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MERIDIAN

Magnetic resonance imaging to enhance the diagnosis of fetal developmental brain abnormalities in utero

Funded by the National Institute for Health Research's Health Technology Assessment programme (project number 09-06-01)

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Magnetic resonance imaging to enhance the diagnosis of fetal developmental brain abnormalities in utero

MERIDIAN

Contents

Abbreviations

AE	Adverse event
CI	Chief Investigator
CRF	Case report form
CT	Computed tomography
CTRU	Clinical Trials Research Unit
DMC, DMEC	Data Monitoring and Ethics Committee
GP	General Practitioner
IUFD	Intra uterine fetal demise
SPSS	Statistical Package for the Social Sciences
HADS	Hospital anxiety and depression scale
HRQoL	Health related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
IRAS	Integrated Research Application System
iuMR	In utero magnetic resonance
LREC	Local Research Ethics Committee
MHRA	Medicines and Healthcare products Regulatory Agency
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NHS	National Health Service
NHSFT	NHS Foundation Trust
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
PI	Principal Investigator
QALY	Quality adjusted life year
R&D	Research and development
SAE	Serious adverse event
SMG	Study management group
SSC	Study steering committee; service support costs
STH	Sheffield Teaching Hospitals
TOP	Termination of pregnancy
TMG	Trial management group
TSC	Trial steering committee
UK	United Kingdom
URMS	University Research Management System
US	Ultrasound

Protocol amendments since Version 1.0

Section 6. Enrolment (page 19).
Explanatory note added detailing the arrangements and time provision for consent process.

Protocol amendments since Version 2.0

Contents (page 2).
Page numbering updated.
General information (pages 7-10).
Full membership of study committees specified.
Change of site Principal Investigator for Manchester.
Section 1. Introduction (page 13).
Correction of gestational age range for second trimester ultrasound screening programme.
Section 3. Study Design (page 18).
Independent expert panel to be appointed for assessment of diagnostic agreement rather than individual assessments by two fetal medicine experts.
Section 5. Selection and withdrawal of participants (page 22).
Clarification of wording for inclusion criteria.
Section 7. Study Treatment (page 23).
Clarification of the purpose of second reporting of MR studies by Sheffield team.
Section 8. Assessments and procedures (page 31).
Clarification that in all cases fetal medicine clinic staff (e.g. a research midwife) will determine if and when it is appropriate to give or send survey questionnaires to study participants. A redundant sentence has also been removed from the protocol text (which described how survey questions were to be developed).
Section 8. Assessments and procedures (page 32).
Fetal medicine midwifery staff will also be included in health professional interviews depending on available resources and theoretical saturation.
Section 8. Assessments and procedures (page 37-38).
Clarification of terminology used in Table 2 (Expected serious adverse events). Reference also made to detailed procedures for adverse event reporting within the Appendix.
Section 9. Statistics (page 40).
Reference added to detailed Statistical Analysis Plan (SAP) within the Appendix.
Appendix (page 48).
Full list of Case Report Forms and other study documentation included, along with document links. Each referenced document is subject to individual version and date control distinct from the main protocol text (document links will be maintained to the most recent version). Please note that the Research Ethics Committee will be notified of any amendments to documents listed within the Appendix which are subject to their specific review and approval procedures (these being Forms A – C and I - S).

Protocol amendments since Version 3.0

Section 8. Assessments and procedures (pages 25-26).
Additional procedures and documentation are described to aid collection of pregnancy outcome information , including the offer of postnatal ultrasound scans and post mortem MRI examination.
Appendix (page 50).
New Case Report Forms T, U, V, W, X added to list of document links. An additional document is also listed detailing the requirements of the Expert Panel which will be appointed to assist with data interpretation and analysis.

Protocol amendments since Version 4.0

Title Page
CSP reference added
General Information
Updates to membership of Data Monitoring and Ethics Committee (removal of non-voting member Angelo Franchini). Update to study management group, removal of Mike Reeves and substitution of Allan Wailoo for Simon Dixon. Update of Principal Investigator list to include new sites.

Section 5 Selection and withdrawal of participants
Clarification to inclusion criteria 1 regarding gestational age to make clear that participants can be consented at 17 weeks but MRI must take place at 18 weeks.
Section 8 Assessments and procedures
Additional text to say that information on participants parity will be collected
Section 8 Assessments and procedures
Additional text to explain that 3rd trimester ultrasound data can be used as a reference standard in cases of losses to follow up and where local clinicians have decided against postnatal imaging
Section 8 Assessments and procedures
Additional text to explain that Health Professionals may be contacted for interview by telephone
Section 8 Assessments and procedures – Study Safety
In table of expected SAEs added definition of pre-term delivery as being less than 37 weeks
Section 9 Statistics
Added definition that the date the MRI is performed is used as the of date of management choice. Meaning that the sub-group of women whose management choice is made by 24 weeks gestation will be those women whose MRI scan was performed before 24 weeks.
Section 9 Statistics
Changed the information about when the interim analysis will be carried out from after approximately 350 reference diagnosis have been obtained to after approximately 100 reference diagnosis have been obtained.

Protocol amendments since Version 5.0

Section 10 Study supervision
Update to figure 4.0 with revised project management plan reflecting 10 month extension to the recruitment period.
Appendix
Removal of list of list of Case Report Forms and other study documentation. Insertion of "Add On" sub study appendix

Protocol amendments since Version 6.0

General Information (Core staff and Principal Investigators)
Study manager and sites have been updated to reflect changes to the trial team. **Study summary; Section 3 Study Design including Figure 1; Section 9 Statistics**
Updated the recruitment target to 'at least 750' rather than 750 in order to achieve the 366 and 504 target.
Study summary; Section 3 Study Design including Figure 1
Updated the number of sites to 'at least 13' rather than 13.
Study summary; Section 3 Study Design including Figure 1; Section 5 Exclusion criteria; Section 7 Study Treatment; Section 8 Key outputs
Amended Edinburgh to Belfast as Edinburgh is not a site, and Belfast is.

Protocol amendments since Version 7.0

Appendix Study Design and Assessment and Procedures
Details of £10 voucher incentive added

Protocol amendments since Version 7.1

Appendix Study Design, Exclusion criteria and Assessments and Procedures
Updated to include St George's Hospital as an iuMR scanning site for St George's participants.

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Study Summary

The aim of this research study is to assess magnetic resonance (MR) imaging as a technology to aid in the prenatal diagnosis of fetal developmental brain abnormalities. The study will recruit at least 750 pregnant women from 18 weeks gestation onwards where the fetus is known or suspected of having some form of developmental brain abnormality based on antenatal ultrasound (US) examination. Study participants will be consented from at least 13 collaborating fetal medicine units drawing from a large and varied geographic and socio-economic referral area in England and Scotland. The study is designed primarily to assess the diagnostic accuracy of MR imaging (compared to the diagnostic accuracy of US alone), along with the related aspect of diagnostic confidence. This will be determined by comparing prenatal diagnosis with an anatomical reference diagnosis gained from either post-natal imaging in live born infants (up to 6 months of age) or post-mortem examination in the event of fetal demise, termination of pregnancy (TOP), stillbirth or early neonatal death. Figure 1 in the study design section of the protocol provides an overview of the study.

The clinical impact of MR imaging in this context will also be assessed both quantitatively, as prospectively reported changes in clinical management attributable to MR imaging results, and qualitatively by assessing the impact of the 'new technique' on the clinicians who interact with the pregnant women. In parallel, the opinions of the women included in the study will be sought in order to assess perceptions of MR imaging on acceptability and decision making. Finally, health economic modelling will be performed for the specific changes in management attributable to the inclusion of MR imaging in the diagnostic pathway.

The work is centred at the Academic Unit of Radiology, University of Sheffield. The MR examination itself will be performed either in Sheffield, Newcastle, Leeds, Birmingham, Belfast or Manchester. The aim is to deliver a programme of research able to inform fetal medicine practice within the United Kingdom in four years from the start of the study. More specifically, it will provide evidence related to the clinical and cost effectiveness of in utero MR imaging in the management of pregnancies complicated by fetal brain abnormalities. The study will provide evidence relevant to a range of health policy options, for instance indications for in utero MR imaging based on gestational age (before and after 24 weeks) and for specific types of suspected brain abnormality. The results should also provide some indication of the clinical and patient acceptability of centralised versus regional MR services.

1. Introduction

Fetal imaging with ultrasound has been the mainstay of screening programmes and detailed anomaly scanning for many years. No imaging methodology is perfect and various technical factors and physical limitations may conspire to produce a situation in which suboptimal images of the fetus are obtained. This may lead to an erroneous diagnosis of structural abnormalities and incorrect prognostic information being given to parents. The fetal brain is a particular area of concern because of the relatively high frequency of developmental abnormalities and also the number of clinically significant pathologies which give rise to subtle imaging changes. Advances in MR technology allow highly reliable and accurate diagnoses of comparable pathology to be made in children because of great improvements in spatial and contrast resolution. Further advances in hardware and software in the 1990's meant that in utero MR imaging became a realistic clinical possibility and our group were pioneers in this field [1]. From those first attempts at devising clinically usable sequences without recourse to maternal sedation or fetal paralysis, several groups, including our own, have confirmed that in utero MR for fetal brain abnormalities is a powerful adjunct to ultrasound as early as 18 weeks gestational age.

A large proportion of the published early literature described the techniques required to perform in utero MR along with anecdotal cases in which it had provided additional information as an adjunct to ultrasound [2-7]. Although relatively large case series were reported, most lacked comparison with a reference standard. This is vital to confirm improvements in diagnostic accuracy. The status of the clinical applications and ethical issues surrounding in utero MR was described by our group in an invited review for the British Medical Journal [8]. All groups, including our own, have been criticised by specialist fetal neurosonography experts on the basis of artificially high detection rates for in utero MR resulting from biased patient selection [9, 10]. Our study published in 2004 [11] was significantly biased as it focused on 100 cases where ultrasound had not provided useful/optimal diagnostic information, for instance due to fetal lie, oligohydramnios or unfavourable maternal habitus. We showed that there was a 48% improvement in diagnostic accuracy when in utero MR was included in the diagnostic pathway for these cases, and we believe that this figure provides an estimate of the maximum potential improvement attributable to in utero MR. Our more recent study focused on 147 fetuses with isolated ventriculomegaly as judged by ultrasound with high confidence and no technical limitations [12]. In this group in utero MR was still able to identify other clinically relevant brain findings in 17% of cases. Recent published research in the field of fetal neuroimaging with MR has concentrated on ventriculomegaly, and this is undoubtedly highly relevant because of the high prevalence of the finding (1-2/1000 pregnancies). Launay et al. concluded that in utero MR was "more informative than ultrasound in 32.8% of cases" and identified the cause of the ventriculomegaly in 21.3% of cases in a study of 61 fetuses [13]. Salomon et al. studied 185 third trimester fetuses with isolated mild ventriculomegaly [14] and found that 11/185 (5.9%) had other brain abnormalities.

A large study of developmental brain abnormalities, with unbiased selection of cases, is now required in order to inform clinical practice in the UK. This study will recruit pregnant women identified during routine second trimester ultrasound screening (i.e. between 18^{+0} and 20^{+6} weeks gestation), but also will include abnormalities first recognised later in pregnancy; i.e. this study will offer in utero MR to any woman whose fetus may have a developmental brain abnormality at 18 weeks gestational age or later. Our previous experience in the field has shown that this is both practicable and likely to be of clinical benefit.

There is a paucity of secondary research data in the area, with no meta-analyses performed to date (to our knowledge). There is only limited evidence concerning the effect of in utero MR on management and clinical outcome. Simon et al. showed that 46% of 52 cases were managed differently after in utero MR [15], while Levine et al. found that counselling and management were changed after in utero MR in 49.7% and 13.5% of cases respectively [16]. While both authors concluded that MR was helpful in fetuses with ventriculomegaly to visualise associated abnormalities, they did not stipulate which other cases should be selected for in utero MR examination [9]. Significant changes in clinical management were shown in the majority of cases from our study of isolated ventriculomegaly when further brain abnormalities were shown on in utero MR, and this occurred most frequently between the gestational ages of 20 to 24 weeks [12].

The evaluation of in utero MR needs also to include patient views about the acceptability of MR imaging for informing their understanding of fetal anomaly. New technologies in fetal medicine raise ethical and social dilemmas for the patients involved. The views of such women and their partners are important when considering issues of clinical implementation [17]. Data from studies of MR experience outwith pregnancy suggest that this technology may be perceived positively in terms of e.g. comfort and impact on care [18]; however, it can also be associated with anxiety [19, 20] and may be evaluated as less acceptable than ultrasound [21]. Overall satisfaction with prenatal diagnosis is high [22]; key factors that impact on satisfaction include participation in decision making [23], staff attitudes [23, 24] and the amount of information provided [24]. The limited data available on the use of in utero MR imaging suggest that it may generate additional distress (especially where fetal prognosis is poor [25, 26]) and more anxiety than ultrasound [27].

The research undertaken in this study is therefore a logical extension of our previous work. It will come from a large, widely representative population group and should provide definitive data on diagnostic accuracy, diagnostic confidence, effect on management and acceptability of in utero MR in a timely fashion. The study is observational, however the results of in utero MR imaging will be available to fetal medicine clinicians during the study and may therefore influence clinical management decisions in individual cases (according to clinical judgement). This scenario is already considered acceptable clinical practice in previous and ongoing research studies both within our site and in other national and international centres. Any change in clinical management and decision making directly attributable to the information provided by in utero MR imaging will be recorded prospectively, and the accuracy of that information will be compared against a postnatal or post mortem reference diagnosis.

The sociological aspects of the study will examine patients' views of care, including overall satisfaction with care, acceptability of in utero MR in the process of prenatal diagnosis, and the impact of in utero MR on decision making. Although measuring phenomena like 'confidence' or 'satisfaction' in public sector services can be problematic [28, 29], patient satisfaction remains a key indicator in the evaluation of health care services from a user perspective [30, 31]. A synthesis of qualitative and quantitative methods has been identified as useful in researching user perspectives with health services like maternity care [29, 32]. Hence in order to understand patient perspectives on the use of in utero MR in prenatal diagnosis we will adopt a mixed methods approach. This methodological approach is particularly important given that there is evidence that MR imaging technology is often misrepresented in non-professional domains [33, 34].

Understanding the possible implications of applying innovative health technologies requires an approach that can situate such developments in their social and cultural context [17, 35]. This means that whilst patient perspectives are important, the perspectives of health professionals must also be explored if innovative use of in utero MR is to be understood adequately. Diagnosis is a technical process, but also a 'powerful social tool' [36], and the history of MR use in medicine suggests that understanding health professionals' views is essential in producing an adequate analysis of what innovative technology means in practice [37]. The inclusion of an in-depth qualitative study of health professional perspectives alongside patient perspectives therefore allows for a more comprehensive understanding of the utility of in utero MR in this setting [32].

In terms of professional service users, the current study group includes 13 fetal medicine units with a long record of collaboration with the Academic Unit of Radiology in Sheffield. Specialist patient support groups relevant to the research, some of which are already in close contact with our research network (for instance the Association for Spina Bifida and Hydrocephalus, ASBAH; Antenatal Results and Choices, ARC), have been consulted regarding the design of the study and to give their views on the proposed patient pathway.

In addition to the patient and public involvement outlined above, which has guided the design of this protocol, the study will be conducted in compliance with the principles of Good Clinical Practice (GCP) and relevant research governance regulatory requirements.

2. Aims and objectives

The aim of the research is to assess magnetic resonance (MR) imaging as a technology to aid the prenatal diagnosis of fetal developmental brain abnormalities.

1) We will assess diagnostic accuracy of in utero MR compared to antenatal US through:
a) Measurement of diagnostic accuracy of antenatal US alone (i.e. prior to in utero MR) relative to a reference diagnosis (post-natal imaging or post-mortem examination).
b) Measurement of diagnostic accuracy of in utero MR (following antenatal US) relative to a reference diagnosis (post-natal imaging or post-mortem examination).

2) We will assess the clinical effectiveness of in utero MR through:
a) Change in clinical diagnostic confidence before and after an MR scan
b) Effect of in utero MR on prenatal counselling and management intent

3) Through quantitative and qualitative psychosocial measures we will assess the acceptability of the clinical care package with the use of MR imaging included.

4) A health economics analysis will be performed to assess whether the use of MR scans are cost effective.

Primary Hypothesis

Null

The diagnostic accuracy achieved by in utero magnetic resonance (MR) imaging following detailed ante-natal ultrasound examination for suspected developmental brain abnormalities is no greater than that achieved by ultrasound alone.

Alternative

The diagnostic accuracy achieved by in utero magnetic resonance (MR) imaging following detailed ante-natal ultrasound examination for suspected developmental brain abnormalities is greater than that achieved by ultrasound alone.

Secondary Alternative Hypotheses

Information provided by in utero MR makes a clinically effective contribution to prenatal counselling and management.

Parents view in utero MR as a useful and constructive event in their clinical pathway.

Referring fetal medicine experts believe that the images and information from in utero MR examination make a positive contribution to prenatal clinical management.

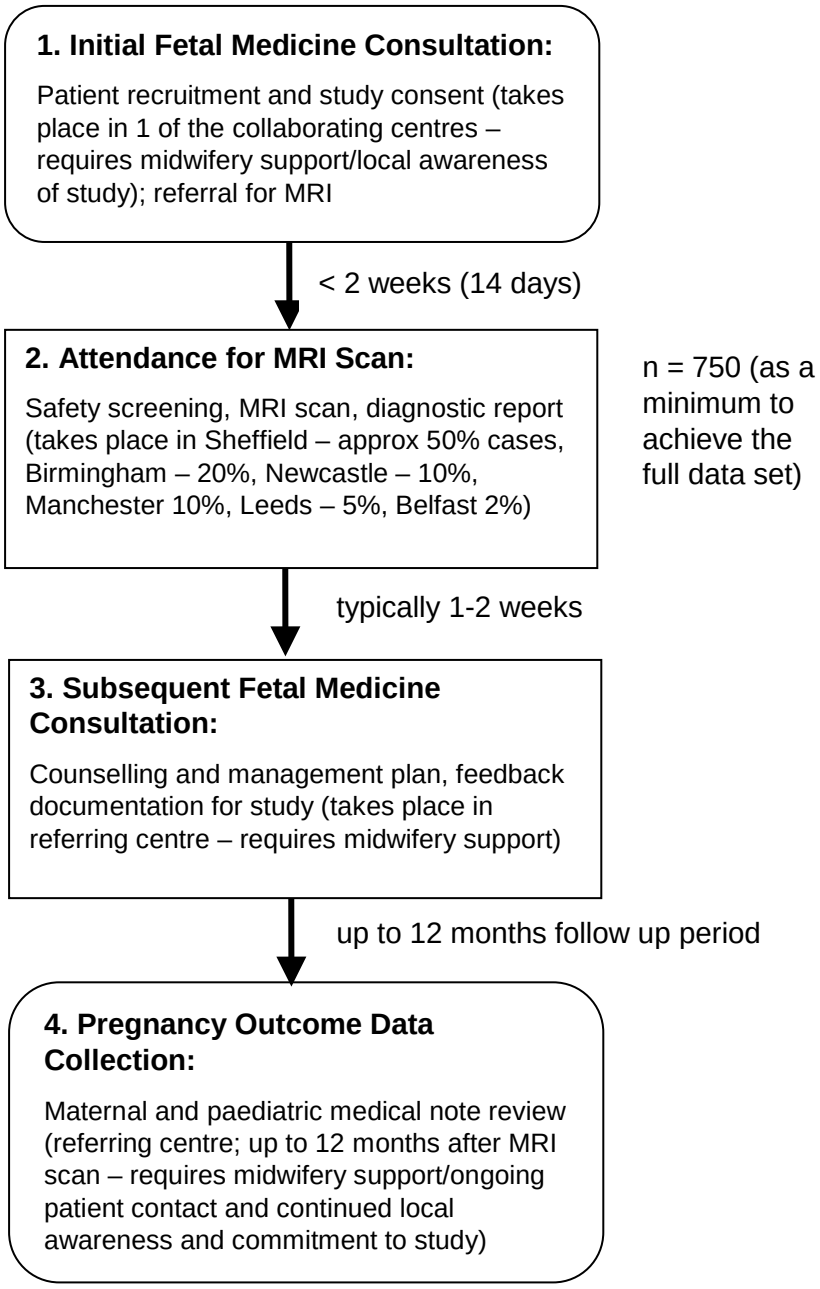
In utero MR makes a cost effective contribution to the prenatal diagnosis and management of suspected developmental brain abnormalities.

3. Study Design

Multi-centre prospective observational study of diagnosis, management and outcome in a large cohort of pregnancies affected by abnormal fetal brain development.

The study is designed to include all developmental brain abnormalities identified by ante-natal ultrasound screening from 18 weeks gestation onwards. Participants are recruited from at least 13 sites within the UK incorporating a wide geographic and socioeconomic base. MR scanning is then carried out either in a primary unit (Sheffield) or in one of five secondary units (Newcastle, Leeds, Birmingham, Belfast and Manchester). Figure 1 outlines the study design and length of time that each participant may remain in the study process.

Figure 1. MERIDIAN study design



Primary Outcomes

1) Absolute diagnostic accuracy of MR as assessed by percentage of cases where in utero MR diagnosis agrees with post-mortem autopsy/MR or postnatal imaging.

2) Absolute diagnostic accuracy of US as assessed by percentage of cases where US diagnosis at the time of referral for MR agrees with post-mortem autopsy/MR or postnatal imaging.

Agreement between prenatal diagnosis (both before and after MR) and outcome diagnosis will be judged by an appointed independent expert panel consisting of a fetal medicine clinician, paediatric neuroradiologist and paediatric neurologist or neurosurgeon.

Secondary Outcomes

Effect of including MR scan on diagnostic confidence
Change in diagnostic confidence will be measured before and after the MR scan as assessed by a 5 point Likert scale.

Effect of including MR scan on prognosis
Change in prognosis will be measured before and after the MR scan as assessed by a 4 point categorical scale (poor – less than 50% chance of normal neuro-developmental outcome, intermediate - 50-90% chance of normal outcome, favourable - greater than 90% chance of normal outcome, normal – no abnormality found after detailed fetal medicine investigation).

Effect of including MR scan on management
Change in management will be measured before and after the MR scan as assessed by a 2 point categorical scale. This scale will record whether termination of pregnancy was discussed on the basis of poor neuro-developmental prognosis.

4. Ancillary sub-studies

Sociological Study

A Sociological study will be integrated into the trial in order to provide insight into the experiences and acceptability of the new intervention, from the perspective of both study participants (women and, where possible, their partners) and clinicians (fetal medicine consultants and radiologists). This will be completed using a mixed methods approach of quantitative (surveys) and qualitative (interviews) methods.

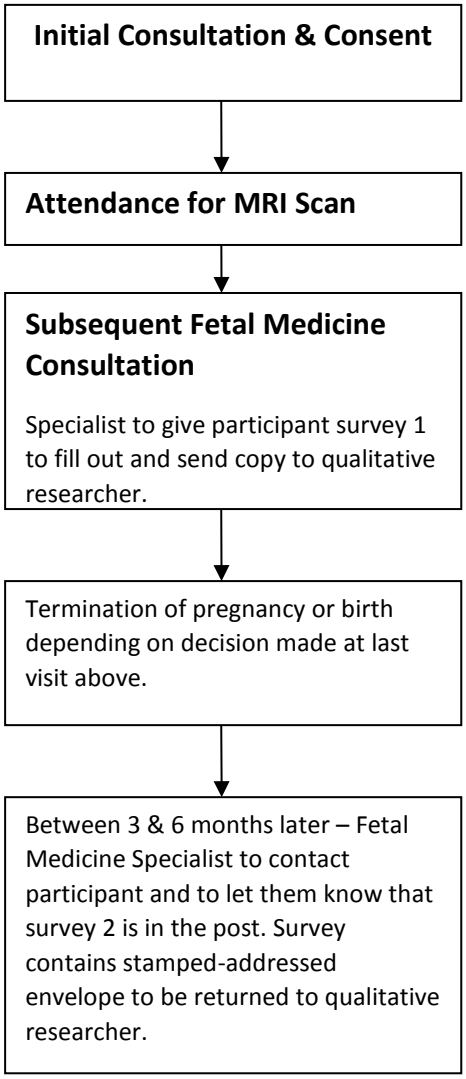
Quantitative Study of Participants

Introduction

The quantitative data from participants will provide insight into the impact of the intervention (MR scan) on their perceptions and experiences of their health care in relation to overall satisfaction, acceptability of care, and impact on understanding and decision making about fetal anomaly in pregnancy.

Study Design

This will consist of 2 surveys for the participants to fill out. The first will consist of a short questionnaire completed after the fetal medicine consultation at which the in utero MR scan findings are discussed and a provisional management plan is made. The second will be a repeat measurement of the first survey at 3-6 months after the outcome of the pregnancy (either birth, or termination of pregnancy) has taken place, with an additional qualitative open text question.



Outcome Measures

Both surveys will contain the following measures:

1. The Hospital Anxiety and Depression Scale (HADS)

HADS measures anxiety on one subscale and depression on another through the use of 7 questions for each characteristic. This will provide indicators for evaluating the impact of the intervention and associated care pathways on participants. The existence of baseline data in the wider community (in health care research) means that some form of comparison will be possible to evaluate to what extent the participants' experiences are influenced by their situation at the time when the MR scan is completed. This can also be compared at the different time points of the study.

2. A series of 6 purpose specific questions developed for use in this study
Qs 1 and 6 will be used to evaluate overall satisfaction with care that includes the intervention
Qs 2-4 will be used to evaluate the practical utility of the results from the MR to inform understanding and decision making during a challenging and difficult time in pregnancy that involves anomaly detection.
Q5 will be used to evaluate the impact of practical issues related to referral pathways (e.g. having to travel long distances to access the MR scan) on parent views about acceptability of their care package.

Survey two will include two additional components:
(i) an open text question to allow participants to raise issues that they feel are important to their evaluations of their health care experience
(ii) a filter question to allow participants to express an interest in taking part in the qualitative in-depth interview phase of the study

Qualitative Study of Participants and Health Professional Interviewees

Introduction
The qualitative data from participants and health professional interviewees will provide insight into how those most closely involved in the implementation of the intervention describe, experience and understand the intervention, in the context of their overall care package or working life.

Study Design
A diverse sub sample of 30 participants, and possibly their partners, will be selected to take part in interviews at the end of the study.

In addition to the participant studies, we will undertake in-depth interviews with a purposively selected sample of health professionals, including fetal medicine specialists and radiology specialists, involved with the delivery and organisation of the care pathways. These in-depth interviews will take place at two separate time points in the study overall – in-depth interview one will take place in the first six months of the recruitment phase of the study, and in-depth interview two will take place in the third year of the study.

Outcome Measures

Participant interviews
To describe, explore and understand how women (and where appropriate, their partners) experience an MR scan of the fetus as part of their fetal diagnosis care pathway.

Health Professional Interviews
The aim is to describe, explore and understand how health professionals who provide services for women with anomaly affected pregnancies evaluate the inclusion of an MR scan as part of the fetal diagnosis care pathway.

The interviews will be informed by a generative thematic approach so there are no other specific outcomes identified other than the aims above. However there are key themes that the interviewers will cover as identified in the topic guide.

Health Economics Study

Introduction

Whilst cost effectiveness analysis using the quality adjusted life year (QALY) as the denominator is widely accepted as being of most use to NHS decision makers, and has long been considered standard for bodies such as NICE, the relevance of the QALY to in utero MRI is questionable.

The potential benefits of in utero MRI are varied and include quality of life benefits that may not be well reflected in standard health related quality of life instruments (HRQoL). It is highly likely that the rate of terminations of healthy fetuses will be lower if MRI achieves a lower rate of false positive diagnosis than ultrasound (US). It is also possible that terminations of abnormal fetuses will be higher if MRI achieves a lower rate of false negative diagnosis than ultrasound. We know that decision makers may be uncomfortable with the use of QALYs to reflect the value of an unborn child. This situation raises the additional complication of differential valuation of the unborn child according to the presence or absence of brain abnormalities. There is also the potential for such an approach to lead to the perverse situation of recommending the approach with the lowest rate of true negative detections.

Study Design

A cost consequences analysis will be performed, whereby multiple outcomes are to be presented alongside costs, reflecting the incremental impact of the use of MRI. The study's basecase will take a NHS perspective using a time horizon limited to the due date of the baby. Both societal perspectives and a life-time horizon will be examined in a sensitivity analysis.

Outcome Measures

Incremental cost per management decision appropriately revised after in utero MRI as compared to ultrasound alone

This will be recorded as outlined above from the 2 point categorical management decision. The decision is classified as appropriate if the revised decision is consistent with the presence or otherwise of neuro-developmental abnormalities at birth or post-mortem. So, for example, a change to termination, from no termination, would be considered appropriate if a post mortem were to show neurological abnormalities.

Wider Management Effects

Other secondary outcomes will also be presented alongside the incremental cost-effectiveness ratio, in order that wider effects are considered within the economic analysis. These are:

1) Diagnoses correctly revised derived from the US and MRI reporting forms and the results of post-mortem or birth records.
2) All diagnoses revised (as above)
3) The number and proportion of cases where management intent is changed as a consequence of information made available by MRI, classified by gestational age (prior to 22 weeks, between 22 and 24 weeks, and after 24 weeks gestation).

5. Selection and withdrawal of participants

Inclusion Criteria

A participant is eligible for the trial if the following criteria are met:

1. Has an ongoing singleton or multi-fetal pregnancy of at least 18^{+0} weeks gestation* by ultrasound dating.
2. Is thought to be carrying a fetus with a brain abnormality following detailed specialist ultrasound examination.

Exclusion Criteria

A participant is excluded from the trial if any of the following criteria are met:

1. Inability to give informed consent.
2. Has a cardiac pacemaker, intra-orbital metallic foreign body, or recent surgery with metallic sutures or implant.
3. Has previously experienced or is likely to suffer severe anxiety or claustrophobia in relation to MR imaging examination.
4. Is unable or unwilling to travel to Manchester, Belfast, Birmingham, Leeds, Newcastle or Sheffield for specialist MR imaging.
5. Is unable to understand English (except where satisfactory translation services are available).
6. Is under the age of 16 years.

* It is a requirement that MR scans are not carried out prior to 18 weeks gestation. Women can be consented at 17 weeks gestation where there is a continuing pregnancy and they will be 18 weeks at the time of the MR examination.

Withdrawal Criteria

Withdrawal from the Study

1. Participant wishes to withdraw from the study.

6. Enrolment

All participants will be recruited by a fetal medicine specialist following an ultrasound scan which has identified a known or suspected brain abnormality in their fetus. In all cases, the fetal medicine specialist would complete non-patient identifiable details (see Appendix, Form A). In cases where the woman is eligible to enter the study, but the fetal medicine specialist does not feel it would be clinically appropriate or would introduce unnecessary delay in management, then details of the case and the reasons for not offering MR examination would be recorded on this form. An inclusion/exclusion checklist would then be completed for any woman who has indicated interest in the study. The specialist would give the

woman a patient information sheet describing the study and also the consent form (see Appendix, Forms B and C). At this point, the patient may sign the consent form straight away if they are happy to do so, or they may take the patient information sheet and consent form away to consider whether or not they want to participate. The patient will be given as much time as they need to consider their decision and, if needed, they will be offered a counselling room or other suitable nearby quiet space with adequate privacy (within reasonable and practical constraints of the ongoing clinical session). Clinic staff, such as the specialist midwives, will be able to answer queries and discuss concerns as they arise. If the patient does then wish to consent to the study the MR scan can be booked at this point, otherwise she will be given the number of the fetal medicine clinic in order to ask any further questions and possibly return to discuss the study further and give consent at a later date if they wish.

The MR attendance will be arranged within five working days, where at all possible, from the time that the woman has consented to be in the study. Immediately before the in utero MR examination a member of the imaging research team will answer any questions the women may have relating to the scan procedure itself. Women under the age of 16 years will be entitled to receive in utero MR imaging, however their imaging results and clinical details will be considered ineligible for inclusion in the research study.

The patient information sheet and study consent form refer to the need for collection of data following the outcome of the pregnancy. The data which needs to be collected is specific to the nature and timing of the outcome, and would be sought initially by an appropriate member of the fetal medicine department (consultant, specialist trainee or midwife) with knowledge of the case and prior contact with the woman. Retrieval of information from medical notes may then be delegated to a suitably qualified member of the research team. In cases of surviving livebirths this would involve access to paediatric case notes and the result of postnatal imaging investigations. In cases of termination of pregnancy, intrauterine fetal demise, stillbirth or early neonatal death this would require access to the results of post-mortem examination (autopsy and/or post-mortem MR).

7. Study Treatment

There is no direct study intervention or treatment. An in utero MR examination will be performed in all cases, and the results of this will be made available to the woman and her referring clinician. The referring clinician will use any information made available by the MR examination according to clinical judgement, and this may or may not have an influence on subsequent clinical management.

There will be a standardised in utero MR imaging protocol for all six centres (Sheffield, Newcastle, Leeds, Birmingham, Belfast and Manchester) undertaking in utero MR examinations (see Table 1). The unified protocol has been devised so that it can be easily reproduced on any MR manufacturer's equipment and is based on the current and published methods in use at the University of Sheffield, Academic Unit of Radiology. Referrals from Newcastle, Birmingham and Belfast will receive their in utero MR in their corresponding MR unit, attended and reported by a local specialist radiologist; a proportion (up to around 50%) of referrals from Leeds and Manchester will also be selected randomly to receive their MR examination locally. In such cases a second report will be produced at a later date by the Sheffield team, following the outcome of the pregnancy, for the sole purpose of a retrospective analysis of inter-observer variability (i.e. to estimate the level of discrepancy between regional and central reporting).

Sequence	Weighting	Plane	Slice thickness
SSFSE	T2	Axial	5mm
SSFSE	T2	Sagittal	5mm
SSFSE	T2	Coronal	5mm
SSFSE	T2	Axial	3mm
SSFSE	T2	Sagittal	3mm
SSFSE	T2	Coronal	3mm
FGRE	T1	Axial	5mm
FIESTA GRE	T2	Axial	5mm
SSFSEIR	T2 FLAIR	Axial	5mm
DWI	DIFFUSION	Axial	5mm

Table 1. In utero MR examination protocol.

8. Assessments and procedures

Initial Fetal Medicine Consultation

Once the fetal medicine expert has identified a woman eligible for the study, he/she will send a standardised referral sheet to Sheffield or, where appropriate, to their local MR department (see Appendix, Form D). This form includes details of the working diagnosis, diagnostic confidence, prognosis and intended management immediately prior to referral for in utero MR. Information about the parity of the woman will also be collected.

Attendance for MRI Scan

The participant will then attend for an MR scan from which a report on the in utero MR examination will be issued to the referring clinician, in most cases the next working day, giving details of the MR diagnosis and the radiologist's associated diagnostic confidence (see Appendix, Form E). A clinical report will also be issued at this time, as per standard radiological practice; a report template is available for all reporting radiologists to provide guidance and consistency across sites (see Appendix, Form F).

Subsequent Fetal Medicine Consultation

With respect to clinical management, the fetal medicine specialist will then be in a position to counsel the parents in the light of both ultrasound and in utero MR findings according to their own clinical judgement. For the purposes of the study, the referring clinician will subsequently be asked to complete and return a standardised feedback form to Sheffield (see Appendix, Form G) within 7 days of the subsequent consultation with the patient (i.e. when a management plan is agreed). This form closely resembles the standardised referral form and is intended to record details of the effect of in utero MR on prognosis and management intent.

Web-based, online data validation and capture will be employed in Sheffield, and will be made available at referring centres as an alternative to paper-based referral and feedback. This will ensure that the diagnostic information provided by referring centres conforms to a pre-defined and agreed framework suitable for subsequent analysis. It is anticipated that a small proportion of cases (around 10%) will undergo a repeat MR examination in later pregnancy prior to formulation of a definitive management plan. In these cases the most up-to-date ultrasound and clinical information will be used when assessing the impact of in utero MR on management.

Pregnancy Outcome Data Collection

Within 12 months of the initial fetal medicine consultation the fetal medicine specialist, or another member of staff from the fetal medicine clinic with prior knowledge and involvement in the case, will request relevant medical and maternity records for the collection of outcome data. In some circumstances this may require contact with the participant herself, particularly for live-births where paediatric case notes have not been located, or where there has been a change of address, hospital or consultant. The specific data to be collected will vary depending on the known outcome of the pregnancy (see Appendix, Form H).

A number of methods are available to allow research midwives to gather information about where and when women enrolled in the study deliver their baby. An "alert" sticker can be placed on the woman's maternity notes requesting that the delivering midwife notifies the MERIDIAN research midwife of the pregnancy outcome. A pro forma sheet (see Appendix, Form X) with pre-paid return envelope can also be given to the woman to be kept along with her handheld pregnancy notes; this could be done at one of their fetal medicine clinic visits or alternatively the sheet could be posted to the woman closer to the time of delivery where appropriate. The sheet can then be filled in after delivery by the woman herself or given to a relevant health professional for completion (labour ward midwife, reviewing paediatrician, obstetrician or community midwife). The sheet itself requests delivery details and also any known plans for neonatal follow up. These details can then be posted, faxed or phoned through to the research midwife. Using the delivery details gathered in this way the research midwife should be able to request outcome information a few months later (including results of postnatal imaging) from the relevant hospital department and clinician.

It is anticipated that the majority of postnatal scans for liveborn babies will be performed as part of their standard care. In some cases this may not occur however, perhaps because the suspected abnormality was relatively mild. Where it becomes clear that no such follow up is planned by 2 months of age the woman may be offered a postnatal ultrasound brain scan for their baby as part of the research study. The research midwife would need first to check with the appropriate hospital department that no follow up is arranged, and that they have no knowledge of any adverse neonatal outcome or specific difficulties in that case. The research midwife would also check the baby's details against the "NHS Tracking" system for any record of neonatal death, and only then proceed to make contact with the woman herself to offer a scan. After a discussion by phone, the midwife can send out a supplementary information sheet and consent form (see Appendix, Forms T and U) to the woman describing the ultrasound scan and its use within the study. The woman would then be free to review the information, phone back or arrange to come into clinic if she has further questions. When ready she can sign the consent form and return it by post to the midwife. Alternatively, it may also be possible to gain verbal consent to the scan by phone, so that a scan can be arranged, and then the midwife can meet the woman prior to the scan appointment to complete the consent form in person. The scan itself would be arranged by contacting the appropriate consultant neonatologist with involvement in the MERIDIAN study, asking them to request the scan and arrange for a clinic follow up appointment shortly afterwards.

In cases where post natal imaging has not be carried out due to loss of follow up or because it has been deemed inappropriate by local clinicians then a 3rd trimester ultrasound may be used as the reference standard.

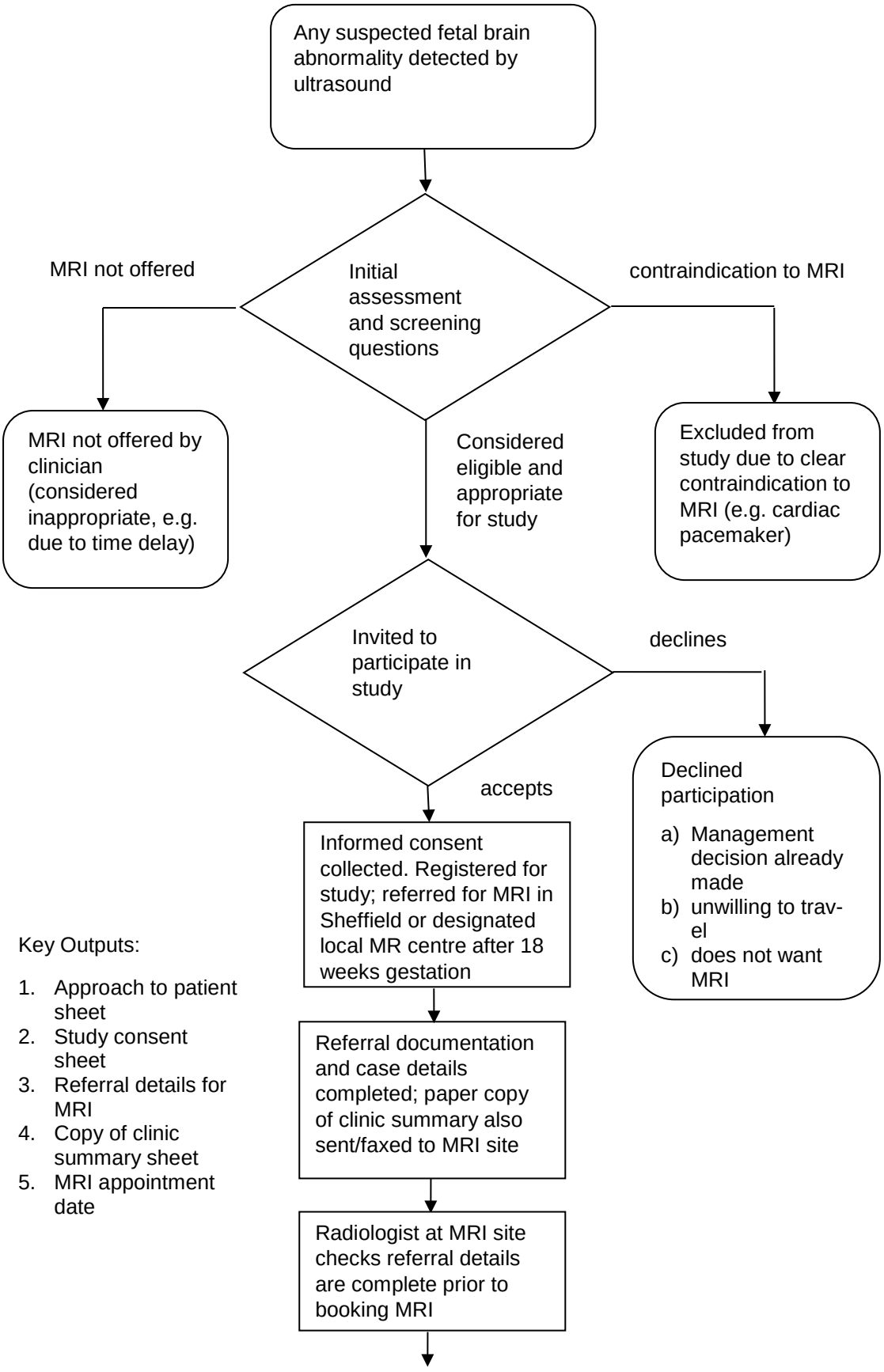
Where the woman has opted for termination of pregnancy, or where there has been neonatal death, the study aims to gather any relevant information from autopsy (where offered and accepted for clinical reasons). As part of the study, women may also be offered a non-

invasive post mortem MRI of the baby's brain, either where they have declined the offer of conventional autopsy, or in order to supplement the information which may be available from autopsy regarding the nature of the brain abnormality. The offer of post mortem MRI would only be made in person, by the fetal medicine consultant or other specialist clinician who has been responsible for the woman's care, and only as part of the discussion and counselling for conventional autopsy. If the woman did decide that a post mortem MRI might be helpful for them, and agreed to the examination, then a specific information sheet and consent form would be provided at that time (see Appendix, Forms V and W).

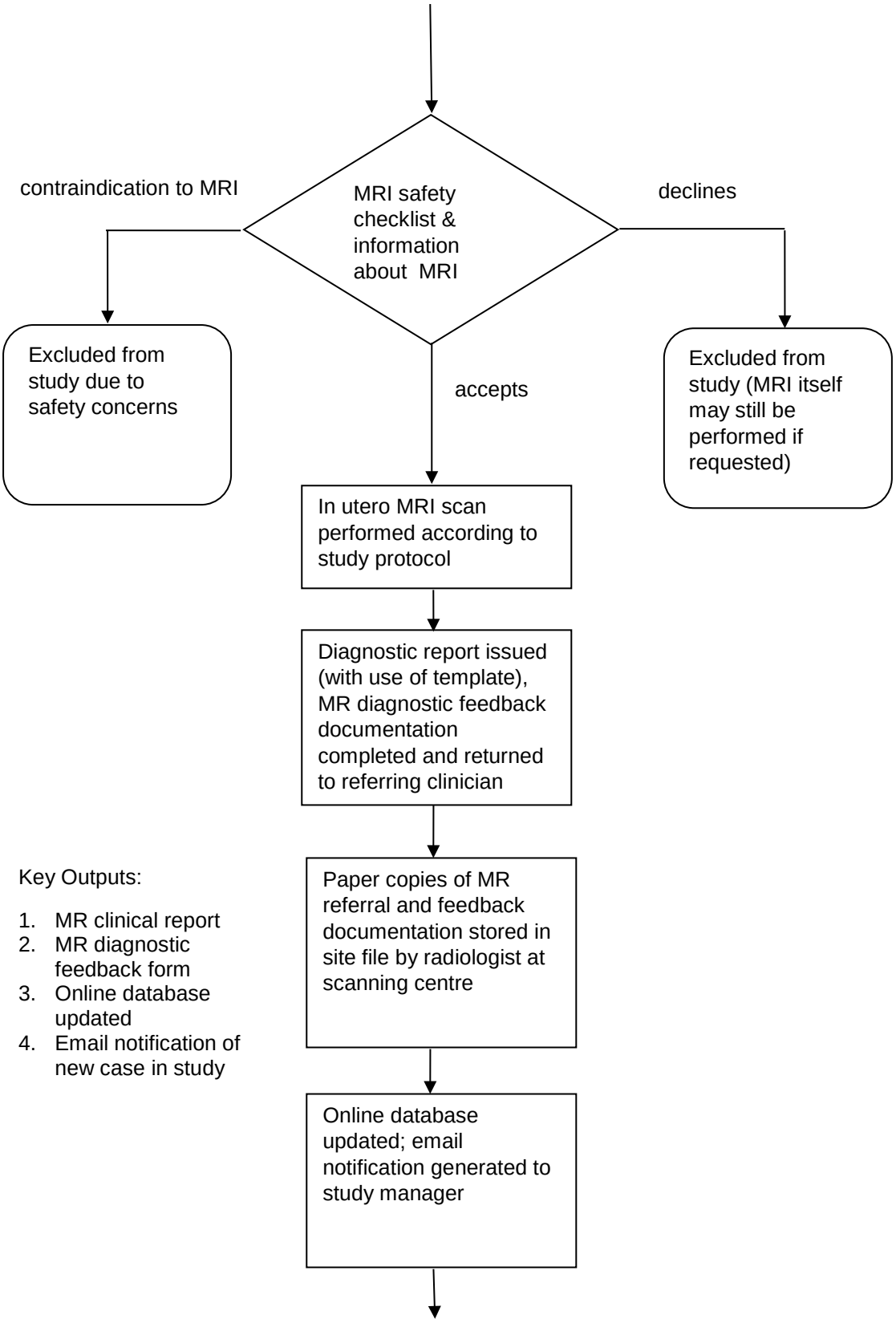
Please see Figure 2 below for details of the procedures and data collection documents.

Figure 2. Procedure for MERIDIAN study

1. Initial Fetal Medicine Consultation:



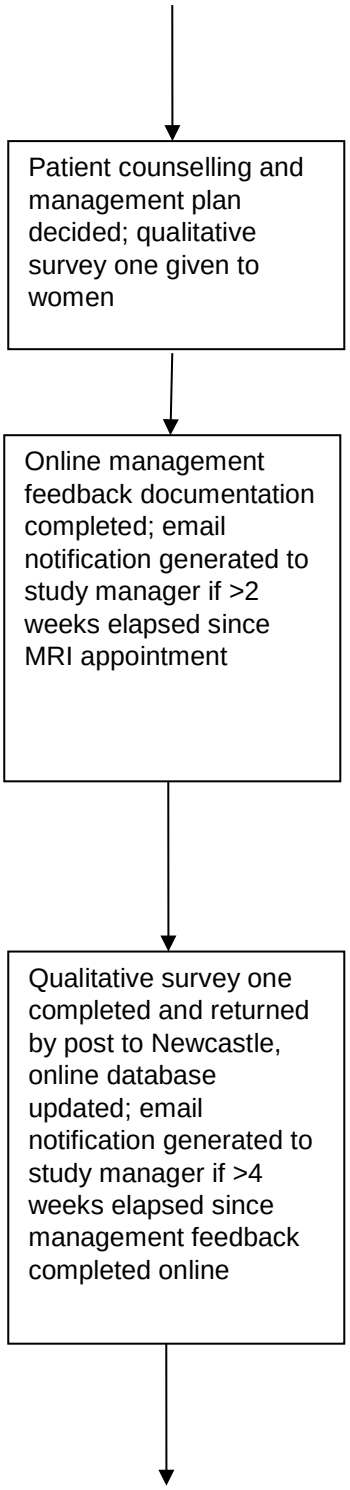
2. Attendance for MRI Scan:



Key Outputs:

1. MR clinical report
2. MR diagnostic feedback form
3. Online database updated
4. Email notification of new case in study

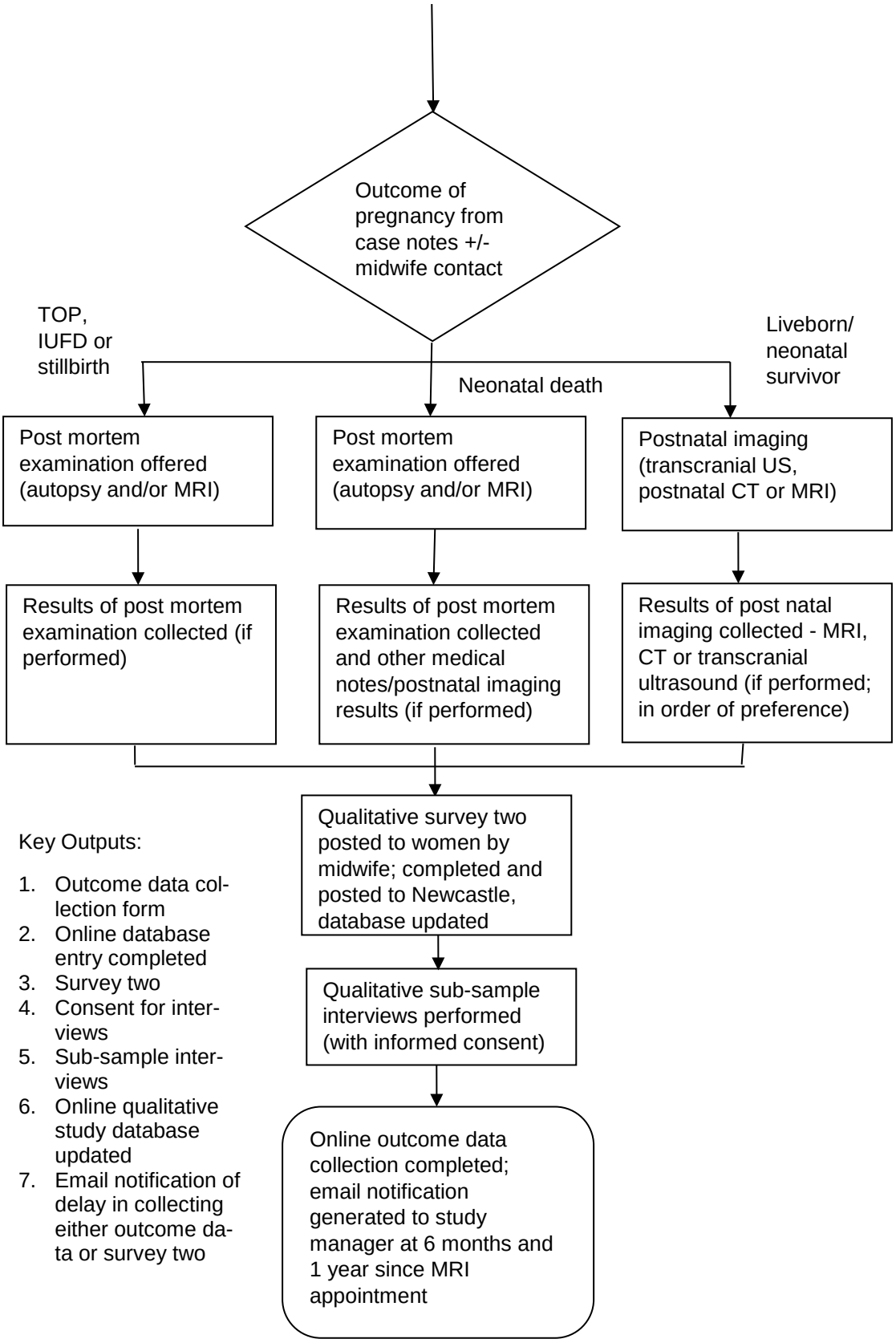
3. Subsequent Fetal Medicine Consultation:



Key Outputs:

1. Clinical feedback form
2. Online database updated
3. Survey one
4. Online qualitative study database updated
5. Email notification of delay in collecting either clinical feed-back or return of survey one

4. Pregnancy Outcome Data Collection:



Key Outputs:

1. Outcome data collection form
2. Online database entry completed
3. Survey two
4. Consent for interviews
5. Sub-sample interviews
6. Online qualitative study database updated
7. Email notification of delay in collecting either outcome data or survey two

MERIDIAN – Key Outputs

	1. Initial Fetal Medicine Consultation	**2. Attendance for MRI Scan**	**3. Subsequent Fetal Medicine Consultation**	**4. Pregnancy Outcome Data Collection**
Where:	Referring fetal medicine clinic (13 collaborating centres)	Radiology MRI department (Sheffield, Newcastle, Leeds, Birmingham, Manchester or Belfast)	Referring fetal medicine clinic follow up	Referring fetal medicine clinic
Who: (primary responsibility)	Fetal medicine specialist	Fetal MR Radiologist	Fetal medicine specialist and qualitative researcher	Fetal medicine clinic midwife and qualitative researcher
Outputs:				
Approach to patient sheet	X			
Study consent sheet	X			
Referral details for MRI	X			
Copy of clinic summary sheet	X			
MRI appointment date	X			
MR clinical report		X		
MR diagnostic feedback form		X		
Online database updated		X	X	X
Email notification of new case in study		X		
Clinical feedback form			X	
Survey one			X	
Online qualitative study database updated			X	X
Email notification of delay in collecting either clinical feedback or survey one			X	
Outcome data collection form				X
Survey two				X
Consent for interviews				X
Sub-sample interviews				X
Email notification of delay in collecting either outcome data or survey two				X

Quantitative Sociological Data Collection and Analysis Procedures

Survey 1 (see Appendix, Form I)
Survey 1 will consist of a short questionnaire completed after the fetal medicine consultation at which the in utero MR scan findings are discussed and a provisional management plan is made. The study pack will be given to participants by a member of the clinical team caring for them at their fetal medicine clinic. The participant will be given time and privacy at the health care institution to read the study pack and complete the questionnaire if they wish to do so. The participant can then hand back the questionnaire in a sealed envelope to the appropriate member of the clinical team at that site, who will post the sealed return envelopes to the sociology researchers in Newcastle (where the data will be entered and stored in the centralised database). Women who do not wish to complete survey 1 at that time may take the forms away for completion at home, with instructions and a pre-paid envelope for returning the survey to Newcastle. If they do not wish to complete the survey at all they can do so anonymously be returning a blank questionnaire in the sealed envelope. In circumstances where the woman does not return to fetal medicine clinic in person, and hence cannot be given survey 1, this will instead be posted out to her home address according to the judgement of the fetal medicine clinic staff responsible for her care.

Survey 2 (see Appendix, Form J)
Survey 2 will be sent out to all participants 3 months after delivery or termination of pregnancy (depending on which care pathway was followed). This questionnaire will also include a filter question to ascertain whether the participant is willing to be contacted about an in-depth interview for the qualitative sub-study. The study pack will be posted out to participants by a member of the fetal medicine clinic staff responsible for their care (as they will be in a position to follow the management decisions taken by the participant and hence judge if and when it is most sensitive, acceptable and appropriate to send out the survey pack). The questionnaire will be sent with a pre-paid envelope to allow the participant to read through the study pack and, if they wish, to complete and return the questionnaire to the Sociology researcher.

The data from the surveys will be exported into an anonymised SPSS database held at Newcastle University, to facilitate descriptive analysis of the data for the two survey points, and any likely correlations will be tested using the Chi Square Test. There will also be a comparative analysis of the descriptive statistics for the two surveys to allow the research team to explore questions about the impact of time and pregnancy outcome on parent experiences of their care. The open text responses from survey 2, which will be analysed using a similar generative thematic approach to that used in the analysis of the interview data using the atlas.ti programme.

Qualitative Sociological Data Collection and Analysis Procedures

For those included in the qualitative sub-study, the interview will take place approximately 3-5 months after Survey Two. It is anticipated that partners will be closely involved in decision making in a substantial number of cases. Fathers' views are important in decision making in this context [38] and images of the fetus can have particular relevance for fathers [39]. Where appropriate, women's partners will be included in the in-depth interview aspect of the study, but only if the woman consents to this inclusion. A separate information sheet, consent process and consent form will be completed for any participating partner, prior to the beginning of the in-depth interview.

Sampling and recruitment

(i) parent qualitative sample

From the population of participants who have consented to further contact about the in-depth interview stage, a purposive sample will be selected. The aim of the purposive sampling approach is to generate a sample that covers a broad range of experiences (e.g. in terms of referral pathway, pregnancy outcome, site location, plus other socio-demographic characteristics), rather than to achieve statistical representativeness to allow for broader types of generalisation from the findings. From the pool of participants expressing an interest, the purposive sample will be selected and approached in stages until the total n=30. We envisage that we will select three sites from the study locations (Sheffield as the central site; Newcastle as a secondary site that performs MR scans; and one other secondary site that does not perform the MR scans – to be determined depending on availability of participants) and to aim to recruit approximately 10 participants at each of the three sites. However, there will be a flexible approach to promoting diversity across a socioeconomic population, so the final figures may not be exactly 10 at each of the three sites.

For those who have consented to contact with information about the qualitative in-depth interview, a study pack (cover letter with information sheet – see Appendix, Form K) will be sent out to the woman with a reply slip allowing her to indicate whether she is willing to now consider taking part in an interview. If the woman replies indicating that she does not want to take part, then no further contact will be made. If the woman does not reply, then a follow up phone call will be made to ensure that she received the study pack at two weeks after it has been posted.

If the participant consents to taking part in an interview, then the sociologist will answer any initial questions by phone, and then arrange a suitable time and location for the interview. A joint discussion (with the woman) but separate consent form will be completed for any participating partner, at the beginning of the in-depth interview (see Appendix, Forms L-O). If both partners are taking part, then the couple can decide whether they would like to be interviewed together or separately, but if given the choice, our experience is that usually couples opt to be interviewed together in such research scenarios.

(ii) health professional qualitative sample

We will conduct semi-structured, in-depth interviews on two occasions with 1-2 health professionals from each of the 13 participating centres (n=20). Most of the health professionals will be consultants in Fetal Medicine (approx n=13-15, with at least one consultant from each of the 13 study sites), but it is envisaged that the sample will also include consultant radiologists (approx n=5-7 from the sites which perform in utero MR examinations within the study) and/or fetal medicine midwifery staff.

A full list of eligible health professionals will be compiled in collaboration with the lead contact at each study site, but the final selection of potential interviewees approached will be decided by the sociology study team to improve confidentiality. Although theoretical saturation is not considered an essential criterion for validity of the data in this particular instance, it remains a goal that we hope to achieve. Our prior experience of qualitative research work with health professionals in this area suggests that theoretical saturation is possible with the proposed numbers, but that even if theoretical saturation is not reached, the qualitative analysis would still be of great value to the study overall. The health professionals who are approached will be sent a study pack (cover letter with information sheet – see Appendix, Form P) and asked to respond via a reply slip about their willingness to consider tak-

ing part in two in-depth interviews, approximately 18-24 months apart. If the health professional replies indicating that they do not want to take part, then no further contact will be made. If the health professional does not reply, then a follow up phone call will be made to ensure that they have received the study pack at two weeks after it has been posted. If the health professional gives consent to take part in an interview, then the sociologist will answer any initial questions by phone, and then arrange a suitable time and location for the first interview (see Appendix, Forms Q and R). Alternatively, a telephone interview may be arranged in some cases.

At the end of the first interview, consent to contact regarding the second interview will be confirmed. This process of recruitment will be repeated in the third year of the study for interview 2 (see Appendix, Form S). Ideally, we would aim to interview the same person, but if circumstances demand, (e.g. due to staff changes) we would recruit an alternative person if necessary at any particular site.

Data Collection

The in-depth interviews will last approximately 60-90 minutes and will adopt a semi-structured, exploratory, generative thematic approach, which will allow for anticipated key topics to be discussed, but also for participants to raise issues that are important to them. The data gathered from these exploratory interviews will be used to better understand how in utero MR is perceived by women, and therefore understand better the reasons why in utero MR is/is not satisfactory, acceptable or relevant to their decision making process. In this way, the data collected will be used to inform the analysis of the questionnaire data collected from all women at data collection points 1 and 2. The data will also be used to complement the analysis of the health professional perspectives of MR images and feedback, in the context of overall care provision in this setting.

The interviews will be audio-recorded, and then transcribed by an experienced research secretary. Participants will be made aware when they are consenting that the individual transcribing will be aware of their identity. The transcribed interviews will then be anonymised by the Sociology researchers, and uploaded onto the atlas.ti qualitative analysis package which will assist in the organisation of the data to facilitate the analytic process. The data will be held electronically on a password protected computer. The printed transcripts will be kept in a research office in a locked filing cabinet.

The anonymised transcripts from the in-depth interviews with women and health professionals) will be analysed using a generative thematic approach [40] drawing on the work of Silverman [41, 42]. This approach shares some principles with grounded theory approaches [43], such as theoretical concepts are grounded in the data, but does not follow the strict methodological protocols associated with any one particular grounded theory approach. The data will be coded according to a framework of thematic interpretation, to identify key aspects of similarities and differences in the accounts of those within the sub-sample of women interviewed, within the health professionals interviewed, and between the accounts reported by women and professionals. Each data set will be analysed independently initially, but all aspects of the data will be included in integrated analyses to build up a layered understanding of how the separate component parts of the data relate to one another.

Health Economic Data Collection and Analysis Procedures

Within the study we will estimate the cost of in utero MRI and ultrasound (US) for each patient. Amounts of resource use for each patient will be measured then multiplied by unit costs to produce a patient specific cost.

Resource use

There will be three main components of costs. Firstly, feto-maternal contacts will be taken from patient notes. In essence, dates of contacts will be recorded as 'MRI with consultation', 'US with consultation' and 'consultation without scan'. Secondly, other obstetric/gynaecological care events will be taken from patient notes, including routine ante-natal visits, miscarriages and terminations of pregnancy. Thirdly, "patient" borne costs (mothers, fathers and/or accompanying carer) will be based on surveys of the mothers. Questions within the follow-up questionnaire will ask the amount of time required for the MRI scanning consultation (including associated travel) and whether time was taken off work or not. Patient times for other types of consultation and care will be derived from these using service provider judgements.

Unit costs

Unit costs for the three types of consultations will be taken from NHS Reference Costs (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/index.htm). The definitions of the Reference Costs change over time, and so their relevance to our study will be assessed in the final year of the study, with amendments made if necessary through discussion with the Finance Department of Sheffield Teaching Hospitals Trust. Travel costs will be based on cost per mile based for car travel (http://www.theaa.com/motoring_advice/running_costs/index.html), with distance travelled based on the distance between the patient's postcode and the hospital attended. Patient time costs will be based on national average salaries (http://www.statistics.gov.uk/cci/nscl.asp?id=8242). Costs associated with long-term costs of care for infants born with brain abnormalities will be gathered from the literature. [Note that the references do not show the precise source, as the most up-to-date figures will be used, which as such, have not yet been produced.]

Analysis

The study will compare the addition of MRI to single US using the incremental cost per management decision appropriately revised, together with additional secondary outcome measures. The ICER will be plotted on the cost-effectiveness plane together with its associated cost-effectiveness acceptability curve. The basecase will only consider the costs and benefits identified directly within the study (i.e. up until the due date of the baby). However, we will also develop a simple decision model that will enable us to consider the potential costs and outcomes of repeat ultrasound (see below) and to incorporate the longer term cost implications of improved diagnosis. In particular, we will review existing literature to provide estimates of the NHS and broader societal cost implications of providing support for children born with the types of brain abnormalities identified as relevant in the study.

The principal sensitivity analysis will examine the possible impact of repeat ultrasound, prior to possible MRI, on costs and outcomes. The likely impact of repeat ultrasound will be estimated based on the original ultrasound diagnosis, the information about the true status of the fetus obtained within the study, and combined with the existing literature and clinical expert opinion. Further sensitivity analyses will consider how travel costs may be reduced if MRI is offered at centres closer to parents' homes. This will be approximated by calculating the reduction in distance to hospital given other configurations of services, and reducing travel costs proportionately.

Finally, we will perform value of information analyses in order to identify those areas of uncertainty that may warrant further investigation.

Lost to Follow-Up

Where contact with a participant has not been successfully maintained during the study, she will be considered "lost to follow up" after one final attempted contact by telephone at 6 months following delivery (for livebirths only). This contact will only be attempted if it has not been possible to locate the necessary medical, maternity or paediatric records required for outcome data collection (in particular the outcome reference diagnosis which is drawn from postnatal imaging results). If this contact is required it will be made by the fetal medicine clinician or a midwife who has been involved with the participant's recent/ongoing clinical care. In cases of termination of pregnancy, fetal demise or perinatal death, post mortem examination results will be sought from medical records. If, for any reason, the results of a post mortem examination cannot be located within 6 months of the examination being completed, this case will be considered "lost to follow up". No further attempt will be made to contact the participant under these circumstances.

Wherever an outcome reference diagnosis is not available at the end of the 6 month period of follow up, all such cases will be retained in the study analysis of changes in fetal prognosis and management, but it will not be possible to include them in the analysis of diagnostic accuracy.

Study Safety

The following section outlines the methods for ensuring and assessing participant safety:

Definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject.

Serious Adverse Event (SAE): Any adverse event such that it:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires inpatient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect
- is another important medical event that may jeopardise the subject***

**"life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
***Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.*
****Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.*

Millions of MR examinations are performed each year on adults and children and serious adverse effects are rare. Any serious adverse events and adverse events related to the MR procedure itself will be reported according to standard safety policy and guidelines at the relevant MR site, including reporting procedures for the Medicines and Healthcare products Regulatory Authority (MHRA) where there is significant injury. A copy of the local MR incident form will be stored in the site file to allow these occurrences to be reported in an annual safety report for this study. In addition, any adverse outcome of pregnancy (such as fetal demise, pre-term delivery or stillbirth) occurring during the study will be recorded and summary reports submitted to the Data Monitoring & Ethics Committee (DMEC or DMC) and, as they deem necessary, the Trial Steering Committee (TSC). The DMEC and TSC will thus be in a position to judge whether the rate of such adverse outcomes is in line with reasonable clinical expectation for the patient group being studied.

Table 2 below lists the adverse events and serious adverse events which have the potential to occur during this study. These events will be recorded and reported to the DMEC, and as appropriate to the TSC, and they are defined as "expected" events within this study protocol. Nevertheless, the TSC will ultimately judge whether the rate of occurrence of these events is within acceptable and anticipated levels. Any other medical event which occurs during the study which meet the criteria defined above for a SAE will be recorded and reported to the DMEC.

Table 2. Expected SAE's & AE's.

Serious adverse event (SAE)	Adverse event (AE)
1) MR diagnosis differs from outcome reference diagnosis; TOP performed 2) Spontaneous intrauterine fetal demise (IUFD) or Stillbirth 3) Pre-term delivery (less than 37 weeks) 4) Neonatal death 5) Injury during MR examination related to pacemaker, medical implant or other metallic object (failure of MR safety screening procedures)	1) MR diagnosis differs from outcome reference diagnosis; US diagnosis same as outcome reference diagnosis 2) MR examination incomplete or sub-optimal as a result of patient anxiety and/or claustrophobia

Perhaps the most important clinical risk associated with this study is that the prospective management of a particular pregnancy is modified as a result of information made available by in utero MR imaging, and this information subsequently proves to be inaccurate. For instance, an abnormality is detected on ultrasound, but the fetal prognosis is not considered so poor as to justify termination of pregnancy; the prognosis based on in utero MR imaging is considered to be much worse, however, to an extent where termination of pregnancy is discussed and subsequently performed (and the following post mortem examination does not substantiate the MR findings). Any such case would only be identified after the reference diagnosis is achieved (for instance by autopsy), and only then during retrospective comparison of prenatal and outcome diagnosis. As soon as any such case is identified,

however, the details will be reported to the DMEC in order to judge whether this SAE would be likely to recur among future study participants and any necessary action to prevent this would be taken (for instance feedback to MR radiologists reporting such studies or specific modification of inclusion/exclusion criteria). The converse situation where in utero MR provides information which improves the fetal prognosis relative to the pre-existing prognosis based on ultrasound alone would be an AE rather than an SAE, but is still clinically very important. In this situation a woman may opt to continue a pregnancy based on false reassurance from the in utero MR examination. It is quite likely that ongoing monitoring of these pregnancies with ultrasound (or indeed a repeat MR) would highlight any such diagnostic error, but this would necessarily involve a delay in management and would be likely to affect clinical and legal aspects of the termination of pregnancy. Again, any such cases would be reported to the DMEC when first identified.

Further details of safety reporting are specified within the MERIDIAN Serious Adverse Event standard operating procedures document (see Appendix).

9. Statistics

Sample size

The study will recruit at least 750 pregnant women of gestational age 18+ weeks, leading to 504 completed cases (and a sub-group target of 336 women whose management choice is determined by 24 weeks gestation, a key date within the law governing termination of pregnancy). Recruitment to the study will continue to the end of the recruitment period, even if the target of 750 has been met prior to that; this is to ensure we meet the target of 504, and 336 at the point of follow-up. Pregnancies less than 24 weeks gestation will be defined based on gestational age at the time the MR scan is performed.

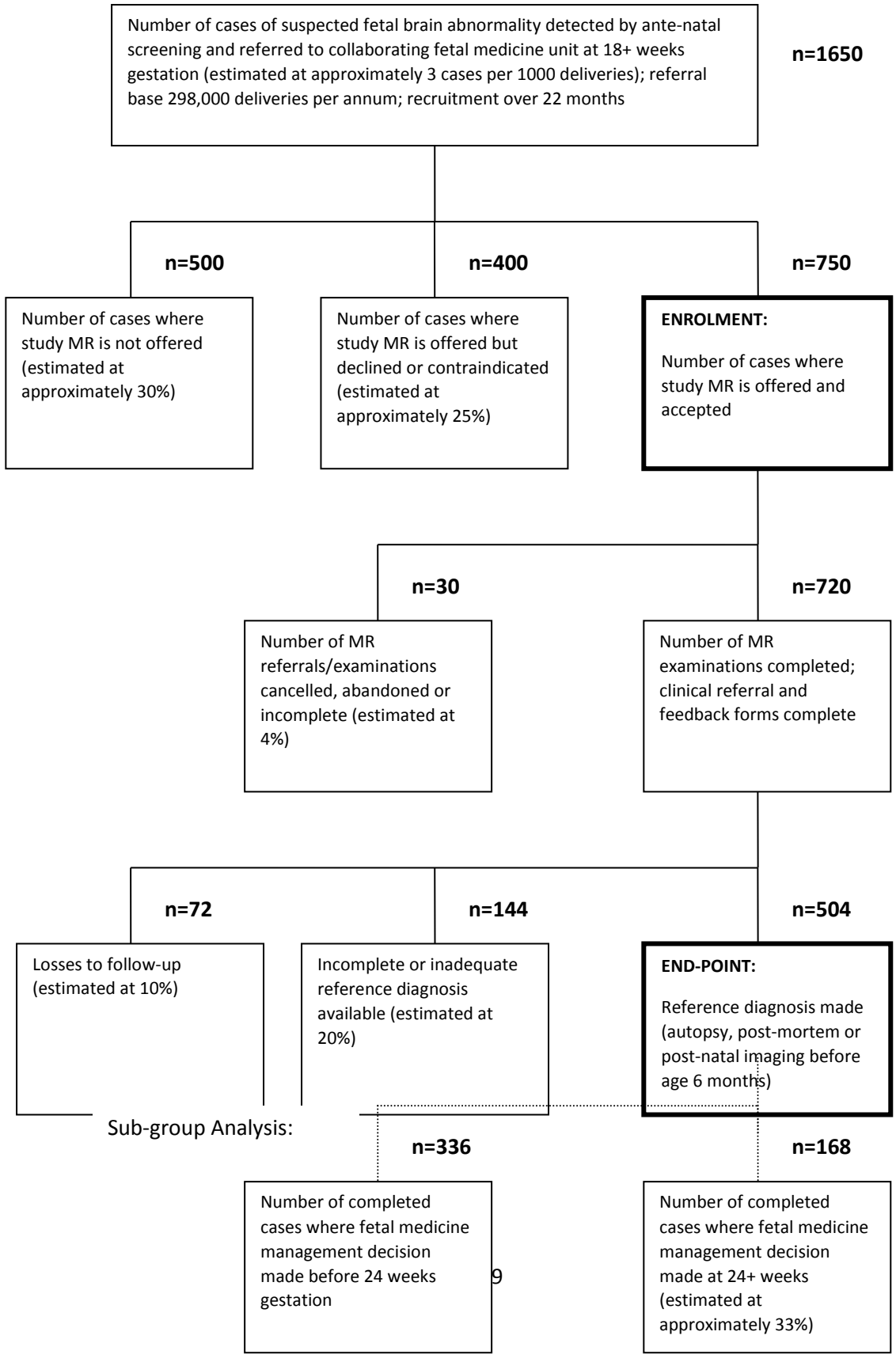
The assumption made in arriving at this sample size is that ultrasound achieves an accurate and complete diagnosis of a developmental brain abnormality in around 70% of cases [44-58], and with the addition of in utero MR, this figure would rise to at least 80%. If the "true" increase is just 10%, then a sample size of 336 would mean we can be sure of detecting an improvement in diagnostic accuracy with 90% power and 95% confidence. We believe that a change of this magnitude would be of clinical importance, as it could very well lead to changes in fetal prognosis and management intent in around 5% of all cases. The proposed sample size is sufficient to detect such changes in these important secondary outcome measures.

We will recruit from at least 13 fetal medicine units in England and Scotland, many of which have previously collaborated with the Sheffield in utero MR group. These centres cover a potential referral base of approximately 298,000 deliveries annually, this being around 40% of all deliveries in Great Britain. The incidence of developmental brain abnormalities detected by second trimester ultrasound screening, and therefore potentially eligible for inclusion in the study, is estimated at 3 per 1,000 deliveries [54, 58-60]. In order to recruit the required total of 750 cases, and allowing for a failure/refusal to recruit 50-60% of these eligible cases , the study will need to recruit for twenty two months.

Losses to follow-up during the study are estimated at just 10%. This figure reflects the nature of the study, as we are dealing with relatively young, healthy adults who have expressed a wish to gather more information about their pregnancy. The rate of incomplete cases, i.e. those where an outcome reference diagnosis is not achieved, is estimated at

around 20%. In support of this estimate, data from a tertiary fetal medicine department within our group indicates that their completion rate for autopsy following termination of pregnancy for fetal ventriculomegaly is 83% [58]. Allowance is also made for a small number (4%) of cancelled, abandoned or incomplete MR examinations. See Figure 3 below for estimated recruitment numbers and drop out rate at each stage of the study.

Figure 3 – Recruitment & Drop Out Estimates



If losses to follow up are very high we will inform the fetal medicine experts who would be able to influence recruitment and retention. We will also use interim data in order to assess the chances of a successful outcome with the required sample size. If the sample size seems too low then we will make a decision whether to stop the study or to request further funding.

An interim analysis is planned after approximately 100 reference diagnoses have been obtained. This will be undertaken to assess two of the assumptions, namely that the accuracy of ultrasound is around 70% and that about two-thirds of babies will have a reference diagnosis.

Data analysis

Primary Analysis

The primary outcome analysis will report diagnostic accuracy within 95% confidence intervals. McNemar's test will be used to assess significant difference between diagnostic accuracy, with and without MR . In addition there will be conditional logistic regression analysis to look at effect modifiers such as gestational age and the nature of the suspected brain abnormality (e.g. ventriculomegaly, posterior fossa abnormalities and abnormalities of the corpus callosum).

Secondary Analyses

Analysis of the change in diagnostic confidence will use the Wilcoxon signed rank test. The effect on prognosis will be presented as a simple percentage (with 95% confidence interval) of cases where the prognostic category was changed.

Change in management will be analysed using McNemar's test.

Finally, a score-based weighted average analysis will be employed, as described by Ng and Palmer [61], which combines changes in diagnostic accuracy, diagnostic confidence and management to provide a summary measure of the clinical impact attributable to in utero MR.

Sub- group Analyses

Both singleton and multi-fetal pregnancies will be included in the primary analysis of diagnostic accuracy, however because of the specific complexities of prognosis and management in multi-fetal pregnancies these cases will be analysed as a distinct sub-group in these respects.

Missing Data

Patterns in missing data will be analysed using conditional logistic regression.

Further details of the proposed analyses are specified within the MERIDIAN Statistical Analysis Plan (see Appendix).

10. Study supervision

Three committees are being established to govern the conduct of the study:
1. Trial Management Group (TMG)
2. Trial Steering Committee (TSC)
3. Data Monitoring and Ethics Committee (DMEC)

All committees are governed by Sheffield CTRU standard operating procedures. The TMG consists of the Chief and Principal Investigators, the qualitative researcher and key staff within the CTRU. The role of the TMG is to implement all parts of the trial and to act on the recommendations from the TSC and DMEC. The TSC consists of the Chief Investigator and key staff within the CTRU (all as non-voting members), an independent chair, at least 2 independent members and a consumer representative. The roles of the TSC are to provide supervision of the protocol and statistical analysis plan, provide advice on and monitor progress of the trial, to review information from other sources and to consider recommendations from the DMEC. The DMEC will consist of an independent chair and 2 independent members including a statistician. The DMEC has responsibility for monitoring the results provided by the trial statistician to the plan described in the trial protocol with reference to efficacy and safety, reviewing information from other sources, providing recommendations to the TSC on why the trial might be modified or discontinued in terms of ethics and safety and considering adverse events. The DMEC will review the interim statistical analysis.

The planned project timetable and milestones are summarised in figure 4.

Project month	9-24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56
	Nov 11 - April 13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15
Recruitment																																	
Follow up (9 months)																																	
Data cleaning (3 months)																																	
Database lock (1 month)																																	
Data analysis (3 months)																																	
Final report writing (4 months)																																	
Completion date																																	*

Figure 4 – study Gantt chart

11. Data handling and record keeping

Participant confidentiality will be respected at all times. There is a requirement for patient identifiable data on CRFs to be faxed and/or mailed between the referring site and the appropriate scanning centre where an MRI scan is to be performed. Similar patient identifiable data will also be passed back to the referring centre following the scan. These transactions form an essential part of clinical referral and reporting procedures. The fetal medicine specialist will collect participant names and contact details so that participants can be contacted for the sociological interviews and to follow up on data. These will be immediately entered with an ID number on to an identification section of the database, which may be accessed by the fetal medicine expert who entered the data, delegated staff at collaborating sites, the qualitative researcher for follow up on this element of the study, and the study managers for follow up and verification of all data. Access will be controlled by usernames and encrypted passwords.

All other data will be anonymised and will only be identifiable by ID number. The CRF/questionnaires will have demographic details on them, including the participant's postcode. This will be used in analysis as an indicator of the participant's socioeconomic status. All data will be entered on to a centralised database held within the CTRU in Sheffield (either directly by a research study member at the referring fetal medicine institution, or where paper forms are used for recruitment and referral, these will be faxed to the primary site and entered by the study manager in Sheffield). This section will also be controlled by usernames and encrypted passwords.

All consent forms, CRFs, questionnaires and interview transcripts will be kept in a locked filing cabinet in a secured area at each relevant participating site, and will be destroyed no sooner than 5 years after study completion. The consent forms will be kept in a separate place to the anonymised CRF's and questionnaires so that none of the data will be identifiable.

12. Data access and quality assurance

The study managers, data manager, PI's, fetal medicine experts and delegated site staff will have access to the anonymised data on the database through the use of usernames and encrypted passwords. In addition to this, access to hard copies of the CRF and questionnaire data will be required by the fetal medicine experts, qualitative researchers and clinical radiologists for study monitoring and audit purposes.

The secure data management system will incorporate quality control procedures to validate the study data. Error reports will be generated where data clarification is required.

13. Publication

Authorship of research papers arising from this study will include co-applicants relevant to the topic, other specific contributors, and a generic reference to all study collaborators; in practice this would read as a list of named authors followed by "…and on behalf of the MERIDIAN study group". All members of the MERIDIAN study group would be named within the appropriate acknowledgements section of the journal article.

Results of the trial will be disseminated in peer reviewed scientific journals and clinical and academic conferences. No report, either verbal or written may be made without the approval of both the TMG and TSC.

Details of the trial will also be made available via a study website. Summaries of the research will be updated periodically to inform readers of the ongoing progress.

14. Finance

The trial has been financed by the Health Technology Assessment (HTA) programme of the National Institute for Health Research (NIHR) and details have been drawn up in a separate agreement.

15. Ethics approval

The trial will be submitted to a Local Research Ethics Committee (LREC) through the IRAS central allocation system. The approval letter from the ethics committee and copy of approved patient information leaflet, consent forms, CRF's and questionnaires will be sent to the Clinical Trials Research Unit (CTRU) in Sheffield before initiation of the study and patient recruitment.

16. Indemnity / Compensation / Insurance

Sheffield Teaching Hospitals NHS Foundation Trust is the sponsor of this research study. The Universities of Sheffield and Newcastle also have in place insurance against liabilities for which they may be legally liable and this cover includes any such liabilities arising out of this research study.

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Appendix

Add-on study

Introduction

There are two elements to this add-on study to MERIDIAN, both of which have been supported by the NIHR-HTA. The first relates to the need to describe the False Negative Rate of ultrasonography as performed by an experienced feto-maternal expert (study A1). Recruitment into MERIDIAN includes only fetuses thought to have brain abnormalities on ultrasound so the false negative rate cannot be estimated by the main MERIDIAN study. The second study will calculate the rate of unexpected brain abnormalities (i.e. not shown on ultrasonography) in fetuses with non-CNS abnormalities (Study A2). The results of both studies will be of great potential importance to the NHS.

In both studies we plan to recruit 200 women whose fetus has had a detailed anomaly ultrasound by a feto-maternal expert which showed no brain abnormality. If a woman has had a previous pregnancy complicated by a brain abnormality the women will not be invited into the study. If participant numbers are not sufficient from this group we intend to recruit pregnant women from the general population who have not had a detailed anomaly ultrasound and arrange a fetal brain ultrasound with a fetal medicine consultant as part of the study.

Aims and Objectives

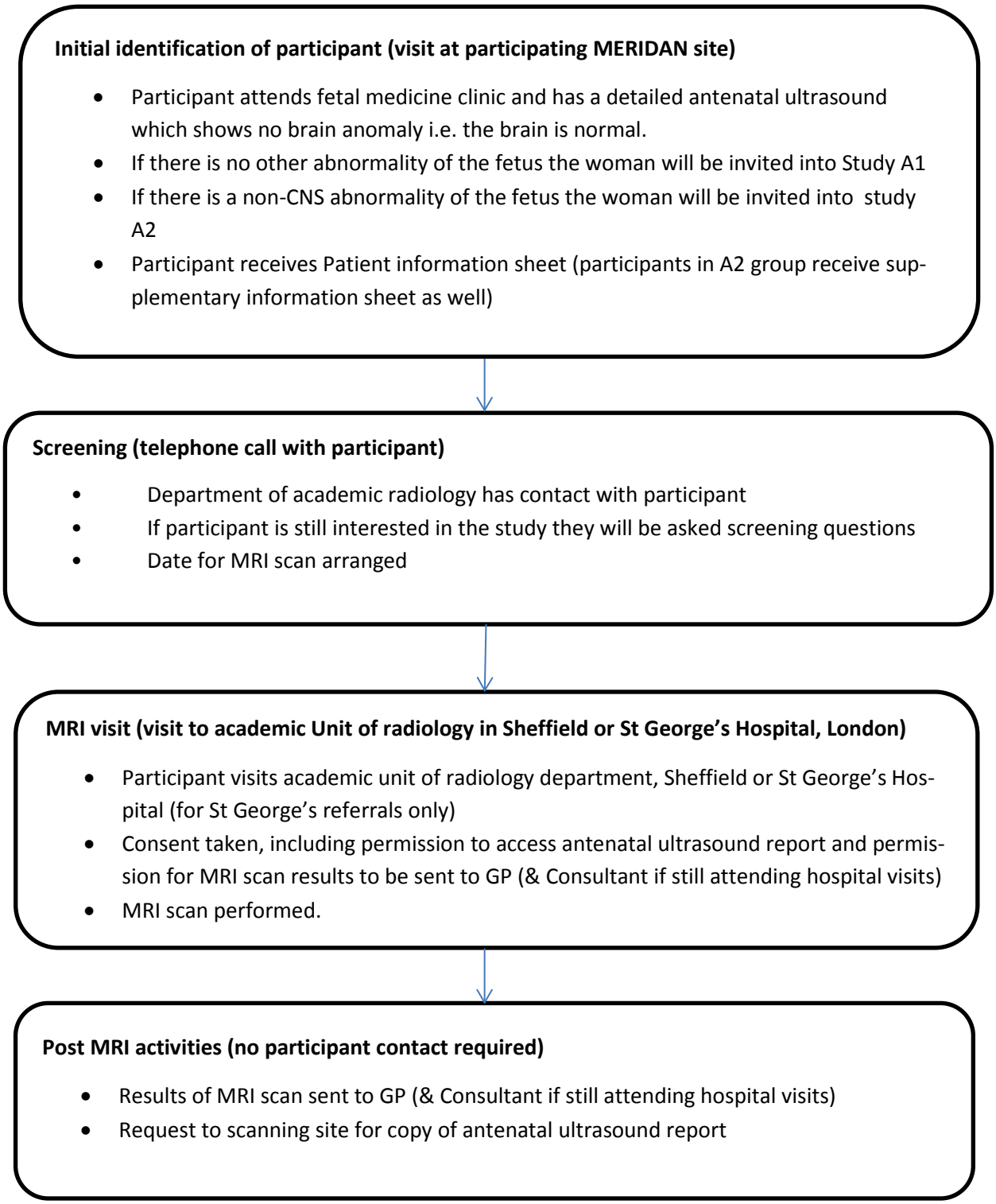
Study A1
The aim is to answer the question:
What is the false negative rate of ante-natal ultrasound performed by feto-maternal experts when trying to detect fetal brain abnormalities?

Study A2
The aim is to answer the question:
What is the rate of unexpected brain abnormalities detected by iuMR imaging in fetuses with known non-CNS abnormalities.

Study Design

Participants will be recruited via option 1. Option 2 will be held in reserve and only used if recruitment via option 1 is insufficient.

Participant pathway diagram Option 1:



Participant pathway diagram Option 2:

Initial identification of participant

- Pregnant women whose pregnancy is normal are sought through:
  - Scanning ultrasound clinics at participating MERIDIAN sites
  - Charitable organisations working in pregnancy, working within the Sheffield area
  - Community midwives in Sheffield area
  - GP lists in Sheffield area
  - Local media
- Participants are given a patient information leaflet and or information sheet and details of how to register their interest in taking part in the study (phone/email)

Screening (telephone call with participant)

- Department of academic radiology has contact with participant
- If participant is still interested in the study they will be asked screening questions
- Date for Ultrasound and MRI scan arranged
- Full patient information sheet sent to participant (if not already received)

Detailed Ultrasound & MRI visit (visit to academic Unit of radiology in Sheffield)

- Participant visits academic of radiology department,
- consent taken, including permission for scan results to be sent to GP
- Brain ultrasound performed
- MRI scan performed
- Participant offered MR image of baby to keep and £10 voucher.

Post MRI activities (no participant contact required)

- Results of Ultrasound & MRI scan sent to GP

Inclusion Exclusion Criteria

Inclusion Criteria

A participant is eligible for the trial if the following criteria are met:

For study A1

1. Has an ongoing singleton or multi-fetal pregnancy of at least 18^{+0} weeks gestation* by ultrasound dating.
2. Is thought to be carrying a fetus with no abnormality whatsoever (i.e. no brain or somatic abnormality) **

For study A2

1. Has an ongoing singleton or multi-fetal pregnancy of at least 18^{+0} weeks gestation* by ultrasound dating.
2. Is thought to be carrying a fetus with no brain abnormality but does have a confirmed somatic abnormality **

* It is a requirement that MR scans are not carried out prior to 18 weeks gestation. Women can be consented at 17 weeks gestation where there is a continuing pregnancy and they will be 18 weeks at the time of the MR examination.

** if recruited via option 1 this criterion will be based on a normal mid pregnancy anomaly scan in a fetal medicine centre. If recruited via option 2 this will be self-reported by the participant based on their medical care to date e.g. screening ultrasound

Exclusion Criteria

A participant is excluded from the trial if any of the following criteria are met:

1. Has a past history of a fetal brain anomaly in a previous pregnancy
2. Inability to give informed consent.
3. Has a cardiac pacemaker, intra-orbital metallic foreign body, or recent surgery with metallic sutures or implant.
4. Has previously experienced or is likely to suffer severe anxiety or claustrophobia in relation to MR imaging examination.
5. Is unable or unwilling to travel to Sheffield or attend St George's Hospital for specialist MR imaging.

6. Is unable to understand English (except where satisfactory translation services are available).
7. Is under the age of 16 years.
8. Is unwilling for GP to be informed about the study and given copies of scan reports

Withdrawal Criteria

- Participant wishes to withdraw from the study.
- Participant was ineligible at the time of consent

Study Treatment (antenatal MRI)

As per main protocol.

Assessments and procedures (option 1 pathway)

Enrolment (option 1 pathway)

Participating MERIDIAN sites will have posters and leaflets in public areas with details of the sub study. Potential participants can then ask staff about the study and receive the full participant information sheet. Also Fetal Medicine specialists can tell women in clinic about the study and give them the full patient information sheet. Women who are given the PIS in person should be asked if they are willing to be contacted by the academic radiology to discuss the study further. In addition clinic lists can be screened and women who have had a detailed ultrasound anomaly scan within the last seven days can be sent a patient information sheet by post.

Staff at the academic unit of radiology or St George's Hospital (for St George's referrals only) will then have a telephone conversation with potential participants and ask them some screening questions. Eligible participants will be offered an appointment for an MRI scan at the academic unit of radiology or St Georges Hospital. If the participant has not had the full patient information sheet this will be sent to them either via email or post. Travel expenses for the participant and partner/friend/relative will be made available. When they attend the appointment informed consent will be taken. An important part of the consent procedure is the willingness of participants to allow their GP to be informed that they are taking part in the study and have a copy of the MRI report (see safety section).

Women in study A2 who are carrying a baby with a suspected non-brain abnormality will be given a supplementary information sheet which clearly states that scanning will be for the brain only. This is covered briefly in the main patient information sheet but we feel it important to emphasise this aspect of the study to this particular group of participants.

The enrolment procedure will be optimised to minimize the time between the ultrasound scan and MRI scan. Potential participants will be telephoned promptly once their details have been received and be offered the earliest available MRI appointments. Ideally an MRI

would be take place within one week of the ultrasound, but participants will still be accepted regardless of the interval between ultrasound and MRI.

Study Visit (option 1 pathway)
Participants will attend a clinic at the academic unit of radiology or St George's Hospital. Informed consent will be taken.

After consent background information about the participant will be recorded by staff.

The participant will have the MRI scan and be offered an image of the baby to keep. Participants will also be offered a £10 voucher . Normally the participants will be able to have a discussion about the results of the scan and be given some immediate feedback, the participants will be reminded that results are going to be sent to their GP.

No further patient contact is required after this visit.

Post Visit activities (option 1 pathway)
After the visit a copy of the MRI report will be sent to the participant's GP and their consultant if they are still receiving care from a fetal medicine unit.

A copy of the detailed anomaly ultrasound report will be requested from the referring MERIDIAN centre (unless the participant had a copy in their hand held maternity notes, if this is the case a copy of the report from the maternity notes will be used).

Assessments and procedures (option 2 pathway)

Enrolment (option 2 pathway)
Participating MERIDIAN sites will be able to identify participants as for option 1, but to a wider group of patients who have not had an ultrasound by a fetal medicine consultant.

In addition suitable organisations working in Sheffield and surrounding areas such as Charitable organisations working in pregnancy, Community midwives, GPs will be approached and asked if they will make information about the study available to pregnant women they work with. Potential participants will have access to participant flyer and full information sheet. The participant flyer will have phone and email contact details for Academic Unit of radiology and participants can register their interest.

Staff at the academic unit of radiology will then have a telephone conversation with potential participants and ask them some screening questions. Eligible participants will be offered an appointment for an ultrasound and a MRI scan at the academic unit of radiology. Travel expenses for the participant and partner/friend/relative will be made available. When they attend the appointment informed consent will be taken. An important part of the consent procedure is the willingness of participants to allow their GP to be informed that they

are taking part in the study and have a copy of the Ultrasound and MRI reports (see safety section).

Women who are carrying a baby with a suspected non-brain abnormality will be given a supplementary information sheet which clearly states that scanning will be for the brain only. This is covered briefly in the main patient information sheet but we feel it important to emphasise this aspect of the study to this particular group of participants.

Study Visit (option 2 pathway)

Participants will attend a clinic at the academic unit of radiology. Informed consent will be taken.

After consent background information about the participant will be recorded by staff.

The participant will have a fetal brain ultrasound with a fetal medicine consultant. If the ultrasound shows normal brain development the participant will go on to have the MERIDIAN Add on study MRI scan. If the ultrasound detects a suspected brain abnormality the fetal medicine consultant will counsel the participant based on the anomaly seen and advise her to see her GP. The patient will have no further data collected for the MERIDIAN study. If it would be beneficial a clinical MRI will be offered to be done immediately during the same visit. This MRI will not be reported as part of the MERIDIAN Add on study.

The participant will then have the MRI scan and be offered an image of the baby to keep. Participants will also be offered a £10 voucher. Normally the participants will be able to have a discussion about the results of the scan and be given some immediate feedback, the participants will be reminded that results are going to be sent to their GP. No further patient contact is required after this visit.

Post Visit activities (option 2 pathway)
After the visit a copy of the scan reports will be sent to the participant's GP.

Safety

Only adverse events that occur during the MRI scan will be captured. There will be no participant follow up as part of this study.

The reports of scans performed for this study will be sent to the participant's doctor(s), in some cases this will be a GP in other cases a consultant. If an anomaly is detected it will be the doctor's responsibility as part of his or her normal clinical care to take appropriate action.

Statistics

Starting from the assumption that no US false negatives will be found, the extension study will recruit 200 fetuses in each group. This figure has been derived from the 3/n rule (Eypasch et al., 1995), a large sample approximation of the upper 95% confidence interval for very rare events. If no adverse events are observed in a sample of size of n, this does not

imply that adverse events are impossible; instead, a confidence interval can be constructed to quantify the upper limit of the event rate. The study will therefore estimate the negative predictive value of US to an upper limit of 3/200 or 1.5% in the absence of false negatives. If false positives are encountered, the study will estimate the negative predictive value to a standard error of <=2% for plausible occurrence rates (i.e. <10%) .

Reference

Eypasch E, Lefering R, Kum CK, Troidl H. "Probability of adverse events that have not yet occurred: A statistical reminder". BMJ 1995;311 (7005): 619–620

The University Of Sheffield.

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MERIDIAN – 2-3 year follow up study

Funded by the National Institute for Health Research's Health Technology Assessment programme (project number 09-06-01)

Magnetic resonance imaging to enhance the diagnosis of fetal developmental brain abnormalities in utero - 2-3 year follow up study

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RESEARCH PROTOCOL
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STH R&D ref **STH19125**
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ISRCTN **ISCRTN27626961**
Authorised by: PD Griffiths

Magnetic resonance imaging to enhance the diagnosis of fetal developmental brain abnormalities in utero – 2-3 year follow up study

MERIDIAN

Contents

Abbreviations

AE	Adverse event
ASQ	Ages and Stages Questionnaire
BSID III	Bayley's Scale of Infant Development III
CI	Chief Investigator
CRF	Case report form
CTRU	Clinical Trials Research Unit
DMC, DMEC	Data Monitoring and Ethics Committee
GP	General Practitioner
GMFCS	Gross Motor Function Classification System
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
IRAS	Integrated Research Application System
iuMR	In utero magnetic resonance
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
R&D	Research and development
SAE	Serious adverse event
SSC	Study steering committee; service support costs
STH	Sheffield Teaching Hospitals
SDQ	Strengths and Difficulties Questionnaire
TOP	Termination of pregnancy
TMG	Trial management group
TSC	Trial steering committee
UK	United Kingdom
URMS	University Research Management System
US	Ultrasound

General information

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Mr Mike Bradburn — Senior Medical Statistician, University of Sheffield

Miss Cara Mooney — Study Manager, University of Sheffield

Protocol amendments since Version 1.0

Section 6. Assessments and procedures (page 17)

Risks and Benefits have been updated with details of strategy for handling incidents where the parent of a deceased child is contacted.

Section 9. Data handling and Record keeping (page 22)

Confirmation that appropriate Trust management systems will be followed when transferring personal data.

Protocol amendments since Version 2.0

Section 2. Aims and Objectives (page 8)

BSID scores updated in line with the scores produced from the BSID III

Section 3. Study Design (page 9 and 10)

Updated text details and flow chart for project 2 to allow the BSID to be completed in other suitable clinics, as well as hospital and participants home

Section 6. Assessments and Procedure (page 14)

Updated to clarify that if GMFCS is to be parent completed then the adapted motor skills questionnaire will be used.

Section 7. Statistics (page 19 and 20)

BSID scores updated in line with the scores produced from the BSID III

Protocol amendments since Version 3.0

Section 3. Study Design (page 10)

Design flow chart updated to change terminology to telephone contact and to allow contact in clinics.

Section 5. Enrolment (page 12 and 13)

Terminology updated to 'research team' rather than research nurse. Updated to allow telephone contact to be a telephone call or text message. Consent procedure updated to allow face to face consent completion in clinics.

Process for sending a reminder letter or text message if completed consent not returned added.

Section 6. Assessments and Procedure (page 14)

Terminology updated for clarity and procedure for contacting in clinic added.

Study Summary

The MERIDIAN study assessed the diagnostic accuracy of in utero magnetic resonance (iuMR) imaging and ultrasound for the detection of fetal brain abnormalities. Between July 2011 and August 2014 832 participants underwent both ultrasound and iuMR, with the primary objective being to ascertain whether iuMR after Ultrasound (US) leads to more accurate diagnoses of brain abnormalities than US alone. The reference diagnosis (against which ultrasound and iuMR were compared) was the findings of post-natal imaging performed within 6 months (age-corrected for gestational age) or, in the case of fetal/infant demise, from post-mortem. Further details of the study are available in the clinical protocol [1].

Following on from this the MERIDIAN 2-3 year follow up study was funded to incorporate additional follow-up of its participants, specifically: i) to incorporate longer term outcomes observed over the first 2-3 years of life, and ii) to undertake a detailed neurodevelopmental assessment of infants.

The study will recruit participants from the MERIDIAN cohort when the children are aged 2-3 years old. The study will update and refine the estimates of diagnostic accuracy from the original study using clinical data which is available when the children are aged 2-3 years. In addition the study will explore the functional development of the children which will be used to assess the prognostic capabilities of iuMR and US.

1. Introduction

Fetal imaging with ultrasound has been the mainstay of ante-natal screening programmes and anomaly studies for many years. No imaging methodology is perfect and physical limitations may produce sub-optimal images of the fetus, leading to incorrect diagnoses and, hence, incorrect information being given to parents. The fetal brain is a particular area of concern because of the relatively high frequency of developmental abnormalities and the number of clinically significant pathologies that give rise to subtle imaging changes. Advances in MR technology allow highly reliable and accurate diagnoses of comparable pathology to be made in children because of great improvements in spatial and contrast resolution. Further advances in hardware and software in the 1990s meant that in utero MR imaging became a realistic clinical possibility and our group were pioneers in this field [2]. From those first attempts, several groups, including our own, have confirmed that in utero MR (iuMR) imaging for fetal brain abnormalities is a powerful adjunct to ultrasound as early as 18 weeks gestational age.

A large proportion of the published data has shown that iuMR provides additional information when compared with ultrasonography [3-8] and the potential clinical applications and ethical issues surrounding in utero MR imaging was described by our group in an invited review for the British Medical Journal [9]. Although relatively large case series have now been reported, most lack comparison with a reference standard, which is vital to confirm improvements in diagnostic accuracy. In addition many groups, including our own, have been criticised by specialist fetal neurosonography experts [10,11] on the basis of artificially high detection rates for in utero MR imaging resulting from biased patient selection. For example, our study published in 2004 [12] was significantly biased as it focused on 100 cases where the results from ultrasound were limited because of technical factors such as fetal lie, oligohydramnios or unfavourable maternal habitus. A more recent study [13], focused on 147 fetuses with isolated ventriculomegaly as judged by ultrasound with high confidence and no technical limitations but did not have reliable reference standard data.

The NIHR funded MERIDIAN study (HTA 09-06-01) is the largest iuMR study to date and hopes to overcome those weaknesses. MERIDIAN focuses on the diagnosis of fetal brain abnormalities but this cohort provides a unique group to reassess the clinical significance of brain abnormalities as the child develops.

The follow-up study has three projects which have been designed to maximise the scientific value of data and translational relevance from MERIDIAN arising from clinical information that will be available when the children are aged 2-3 years old.

The longer follow up period will allow us to refine our estimates of diagnostic accuracy based on reference standard outcome data available when the children are aged 2-3 years old. Participants will also be invited to complete a developmental questionnaire and attend for a developmental assessment using the Bayley Scale of Infant development (BSID) [14]. The results of these assessments will allow us to address the question of the functional significance

of the brain abnormality on the child, and improve the prognostic information available to fetal medicine experts and pregnant women.

The study will be conducted in compliance with the protocol, GCP and regulatory requirements.

2. Aims and Objectives

There are 3 distinct projects within this follow-up study, the aims and objectives have been divided by project to clearly demonstrate how they will be implemented:

Project 1:
The aim of project 1 is to refine our estimates of diagnostic accuracy of MR imaging as a technology to aid the prenatal diagnosis of fetal developmental brain abnormalities.

1) We will reassess the diagnostic accuracy of MR imaging compared to antenatal US through:
a) Measurement of diagnostic accuracy of antenatal US alone (i.e. prior to iuMR) relative to updated reference diagnosis at 2-3 years of age (post-natal imaging or post-mortem examination);
b) Measurement of diagnostic accuracy of iuMR (following antenatal US) relative to the updated reference diagnosis at 2-3 years of age (post-natal imaging or post-mortem examination).

Project 2:
The aim of project 2 is to improve the prognostic information available during pregnancy based on the functional and developmental outcomes of the MERIDIAN cohort.

1) We will quantify the value of prognoses based on MR imaging and on USS by:
a) Assessing the concordance between severe neurodevelopmental impairment (defined by BSID score of <80 on the Cognitive AND language index or a combined score of <85 or a motor score of <70 , evidence of severe disability based on a score <-2SDs for the ASQ, or evidence of cerebral palsy based on GMFCS) and poor prognosis, based on MR and on USS;
b) Comparing the relative prognostic accuracy of USS and MR imaging;

2) We will qualitatively assess the cases for which the USS prognosis and MR prognosis differed, in relation specifically to the original diagnoses;

3) We will look at the concordance in the subgroup of children for which the MR scan was performed within 24 weeks;

4) We will assess ability to predict non-severe impairment (defined as BSID <85 or a score between 1 and 2 SDs for the ASQ).

Project 3:

The aim of project 3 is to assess the clinical significance of isolated, mild ventriculomegaly.

1) We will assess the clinical significance through:
a) Identification of all isolated, mild ventriculomegaly cases diagnosed on in utero MR in the MERIDIAN cohort and define their developmental outcome at 2-3 years (as per project 2);
b) Comparison of developmental outcome to the prognoses made based on USS.

3. Study design

Multi-centre observational cohort study of diagnostic accuracy and functional development of children born from the MERIDIAN study.

The study is designed to include all of the surviving children from the MERIDIAN study over a longer term follow up. The three projects will maximise the scientific value of data and translational relevance from MERIDIAN arising from clinical information that will be available when the children are aged 2-3 years old.

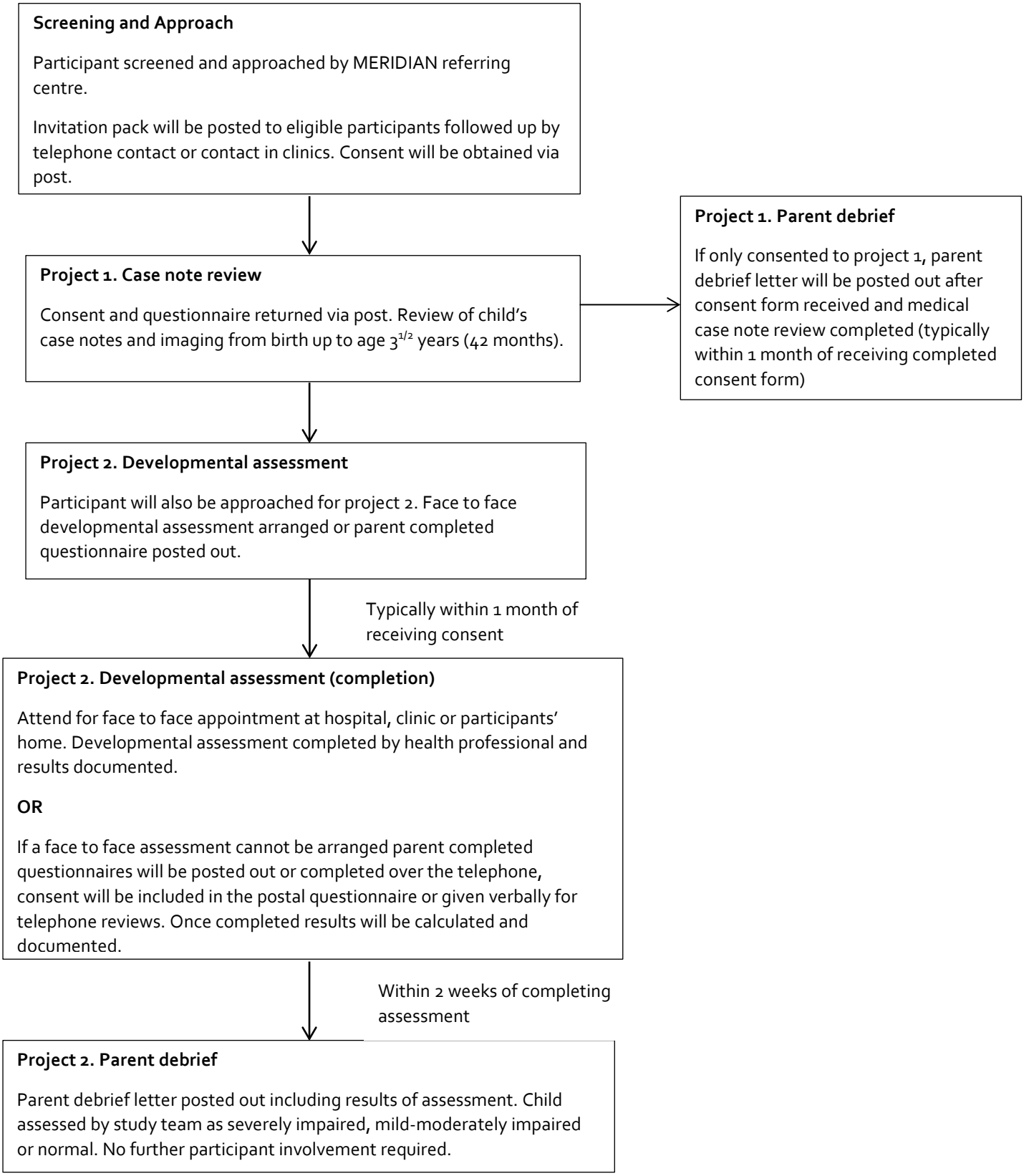
Project 1
A review of the child's medical case notes will be completed at each of the MERIDIAN sites and data extracted onto the paper case report form (CRF) template. New or refreshed diagnoses will be recorded from postnatal imaging and investigations. Where no further information is available or the participant does not consent to further involvement the original diagnosis will be retained as the most credible reference diagnosis.

Project 2
Developmental assessments will be completed within hospital clinics, other suitable clinics such as physiotherapy clinics or the participants' home. The assessments will be completed by a suitably trained health professional and will assess the functional and developmental status of the child, allowing us to classify the child as severely impaired, mild-moderately impaired or normal.

Project 3
All isolated, mild ventriculomegaly cases diagnosed on iuMR in the MERIDIAN cohort will be identified by the study team and their developmental outcome at 2-3 years of age will be classified by the categories in project 2. Project 3 does not require further involvement from the MERIDIAN participants or referring sites.

Figure 1. outlines the study design and involvement required by the participant and their child at each stage.

Figure 1. MERIDIAN 2-3 year follow up design



Project 3. Clinical significance isolated, mild ventriculomegaly assessment

Identification of cases diagnosed with isolated, mild ventriculomegaly on iuMR in the MERIDIAN cohort and their developmental outcome at 2-3 years of age will be defined as severely impaired, mild-moderately impaired or normal as assessed in project 2. No input from MERIDIAN research sites required.

4. Selection and Withdrawal of participants

The participant group of which to recruit from is defined as those who participated in the MERIDIAN study during their pregnancy. Women recruited into the MERIDIAN study were asked about being approached for future studies about their child's development as part of the original consent process.

Inclusion criteria

Participants are eligible for the study if the following criteria are met:

- Participated in MERIDIAN and has a surviving child aged 2 years old or more*
- Underwent an iuMR scan during pregnancy as part of MERIDIAN

*If the child is no longer alive then data will be collected and recorded on date of death and cause of death. No contact will be made with the family.

Children who are over 38 months (term corrected) will not be eligible for a developmental assessment but will be included in project 1 (case note review), additional data will only be collected up until the child was 42 months

Exclusion criteria

A participant is excluded from the study if any of the following criteria are met:

- If the child born from MERIDIAN is no longer alive (*see above)
- If the child is no longer in the care of the biological mother who consented to the original MERIDIAN study
- Is unable to give informed consent
- Is unable to understand English (except where another parent/guardian of the child can translate and provide consent)
- If they were withdrawn at any stage of MERIDIAN
- If they did not attend for fetal MR as part of MERIDIAN

**This exclusion criteria is for consent purposes only. Where English is not the first language of the child the Bayley's assessment may still take place if consent has been given by a parent. The Bayley's assessor will make a judgement as to which aspects of the assessment the child is able to participate in.

To assess eligibility we will:

1. Complete a consent form audit to identify those who have consented to be approached about future studies regarding their child's development (question 7 on original consent form)
2. Research midwives/nurses will complete screening of medical notes and NHS systems to check eligibility and suitability of the study

3. Where available the central study team will check that the child is still alive using the Health & Social Care Information Centre (HSCIC) Patient Tracking system (or equivalent in Scotland and Northern Ireland)

Withdrawal Criteria

- The only criteria for withdrawal is where the participant wishes to withdraw from the study

5. Enrolment

All participants will be screened by the research team for eligibility prior to any contact being made. A Screening Form will be completed which will document whether the participant meets the initial inclusion criteria and does not meet any exclusion criteria. For participants being excluded at this stage, it will be documented on the screening form why they are not eligible. In cases where the participant meets the eligibility criteria but the research nurse or paediatrician does not feel that they would be appropriate to contact then this will also be recorded along with the reason why have been deemed inappropriate to contact. Research nurses and paediatricians or PI's will use their clinical judgement to assess appropriateness. An example of why they may be deemed inappropriate to contact include ongoing social care/services issues.

Eligible participants will initially be approached by a letter of invitation from the referring MERIDIAN site. This letter will be sent by the local or central research team. The letter will include the Parent Information Sheet, a reply slip and a return envelope. Once the reply slip is returned the research team will either contact the participant to discuss the study further if accepted, or will complete the Approach form and mark as not to contact further if declined. If the reply slip is not returned within 2-3 weeks of posting the invitation pack, the participant will be followed up by telephone or face to face contact in clinics.

Telephone contact with the participant may include a telephone call or text message, where a mobile phone for research purposes is available to the research team.

Project 1

All participants will be recruited via telephone contact from the research team and written informed consent will be obtained via post. During the telephone contact the Approach Form will be completed which will include the outcome of the telephone conversation, i.e. decline participation or verbal agreement to participate. If participants agree to participate then the consent forms will be posted out including a cover letter with detailed instructions on how to complete.

Where there is face to face contact, for example during a clinic visit, consent may be taken in person where the participant has been given sufficient time to ask questions and answers been provided.

The Ages and Stages Questionnaire (ASQ) [15] will also be posted out or given to participants to complete and return with the consent form. If participation is declined at this stage then this will be recorded on the Approach form using the original MERIDIAN participant ID number and no further contact will be made. If the ASQ is returned but the consent form is not, then we will assume consent for using the information provided on the ASQ.
If the consent form or ASQ are not returned after 3 weeks of posting to them the research team will send a reminder letter and a second copy of the forms or a reminder text message can where appropriate.

Project 2

Involvement in project 2 will also be discussed during the telephone or face to face contact to determine interest. If participants indicate during this contact that they would like to participate in project 2 as well as project 1 then the combined consent form will be posted out/completed face to face.

Once the appropriate consent forms have been returned the research team will arrange a suitable time and place for the assessment to be completed.

To optimise follow up, if a face to face meeting cannot be arranged, or an appointment is missed there will be the option for data collection via parent completed questionnaires. These questionnaires can be posted out or completed over the telephone.

It will be made clear to the participant that participation in project 2 is entirely optional and does not affect their involvement in project 1.

Consent for Project 1 only will be captured on consent form project 1. Consent for Project 1 and 2 will be captured on the combined consent form.

6. Assessments and procedures

Project 1 (case note review)

Once the completed consent form has been returned to the research team they will review the child's medical notes and record details of further follow up, additional or changed diagnoses, postnatal imaging and other investigations relating to the child's development.

Where, during screening, it is identified that the child is no longer alive then date of death and cause of death will be collected and recorded. In some instances this information may be available from the HSCIC. Where this data is not available from the HSCIC a review of medical notes and hospital records will need to be completed to collect this data.

If the family do not consent, if no further scans or investigations have been undertaken, or the child died during the initial MERIDIAN then the original reference diagnosis used in MERIDIAN will be retained.

The research team will complete the CRF with details from the case note review. The Ages and Stages questionnaire will also have been posted to participants along with the consent form. The results of this questionnaire will be calculated and recorded.

In most cases, the case note review CRF will be completed at the MERIDIAN research site. If the child is no longer alive the central research team may be required to populate this form with the date of death and cause of death as provided by the HSCIC or equivalent, where appropriate approvals are in place.

For any contentious cases our independent expert panel (consisting of a fetal medicine clinician, paediatric neuroradiologist and paediatric neurologist or neurosurgeon) will adjudicate whether additional diagnoses are likely to be acquired conditions (i.e. those which are not detectable by fetal imaging and does not relate to conditions which are, such as infant meningitis); or a congenital pathology that would have been detected by optimal fetal imaging.

If the participant consented to Project 1 only the research team at site will post the Parent Debrief Letter once the case note review has been completed.

Project 2 (Detailed neurodevelopmental assessment)

The assessments will be completed face to face in a hospital, local clinic or, in the participant's home.

The Bayley Scales of Infant Development (BSID) [14] will be used to assess developmental outcome. It is a well validated tool for assessing development in early infancy that is widely used and generates standardised scores that allow corrections for differences in age at measurement. The BSID is an assessment of global infant development, however in a small minority of children with very complex impairments (e.g. spina bifida where children are in a wheelchair) a BSID will not be possible, but we will still complete the Gross Motor Function Classification System (GMFCS) [16] or the adapted Gross Motor Skills questionnaire and Strengths and Difficulties Questionnaire (SDQ) [17], as detailed below.

The GMFCS and the SDQ will also be administered during this appointment. Details of the additional assessments are provided in appendix 1.

Where it is not possible to arrange a face to face appointment, or if for any reason the questionnaires are not completed during the appointment then there will be the option for the GMFCS questions (adapted for parent completion) and SDQ to be posted out or given to parents for them to complete and return to the research team. Alternatively the questionnaires can be completed over the telephone with the child's parent.

The research team will categorise the children as severely impaired (scoring <70), mild-moderately impaired (scoring 70-85) or normal (scoring 85+) based on the results of the developmental assessments. These categories will be used to complete the developmental assessment CRF.

After the developmental assessments all participants will be debriefed via a feedback letter from the research team, which will contain details of the results from the developmental assessment. Where an important previously unrecognised disability has been identified, we will speak to parents about future actions. Typically this would include informing the GP and advising about appropriate referrals either to community paediatrics or therapy services. A member of the study team (NE, an experienced paediatrician) would be available for discussion and advice if the best course of action was not immediately apparent.

Project 3

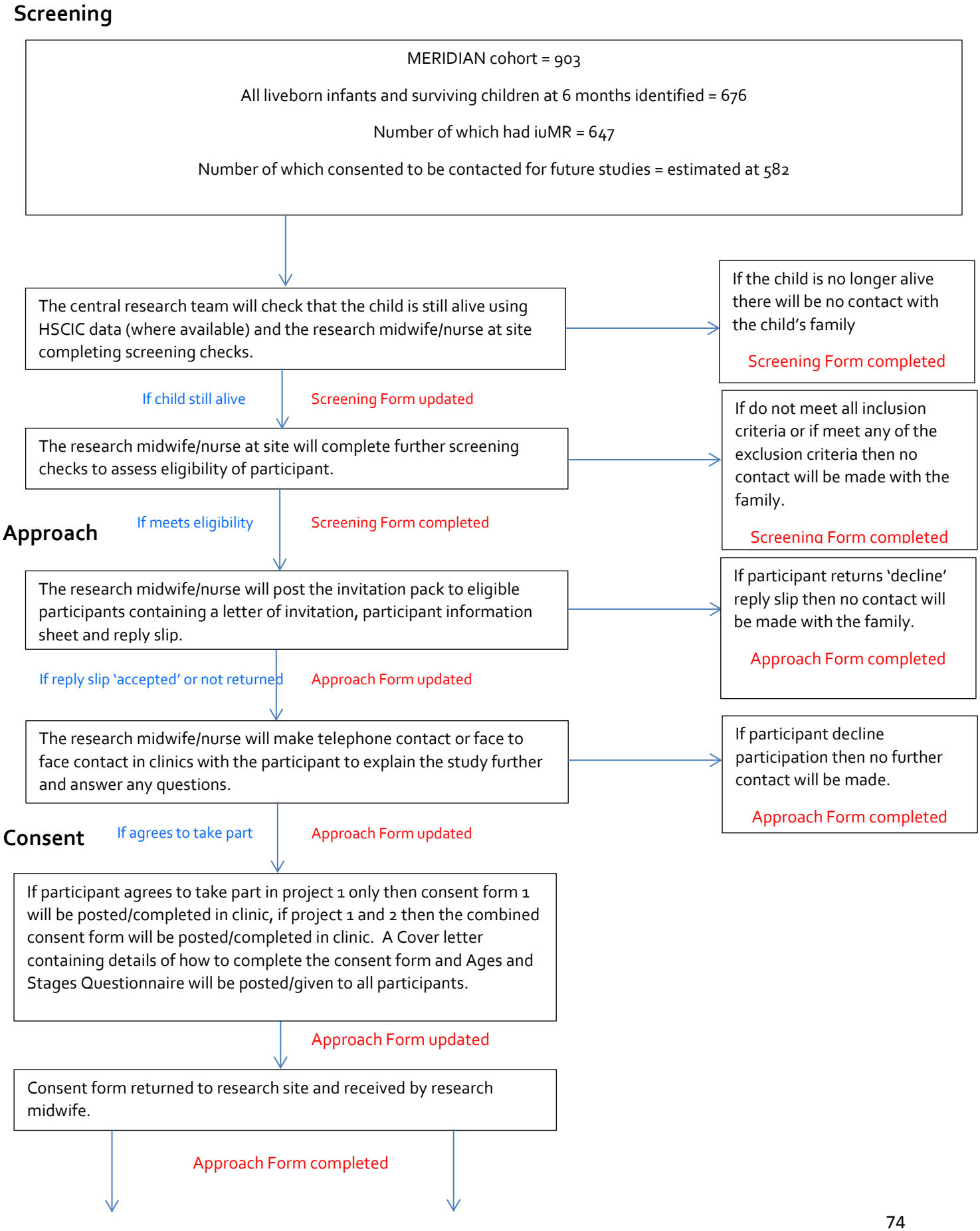
There is no input required from the MERIDIAN participants or research sites for completion of project 3. Project 3 will be completed by the central study team at the University of Sheffield.

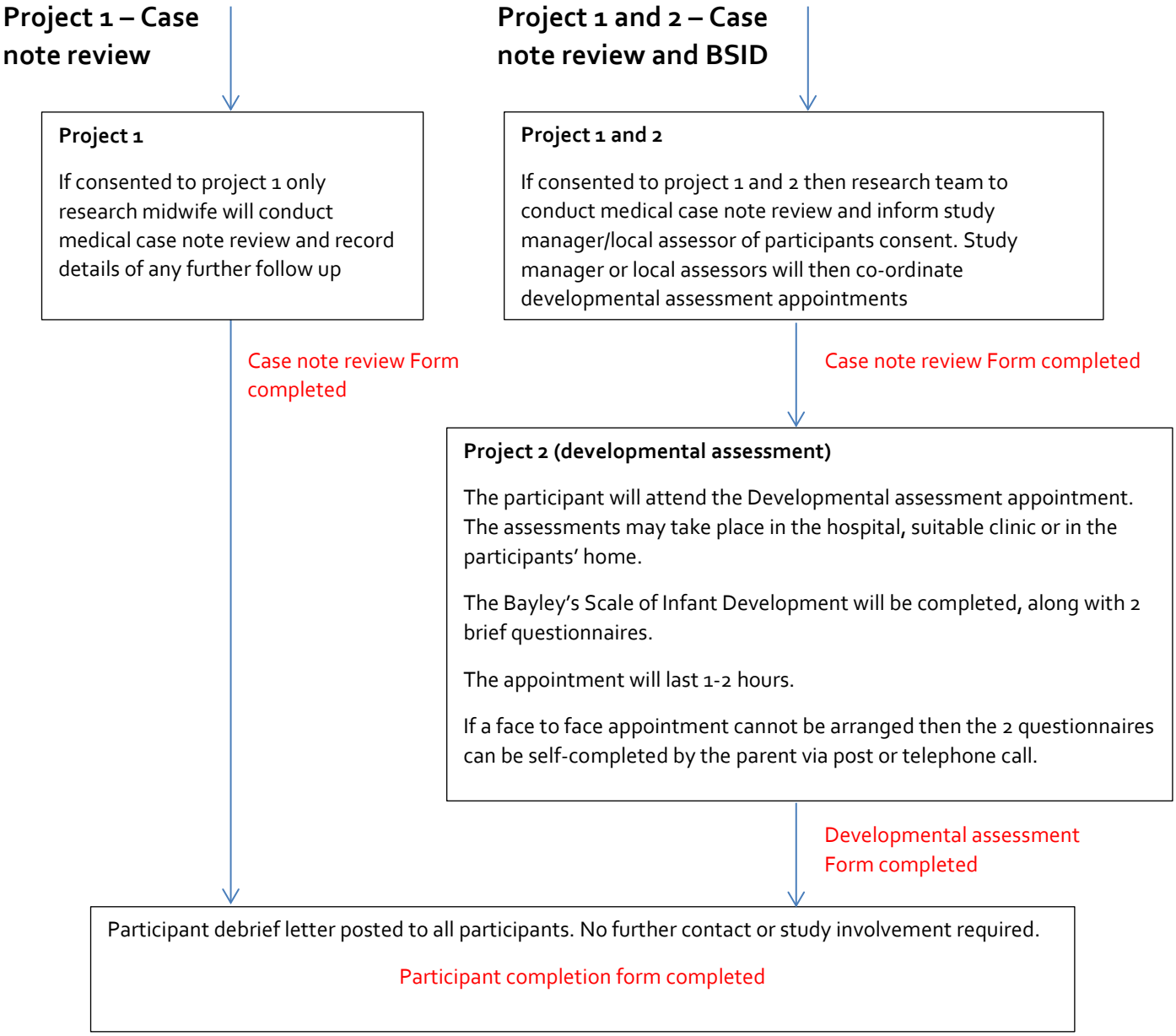
The information for project 3 will come from the assessments described in project 2. We will identify all cases of isolated mild ventriculomegaly diagnosed on iuMR and define their developmental outcome at 2-3 years as severely impaired, mild-moderately impaired or normal as per project 2. In MERIDIAN, the most common information given to women on the basis of isolated mild VM on USS is "favourable (90%)" followed by poor or intermediate and the remainder as normal.

We will calculate the prevalence of severe and non-severe impairments in isolated mild VM cases.

Please see Figure 2. for details of procedures and data collection document

Figure 2. Procedure for MERIDIAN 2-3 year follow up study





Project 3 – Clinical significance isolated, mild ventriculomegaly assessment (Does not require participant involvement or support from the referring sites)

Project 3

The central study team will identify all of the cases diagnosed with isolated, mild ventriculomegaly on iuMR in the MERIDIAN cohort. Their developmental outcome at 2-3 years of age will be defined as severely impaired, mild-moderately impaired or normal as assessed in project 2. No input from MERIDIAN research sites required.

Risks and Benefits

There are very few risks that are likely to be associated with the study. Detailed below are the risks which have been identified as having the potential to occur during the study and the measures being taken to address the risk:

a) Approaching the parent of a child who is no longer alive
   - Research nurses/midwives will complete screening checks to ensure that the child is still alive before approaching the parents. Where possible the central research study team will use the HSCIC Patient Tracking system to check that the child is still alive before approach. If there are any instances where this does occur then this will be captured on the Approach Form.
   - In the event that the study team contact the parent of a deceased child, despite completing the appropriate checks, we will write to parents offering a full apology for any distress caused and explaining how the mistake occurred. This letter will be co-signed by the CI and paediatric lead (NE). In addition we will provide them with information about how to register a formal complaint if they choose. We will also offer them the opportunity to meet with members of the trial team, or local investigator team (typically the PI) in person or by phone, and offer them the opportunity to receive further information on study completion.

b) The child becoming distressed or not wanting to participate in the developmental assessment.
   - The BSID is always conducted with parents present which is usually enough to put the child at ease. Most children enjoy completing the tasks. Occasionally, children become tired or are unwilling to take part. In these situations we will be guided by parents. Some parents may opt to let the child have a short break, in other situations we will stop the assessments and offer a return visit if parents wish. Any cases where the assessment has been terminated early will be captured on the Developmental assessment CRF.

c) There is a small chance that we might identify a previously unrecognised developmental problem. This would be very unusual at the 2-3 year age window we are using. Where this occurs we will speak to parents about future actions. Typically this would include informing the GP and advising about appropriate referrals either to community paediatrics or therapy services. A member of the study team (NE, an experienced paediatrician) would be available for discussion and advice if the best course of action was not immediately apparent.

These events will be captured and reported to the oversight committees as appropriate.

7. Statistics

Analysis of Project 1

We will recalculate the diagnostic accuracy and certainty using any additionally available updated reference outcome data, but utilising the same methods and analyses as for the original reference diagnosis.

This will be recalculated by:

a. Measurement of diagnostic accuracy of antenatal US alone (i.e. prior to in utero MR) relative to updated reference diagnosis at 2-3 years of age (postnatal imaging or post-mortem examination)

b. Measurement of diagnostic accuracy of in utero MR (following antenatal US) relative to the updated reference diagnosis at 2-3 years of age (postnatal imaging or post-mortem examination).

Further details of methods and analyses are available in the MERIDIAN protocol [1].

The impact of non-consent to follow-up is anticipated to be very small and will not directly influence the power of the study. All MERIDIAN cases will be retained (using original diagnosis if no consent is received); meaning that the effective sample size is likely to increase where the additional follow-up yields data where previously none was available.

Sample size Project 1

The original MERIDIAN study requires data on 336 children to detect a 10% improvement in diagnostic accuracy. We anticipate the number of participants consenting to repeat examination will be much greater than 336, and the improvement in diagnostic accuracy to be greater still than 10% due to better quality reference data.

Analysis of Project 2

Results from the BSID will allow us to determine the developmental outcome and categorise as; severely impaired, mild-moderately impaired or normal. For the purpose of this analysis, we will consider a severely impaired neuro-developmental outcome as being one where:

i) The BSID psychomotor component is below 70 (physical impairment)
ii) The BSID score of <80 on the Cognitive AND language index
iii) The cognitive and language index has a combined score of <85
iv) Cerebral palsy on GMFCS
v) Where there was no BSID assessment, but where the ASQ is <2 SDS below the mean corrected for age

The primary analyses will focus on this as a dichotomous outcome (severe impairment: yes/no). Secondary analyses will further assess whether the prognoses also differentiate children with a BSID of between 70 and 85 (which we tentatively term "mild to moderate impairment") from those with unequivocally normal development (85 or above). We will also assess the actual range of scores within each prognostic category.

There are two primary (and sequential) considerations:

1) To quantify the value of prognoses based on MR and on USS
2) To assess whether the prognostic value of MR increases relative to that of USS

The first consideration is a pre-cursor to the second, since the comparison in 2) is irrelevant if neither MR nor USS contain some measure of useful prognostic information. We will quantify 1) by assessing the concordance between severe neurodevelopmental impairment (BSID score of <80 on the Cognitive AND language index or a combined score of <85 or a motor score of <70) and poor prognosis, based on i) MR and ii) USS. The sensitivity, specificity, positive and negative predictive values of MR and of USS will be reported.

The second consideration is to compare the relative prognostic accuracy of USS and MR. We will do so by calculating the difference in the respective sensitivities and specificities using the paired sample methods recommended by Newcombe [18].

	Outcome	
	Severe impairment (BSID<70) N=xxx	No severe impairment (BSID>=70) N=xxx
USS prognosis		
Poor	n (%)	n (%)
Normal/favourable	n (%)	n (%)
% correctly classified*	$P_{sens\ (USS)}$	$P_{spec\ (USS)}$
MR prognosis		
Poor	n (%)	n (%)
Normal/favourable	n (%)	n (%)
% correctly classified*	$P_{sens\ (MR)}$	$P_{spec\ (MR)}$
Difference (95% CI)	$P_{sens\ (MR)} - P_{sens\ (USS)}$	$P_{spec\ (MR)} - P_{spec\ (USS)}$
P-value (McNemar)		

* Here, we consider "Correct" to mean 1) Poor prognosis corresponds to severe impairment, and 2) Normal/favourable prognoses correspond to no severe impairment. The percentages correctly classified reflect 1) sensitivity and 2) specificity respectively.

The secondary outcomes are

3) To assess qualitatively the cases for which the USS prognosis and MR prognosis differed, in relation specifically to the original diagnoses
4) To look at the concordance in the subgroup of children for which the MR scan was performed within 24 weeks
5) To assess ability to predict non-severe impairment

The last of these will further subdivide children without severe impairment (BSID>=70) into "mild-moderate impairment" (BSID between 70 and 85) and "Normal" (BSID>85). The corresponding prognostic categories are "Intermediate" and "Normal or Favourable", and the concordance between the three prognostic categories and the three outcomes will be reported by two-way tabulations.

Sample size Project 2

Our sample size is constrained by the original MERIDIAN cohort, but our data collected to date provides some assurance that we will have adequate power to address the primary outcome defined by this project. As well as approaching all children known to have survived (expected number approximately 500), our analysis will include non-surviving infants (defined as having had poor outcomes; expected number approximately 50-100). Allowing for attrition in the surviving child group we approximate that there will be 400 cases, from data collected in the entire cohort, there are almost 200 instances where prognosis changed as a result of MR imaging, of whom 38 are now classified as the poorest prognosis. Scaling these prevalence's down, 400 cases will have a 90% power to detect a 20% increase in the sensitivity and a 10% increase in specificity using the tests outlined above at a two-sided significance level of 5%.

We will quantify the impact of selective participant retention by comparing prognoses and diagnoses of consenting participants with those who refused. Non-surviving fetuses or children will by definition have no BSID outcome data, but will be included in the primary analyses as having poor outcomes. Outcomes among fetuses for whom TOP was performed are controversial, but some diagnoses (for example TOP for anencephaly) are inevitably fatal. For these cases we will use our existing independent expert panels to adjudicate whether, and how, the data should be included.

Hypothesis

The clinical significance of fetal brain abnormalities are more accurately predicted by MR imaging when compared with USS. Specifically, we predict a 10% improvement in prognostic accuracy by using MR imaging.

Analysis of Project 3

Using the categories detailed in project 2 (severely impaired, mild-moderately impaired and normal) we will calculate the prevalence of severe and non-severe impairments from our data, together with exact binomial confidence intervals and compare this to the prognoses obtained from cases where USS identified isolated mild VM. Where prognosis changed as a result of MR imaging we will assess whether this was attributable to the MR identifying further diagnoses.

Sample size Project 3

With approximately 140 cases and assuming the prevalence of poor outcome is indeed less than 10%, we will be able to estimate the prevalence to within a standard error of 2.5%.

Hypothesis

Isolated, mild fetal ventriculomegaly confirmed by MR is not associated with an increased risk of 'poor' neuro-developmental outcome when compared to the general population.

We propose that the children previously reported to have poor neurodevelopmental outcomes included a proportion of misdiagnosed children. Specifically, we postulate poor outcome is not a result of isolated ventriculomegaly, but rather due to additional conditions

not diagnosed by ultrasound. In these cases MR imaging may have found another brain abnormality.

8. Study supervision

The MERIDIAN study group proposes to continue with the same format of TMG, TSC and DMEC members as already exists, with the addition of a new member with neonatal/paediatric clinical experience.

9. Data handling and record keeping

Participant confidentiality will be respected at all times. As part of the screening process there may be a requirement for patient identifiable data to be passed by the University of Sheffield to the HSCIC for linkage and notification of any deaths. If the option to use HSCIC for death notification is implemented it will be ensured that regulatory approvals are in place and information governance policies adhered to, to monitor this process.

The site research staff may need to collect updated participant names and contact details so that participants can be contacted to arrange an appointment for project 2. These will be immediately entered with the existing MERIDIAN ID number on to a restricted section of the database, which may be accessed by the site research staff who entered the data, delegated staff at collaborating sites, and the study managers for follow up and verification of data. Access will be controlled by usernames and encrypted passwords. Participant contact details may need to be given to delegated Bayley's assessors, permission from the participant to pass on this information will be gained during the consent process.

All other data will be anonymised and will only be identifiable by MERIDIAN ID number. Data will be entered on to a centralised database held within the CTRU in Sheffield by a delegated research study member at the referring fetal medicine centre or at the University of Sheffield. This section will also be controlled by usernames and encrypted passwords.

There may be a requirement for pseudonymised data obtained from the HSCIC to be entered on to the database by the central study team at the University of Sheffield. Access to this data will be restricted and only accessible to those who have completed Data Security Training and adhere to the Universities information governance policies.

To allow for successful data collection there may be a requirement for patient identifiable data to be faxed and/or emailed between the recruiting site and the appropriate centre for completing the medical case note review and developmental assessment (e.g. a local children's hospital where the child has had their follow up care). Pseudonymised data will be passed back to the recruiting centre with the results of the case note review and developmental assessment. In these instances the appropriate Trust management system will be followed for the secure transfer of participant information, ie fax and email.

All screening forms, consent forms, CRFs, and questionnaires will be kept in a locked filing cabinet in a secured area at each relevant participating site, and will be destroyed no sooner than 5 years after study completion. The consent forms and participant contact details will be kept in a separate place to the anonymised CRF's and questionnaires so that the data will not be identifiable.

There may be a requirement for the completed consent forms to be posted to the central study team at the University of Sheffield for monitoring purposes. Permission for consent forms to be posted will be obtained from participants as part of the consent process. These consent forms will be kept in a locked filing cabinet.

10. Data access and quality assurance

The study managers, data managers, PI's, fetal medicine/paediatric experts and delegated site staff will have access to the anonymised data on the database through the use of usernames and encrypted passwords. In addition to this, access to hard copies of the CRF and questionnaire data will be required by the paediatricians, research midwives/nurses, delegated Bayley's assessors and central management team for study monitoring and audit purposes.

The secure data management system will incorporate quality control procedures to validate the study data. Error reports will be generated where data clarification is required.

11. Publication

The MERIDIAN dissemination and publication policy will be adhered to for all publications.

Results of the trial will be disseminated in peer reviewed scientific journals and clinical and academic conferences. No report, either verbal or written may be made without the approval of both the core publications group.

Details of the trial will also be made available via a study website. Summaries of the research will be updated periodically to inform readers of the ongoing progress.

12. Finance

The study has been financed by the National Institute for Health Research's (NIHR) Health Technology Assessment (HTA) programme of the and details have been drawn up in a separate agreement.

13. Ethics approval

The study will be submitted to the South Yorkshire Research Ethics Committee (REC) for review through the IRAS central allocation system. The approval letter from the ethics committee and copy of approved patient information leaflet, consent forms, CRF's and questionnaires will be sent to the Clinical Trials Research Unit (CTRU) in Sheffield before initiation of the study and patient recruitment.

14. Indemnity/compensation/insurance

Sheffield Teaching Hospitals NHS Foundation Trust is the sponsor of this research study. The University of Sheffield has in place insurance against liabilities for which they may be legally liable and this cover includes any such liabilities arising out of this research study.

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Appendix 1 - Developmental assessments

A full assessment will require determination of developmental, sensory, psychomotor and behavioural functioning. We propose to use validated parent completed questionnaires (GMFCS and SDQ) [16-17] where it is not possible to arrange a face to face assessment in order to minimise loss to follow up. These can also be completed via telephone if paper copies are not returned. This is an important and pragmatic approach because it allows us to minimise loss to follow up, whilst robustly determining the true proportion of children with a severe impairment. A face to face assessment will take between 1 and 2 hours and will be completed by a suitably trained paediatrician, physiotherapist or other health professional, and will include:

- BSID III [15] – mental and psychomotor developmental index; time 30-60 minutes.
- Motor function – BSID III and GMFCS [16]; time 5 minutes
- Sensory impairment – parent reported use of hearing or visual aids: time <5 minutes
- Behaviour – SDQ [17] a brief behavioural screening questionnaire which consists of 25 questions

The primary outcomes will be based on BSID III [15], supplemented where necessary by the ASQ [14], and give the proportion of infants surviving without mild, moderate or severe disability at 3 years. This data will be supplemented by using validated questionnaires (GMFCS and SDQ) [16-17] comprising forced-choice items to assess sensory impairment and standardised measures to assess motor and cognitive function and to identify children with:

- Mild/moderate/severe vision or hearing impairment
- Any motor impairment (cerebral palsy with GMFCS level 2)/severe motor impairment (cerebral palsy with GMFCS level 3, 4 or 5)
- Moderate/severe cognitive impairment will also be assessed using ASQ [14] which is a well validated widely used tool appropriate for children at this age, and is easily completed by parents.

Definitions for motor and sensory impairments described above are as defined by British Association of Perinatal Medicine (BAPM 2008).