MERIDIAN – 2-3 year follow up study

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

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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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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.

Protocol amendments since Version 4.0

General information (page 4)

Chief investigator contact telephone number and fax number updated.

Section 4. Selection and Withdrawal of participants (page 11)

Age range for developmental assessment changed from 38 to 42 months.

Section 5. Enrolment (pages 12 & 13)

Process updated to allow consent form to be posted out with initial invitation letter.

Section 6. Assessments and Procedure (page 16)

Figure 2. Procedure for MERIDIAN 2-3 year follow up study updated to reflect new invitation/consent process.

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.

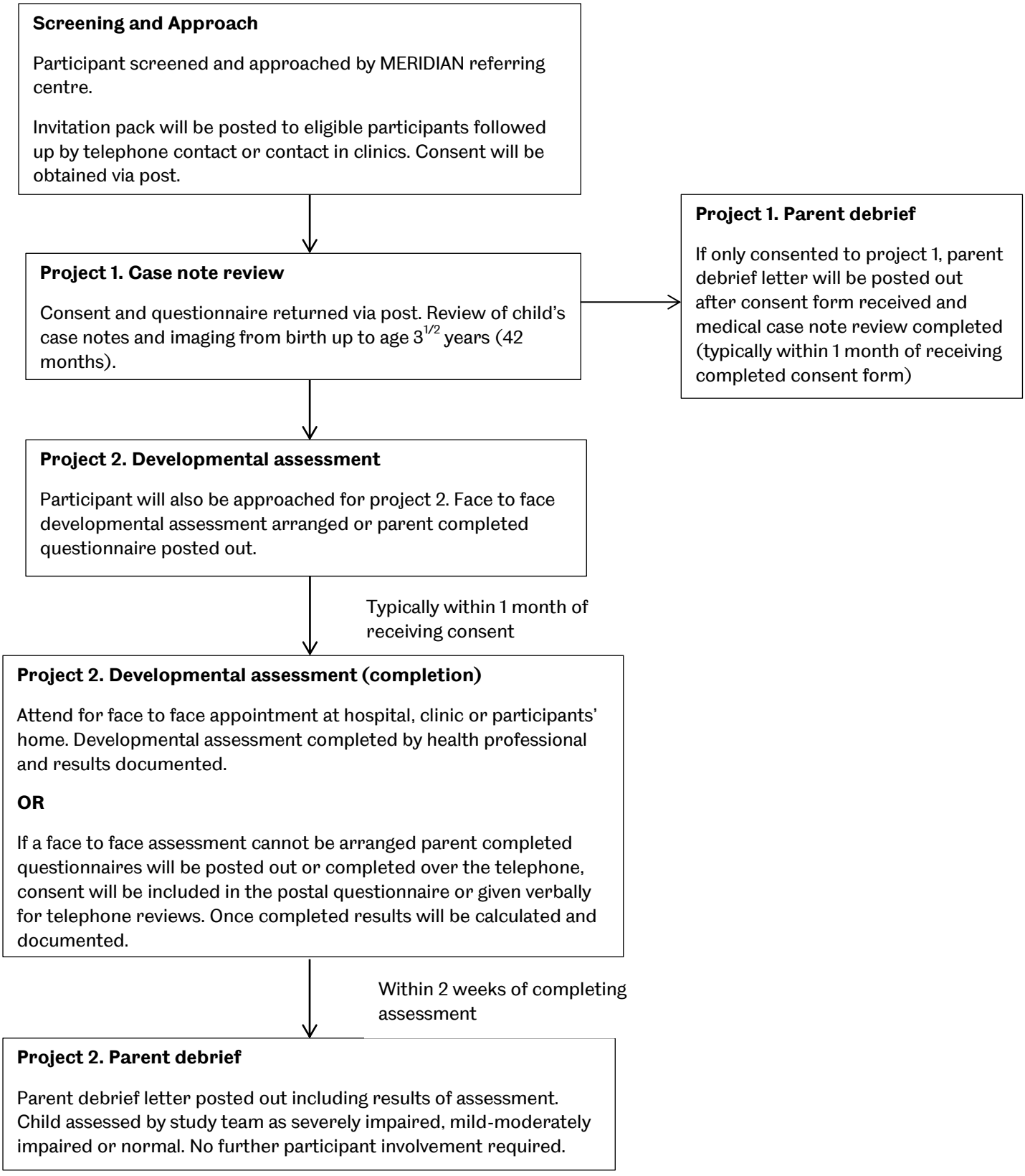
Project 1
A review of the child's medical case notes will be completed at each of the MERIDIAN sites and data extracted onto the paper case report form (CRF) template. New or refreshed diagnoses will be recorded from postnatal imaging and investigations. Where no further information is available or the 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



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 42 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, consent form, and a return envelope. Once the consent form is returned the research team will enter the participant in to the study, this will include completion of the medical case note review and make contact to arrange the developmental assessment (if consented to project 2). If the consent form is returned with the 'decline' section completed then the research team will record this on the Approach form. If the consent form 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 post or telephone contact from the research team. Written informed consent will be obtained for all participants. At this stage the Approach Form will be completed which will include the outcome of the postal invitation or telephone concontact, i.e. decline participation or agreement to participate. If participants agree to participate after telephone contact then the research team will ensure that they had received the invitation pack including consent forms, if they had not been received these will be re-sent for completion.
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
Details of project 2 will also be included in the invitation pack or discussed during the telephone or face to face contact to determine interest. If participants are eligible for projects 1 and 2 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 recorded in the study database.

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

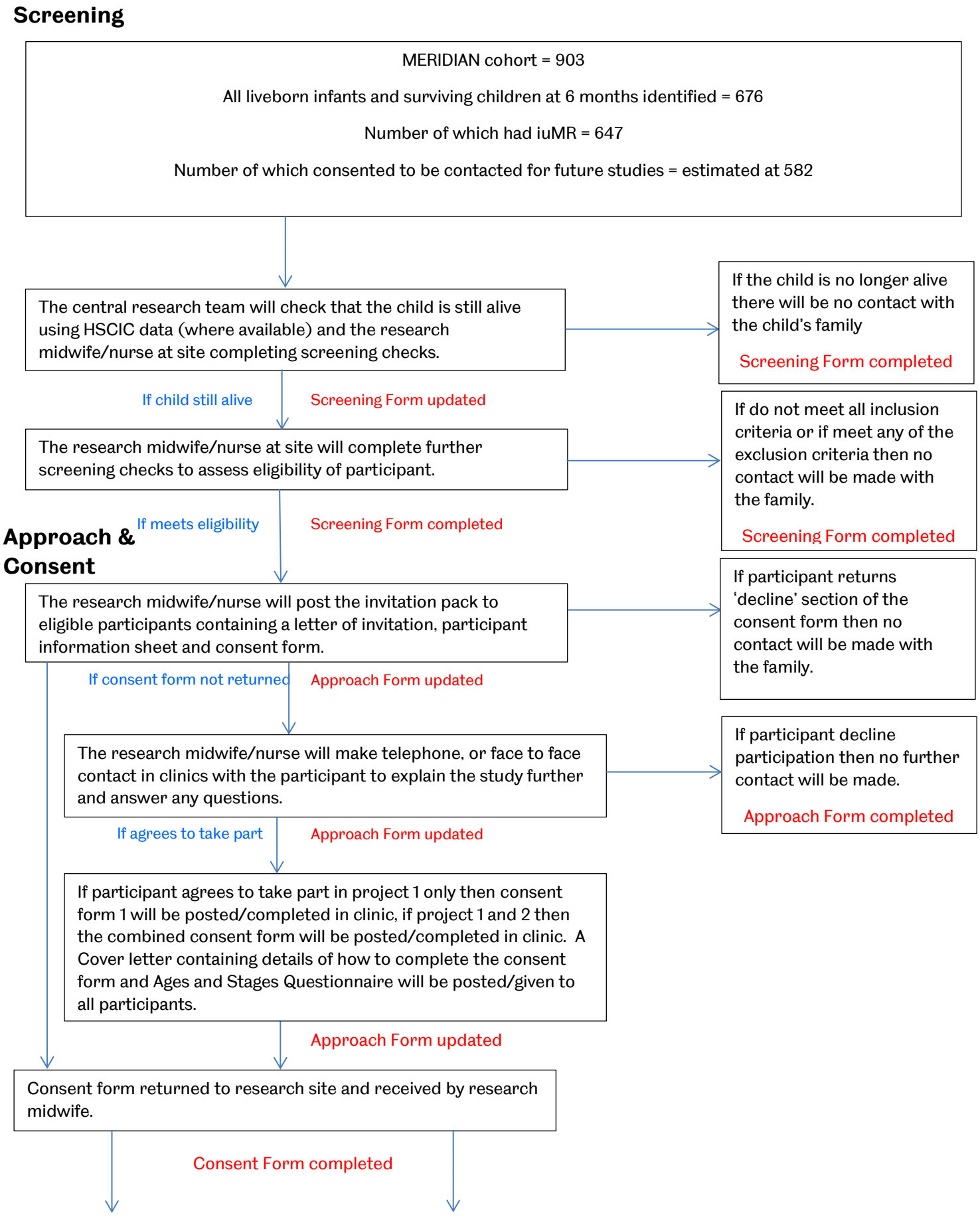
There is no input required from the MERIDIAN participants or research sites for completion of project 3. Project 3 will be completed by the central study team at the University of Sheffield.

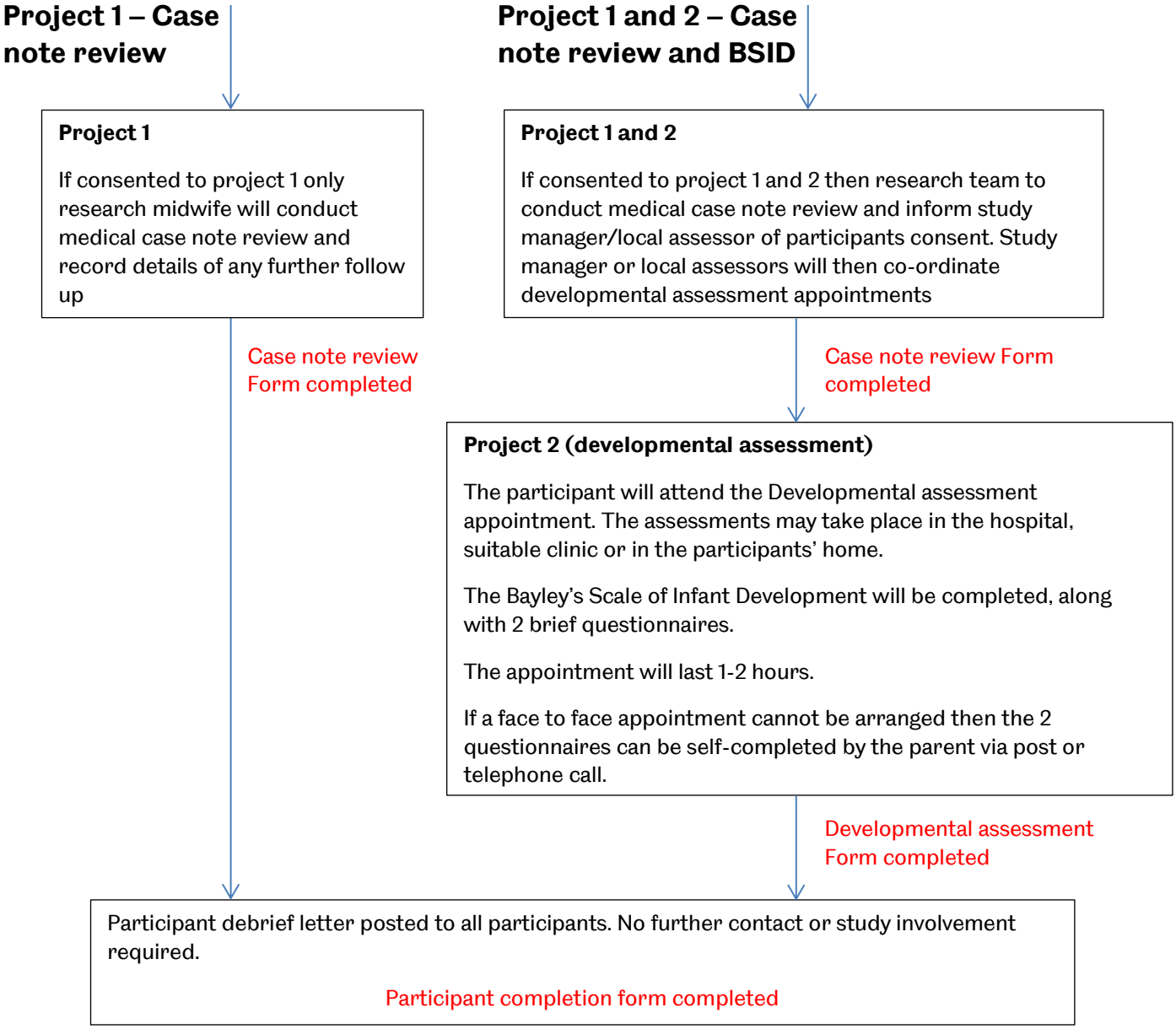
The information for project 3 will come from the assessments described in project 2. We will identify all cases of isolated mild ventriculomegaly diagnosed on iuMR and define their developmental outcome at 2-3 years as severely impaired, mild-moderately impaired or normal as per project 2. In MERIDIAN, 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 Normal/favourable % correctly classified*	 n (%) n (%) $P_{sens\ (USS)}$	 n (%) n (%) $P_{spec\ (USS)}$
MR prognosis Poor Normal/favourable % correctly classified*	 n (%) n (%) $P_{sens\ (MR)}$	 n (%) n (%) $P_{spec\ (MR)}$
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.

<u>Hypothesis</u>

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.

15. References

1) Magnetic resonance imaging to enhance the diagnosis of fetal developmental brain abnormalities in utero v7.1, 02/11/2015

2) Whitby E, Paley MN, Davies N, Sprigg A, Griffiths PD. Ultrafast MR assessment of CNS abnormalities in third trimester pregnancy: Methodology and early experience. Brit J Obs Gynae 2001;108:519-526

3) Hubbard AM, Adzick NS, Crombleholme TM, et al. Congenital chest lesions: diagnosis and characterization with prenatal MR imaging. Radiology 1999;212(1):43-8

4) Levine D, Barnes P, Korf B, Edelman R. Tuberous sclerosis in the fetus: second-trimester diagnosis of subependymal tubers with ultrafast MR imaging. AJR Am J Roentgenol 2000;175(4):1067-9

5) Levine D, Barnes PD. Cortical maturation in normal and abnormal fetuses as assessed with prenatal MR imaging. Radiology 1999;210(3):751-8

6) Levine D, Barnes PD, Madsen JR, Li W, Edelman RR. Fetal central nervous system anomalies: MR imaging augments sonographic diagnosis. Radiology 1997;204(3):635-42

7) Garel C. MRI of the fetal Brain. 1 ed: Springer; 2004

8) Girard N, Gire C, Sigaudy S, et al. MR imaging of acquired fetal brain disorders. Childs Nerv Syst 2003;19(7-8):490-500

9) Griffiths PD, Paley MNJ, Widjaja E, Taylor C, Whitby EH. The emergence of in utero MR imaging for fetal brain and spine abnormalities. British Medical Journal 2005;331(7516):562-565

10) Malinger G, Ben-Sira L, Lev D, Ben-Aroya Z, Kidron D, Lerman-Sagie T. Fetal brain imaging: a comparison between magnetic resonance imaging and dedicated neurosonography. Ultrasound Obstet Gynecol 2004;23(4):333-40

11) Malinger G, Lev D, Lerman-Sagie T. Fetal central nervous system: MR imaging versus dedicated US--need for prospective, blind, comparative studies. Radiology 2004;232(1):306; author reply -7

12) Whitby EH, Paley MNJ, Sprigg A, Rutter S, Davies NP, Wilkinson ID, Griffiths PD. Outcome of 100 singleton pregnancies with suspected brain abnormalities diagnosed on ultrasound and investigated by in utero MR imaging. Brit J Obs Gynae 2004;111:784-792

13) Griffiths PD, Reeves MJ, Morris JE, Mason G, Russell SA, Paley MNJ, Whitby EH. A prospective study of fetuses with isolated ventriculomegaly investigated by ante-natal ultrasound and in utero MR. American Journal of Neuroradiology 2010;31(1):106-11

14) Bayley N. Bayley scales of infant and toddler development, third edition. San Antonio, TX: Harcourt Assessment, Inc. 2006.

15) Squires J, Bricker D, Potter LW. Revision of a Parent-Completed Developmental Screen ing Tool: Ages and Stages Questionnaires. Journal of Pediatric Psychology 1997; 2(3):313-328.

16) Palisano R, Rosenbaum P, Bartlett D, Livingston M. Gross Motor Function Classification System – Expanded and Revised. CanChild Centre for Childhood Disability Research 2007.

17) Goodman R. The Strengths and Difficulties Questionnaire: A Research Note. Journal of Child Psychology and Psychiatry 1997;38(5):581-586

18) Newcombe RG. Improved confidence intervals for the difference between binomial proportions based on paired data. Statistics in Medicine 1998; 17(22): 2635-2650

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).