course for betamethasone; • The optimal number of doses per course for dexamethasone. • Establish the haemodynamic effects of antenatal corticosteroids on the growth restricted fetus. • Establish the optimal timing of birth following administration of antenatal corticosteroids to women with a fetus with intrauterine growth restriction.
		Randomised trials are needed to investigate the effects, if any, of using antenatal corticosteroids at term gestation (≥37 weeks') in women with diabetes in pregnancy.
		In settings where prophylactic antenatal corticosteroids are being used in women with a multiple pregnancy, with no other identified risk of preterm birth, there is a need for

		a randomised trial.
		Randomised trials are needed to investigate the neonatal effects and childhood disability rates when antenatal corticosteroids are administered to women prior to planned caesarean section at term gestation (≥37 weeks') where their infants are at increased risk of neonatal respiratory disease.
		There is a need to better assess the impact, if any, of in utero exposure to repeat antenatal corticosteroids on: Physiological outcomes: • The glucose-insulin axis in childhood, • Hypothalamic-pituitary adrenal axis, • Bone mass, • Body size and body composition, • Neurosensory impairments, • Respiratory function. Health outcomes: • Cardiovascular disease, • Metabolic disease, • Diabetes, • Psychological health,

		• The later risk of developing diabetes in adulthood. Social outcomes: • Educational attainment, • Behaviour, • Cognitive ability.
		Any future research to investigate the effects of treatment with repeat antenatal corticosteroids should: • Include outcomes for maternal quality of life. • Report on the risk factors for preterm birth of the included participants. • Assess the degree and health impact of changes in maternal blood glucose control.
		Randomised trials are needed to: • Evaluate dexamethasone as the repeat antenatal corticosteroid; • Compare the use of different timing of administration of repeat antenatal corticosteroids prior to preterm birth where preterm birth is definitely expected or planned; • Investigate the effects of repeat antenatal corticosteroids in women ≥32 weeks' and 6 days gestation; • Investigate if antenatal corticosteroids should be

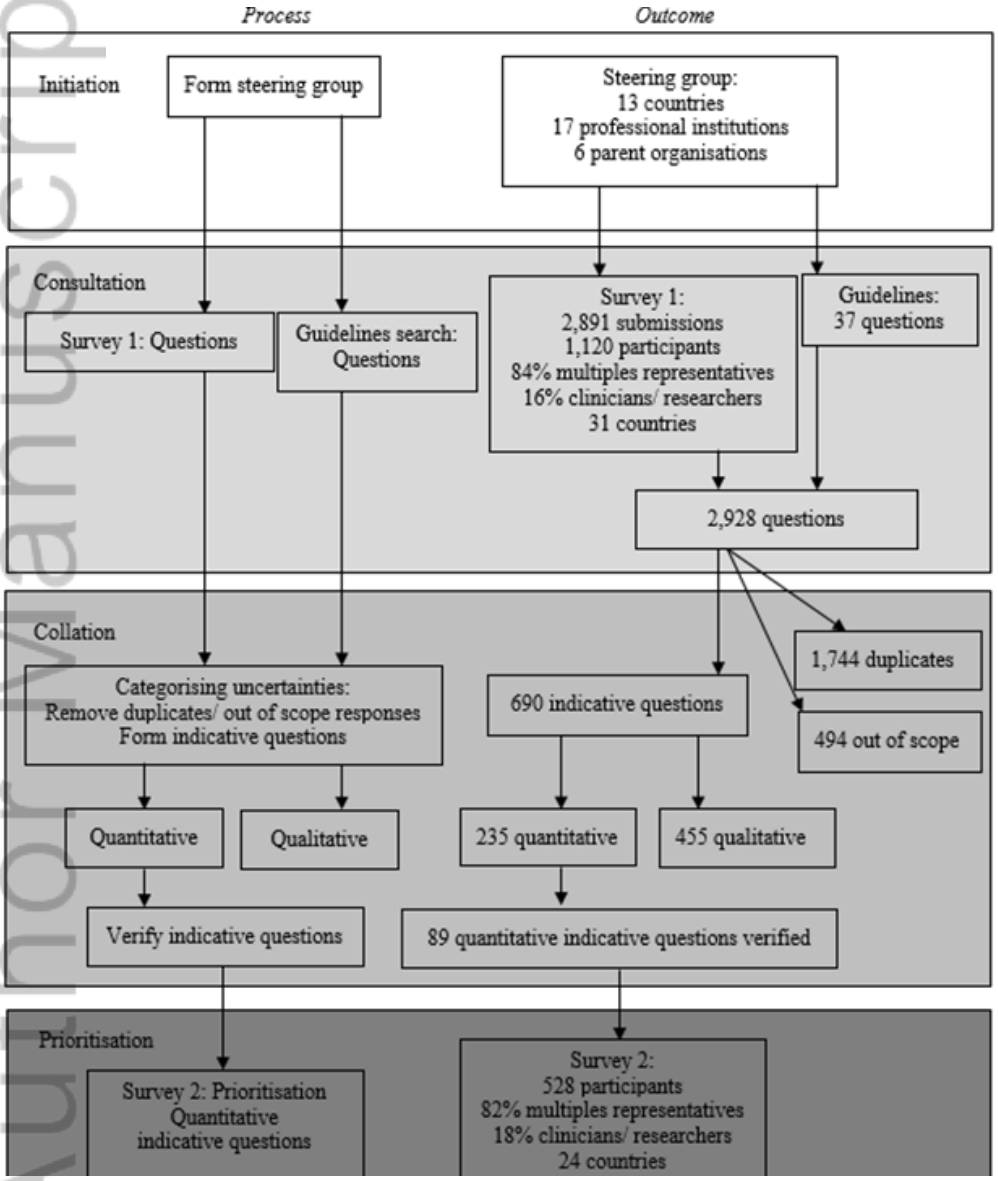
		repeated in women at risk of preterm birth who had antenatal corticosteroids 7 days previously and then present with chorioamnionitis; • Assess the impact, if any, of repeat antenatal corticosteroids in women with systemic infection at risk of preterm birth; • Evaluate in settings where repeat prophylactic antenatal corticosteroids are being used for women with a multiple pregnancy and no other identified risk of preterm birth.
		Conduct an individual patient data meta-analysis to explore key outcomes.
		Further research is required to explore betamethasone and dexamethasone as the repeat antenatal corticosteroid for: • The optimal dose • The optimal number of dose(s) in a course • The optimal interval between courses • The effect of multiple repeat doses/courses.
		Establish the best management of women with diabetes in pregnancy given repeat antenatal corticosteroids.
		Conduct a decision analysis / economic analysis for

		antenatal corticosteroids.
NICE – Multiple Pregnancy: Antenatal Care for Twin and Triplet Pregnancies	2017	What is the incidence of perinatal and neonatal morbidity and mortality in babies born by elective birth in twin and triplet pregnancies?
		What is the effectiveness of information and emotional support in improving maternal satisfaction and psychological wellbeing, and in increasing the uptake of breastfeeding?
		What is the incidence of monochorionic monoamniotic twin and triplet pregnancies, and what clinical management strategies are most effective in such pregnancies?
		Should different information and support be offered according to the chorionicity of the pregnancy?
		Does specialist antenatal care for women with twin and triplet pregnancies improve outcomes for women and their babies?
		What is the pattern of fetal growth in healthy twin and triplet pregnancies, and how should intrauterine growth restriction be defined in twin and triplet pregnancies?

		What interventions are effective in preventing spontaneous preterm birth in women with twin and triplet pregnancies, especially in those at high risk of preterm birth?
RCOG – Scientific Impact Paper No. 8 – In Vitro Fertilisation: Perinatal Risks and Early Childhood Outcomes	2012	When stratified for multiple births, perinatal death rates among preimplantation genetic diagnosis / preimplantation genetic screening singleton and intracytoplasmic sperm injection singleton children were similar (1% versus 1.3%), but there were significantly more perinatal deaths seen in post-preimplantation genetic diagnosis / preimplantation genetic screening multiple pregnancies compared with conventional ICSI multiple pregnancies (11.7% versus 2.5%), and this was not attributable to an increased prevalence of monozygotic twins. Notably, all of these perinatal mortality rates are substantially higher than the general population rates, and further research is required to elucidate the time of death to determine whether timing of induction of labour could be altered to minimise the risk at term.

ACOG, The American College of Obstetricians and Gynecologists; ICOMBO, International Council of Multiple Birth Organisations; ISUOG, International Society of Ultrasound in Obstetrics & Gynecology; NICE, The National Institute for Health and

Care Excellence; RCOG, Royal College of Obstetricians and Gynaecologists UK; WHO, World Health Organization.



- Would staff with specialist training in multiple pregnancies improve outcomes in these pregnancies?
- How can we reduce multiples' admission to the neonatal unit? If admitted, how can we reduce multiples' length of stay in the neonatal unit?
- What interventions prevent and support postnatal mental health problems in parents of multiples?
- How can we prevent maternal complications of multiple pregnancies?
- What are the short- and long-term outcomes in multiple pregnancies? How are these outcomes affected by antenatal events and medical interventions?
- How are higher order multiple pregnancies best managed?
- What are the expected growth patterns of small-for-gestational-age multiples? How can we assess the growth of infant multiples and ensure that they follow a satisfactory growth trajectory?
- What parental interventions can improve the developmental outcomes (i.e. speech, language, education) of multiples?
- What are the short- and long-term maternal health risks following a multiple pregnancy?
- What prenatal factors (including changes to lifestyle, health history, personality characteristics etc.) and supports for parents of multiples have the most benefit on birth and ongoing health outcomes for both parents and their children?

Figure 2