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| **HTA EXPRESSION OF INTEREST - RESEARCH DETAILS** |

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| **Programme** | *Defaults to the programme you are applying for* |
| **Funding Opportunity** | *Defaults to the stream of funding you are applying for* |
| **Call** | *Defaults to the call you are applying for* |

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| **RESEARCH DETAILS** |

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| **Host Organisation**  The host organisation must be selected from our current list – you will need to contact the funding team if your organisation is not listed. | | *This will be financially administerd by STH* |
| **Research Title**  Your full project title *(Limit 300 characters)* | Magnetic resonance imaging in fetuses at Increased Risk of BraIn LEsions  (Fetus-MIRABILE) | |
| **Research Type**  Primary/Secondary/Evidence Synthesis | | *Primary* |
| **Proposed start date, duration (in months) (***end date is calculated from start & duration for you)*  Start date must be in the future and on the first of the month. | | *April 1 2018*  *42 months* |
| **How did you hear about this call?**  Select from drop down list or ‘other’ with description  *(Limit 100 characters)* | |  |
| **Estimated research costs requested (not including NHS support & treatment costs)**  Requested research funding | | *Please add as appropriate*  *Cara’s full salary for 3.5 years*  *Debbies 0.5 salary for 3.5 years*  *Leannes 0.5 salary 3.5 years* |
| **Estimated NHS support & treatment costs / (savings)**  Proposed treatment costs (could be savings) | | *MR costs 850x£130 =*  *Also need to consider time for reading/reporting and if these would be research or treatment.*  *Same for consensus panels.* |

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| **CONTACT INFORMATION** |

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| **Details of Chief Investigator** | *Defaults to the information held in your profile* |
| **Organisation** | *Defaults to the information held in your profile* |

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| **CO-APPLICANTS** |

| **Will you be using co-applicants in your proposal?**  All co-applicants cited in this section **must have agreed** to be part of this proposal | *Yes* |
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| **Name** | **Post Held**  *100 characters* | **Role in this project**  *100 characters* | **Department** | **Organisation** |
| *Dilly Anumba* | *Chair of Obstetrics and Gynaecology* | *Clinical expertise* | *Reproductive and Developmental Medicine* | *University of Sheffield* |
| *Mike Bradburn* | *Senior Medical Statistican* | *Statistician* | *ScHARR* | *University of Sheffield* |
| *Judith Cohen* | *Assistant Director of CTRU* | *Clinical Trials expertise* | *ScHARR* | *University of Sheffield* |
| *Kelly Cohen* | *tbc* |  |  |  |
| *Cindy Cooper* | *Director of CTRU* | *Clinical Trials expertise* | *ScHARR* | *University of Sheffield* |
| *Jane Fisher* | *Director* | *PPI* | *NA* | *Antenatal Results & Choices (ARC)* |
| *Deborah Jarvis* | *Research MR radiographer* | *Radiographic and image processing expertise* | *Academic Radiology* | *University of Sheffield* |
| *Mark Kilby* | *Dame Hilda Lloyd Professor of Fetal Medicine* | *Clinical expertise* | *Institute of Metabolism and systems research* | *University of Birmingham* |
| *Christoph Lees* | *Reader in Obstetrics* | *Clinical expertise* | *Department of Surgery & Cancer* | *Imperial College London* |
| *Cara Mooney* | *Clinical trials manager* | *Clinical Trials expertise* | *ScHARR* | *University of Sheffield* |
| *Stephen Robson* | *Professor of Fetal Medicine* | *Clinical expertise* | *Institute of Cellular Medicine* | *Newcastle University* |
| *Gill Yaz* | *Health dev manager* | *PPI* | *NA* | *Spina bifida, Hydrocephalus Information Networking Equality (SHINE)* |

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| Please declare any conflicts or potential conflicts of interest that you or your co-applicants may have in undertaking this research, including any relevant, non-personal and commercial interest that could be perceived as a conflict of interest. |
| *None* |

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| **PATIENT AND PUBLIC INVOLVEMENT (PPI)** |

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| **Were patients and the public actively involved in identifying the research topic or prioritising the research questions?** | *Yes* |
| **Were patients and the public actively involved in preparing this application?** | *Yes* |
| **Describe how patient and public involvement has informed and/or influenced the development of the application** | |
| The need for this research was identified and discussed with the PPI members who currently sit on the MERIDIAN TSC (Director of Antenetal Results and Choices and Health Development Manager for Spina bifida, Hydrocephalus Information Networking Equality) who agreed that this topic was highly important and wished to support the application.  The PPI members listed above have reviewed and approved the application. If successful they will continue to act as PPI representatives on the TSC, review study processes and help to design patient facing materials.  We have already assessed acceptability of the study design and processes through the qualititive substudy of MERIDIAN, with over 95% stating that it was acceptable. There were also very positive responses to the quality of care received during the study. However to take this further we plan to/have identified 4 families who underwent iuMR due to a suspected brain abnormality in utero to ask for their involvement.  As the topic is extremely sensitive we will discuss with these families about further options for inclusion of PPI as, for example a focus group may not be appropriate in this situation, and one to one meetings may be preferred. | |

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| **HISTORY OF APPLICATION** |

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| **Relevant NETS Programmes previous application information (since 1st April 2012)**  Any previous applications that you have submitted to NETS programmes since 1 Apr 2012 will be listed in this section. You have the opportunity to identify if they are relevant (yes/no) to this current application and to **Edit** information as described in the two questions below. |
| *MERIDIAN - NIHR HTA (09/06/01). Synoptic finding published in The Lancet December 14 2016. Full report to be submitted December 2017* |
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| **Please indicate how your current research proposal differs from this previous application** |
| *This topic builds on the results of the MERIDIAN study by investigating women who have a normal ultrasound scan at 20 weeks but are at increased risk of having a baby with a brain abnormality from pre-defined risk factors. This study has not been submitted to a NETSCC programme before.* |
| **If unsuccessful, please indicate why** |
| *NA* |
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| **Other funders previous application information**  This topic has not been submitted elsewhere |

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| **SUMMARY OF THE RESEARCH PROPOSAL** |

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| **Rationale for Research**  *(Please refer to guidance notes for further information on this section.)*  **1. What is the problem being addressed?**  **2. Why is the research important in terms of improving the health of the public and/ or to patients and the NHS?**  *For commissioned calls where you are responding to an advertised topic, please describe how your proposal meets the specification of the brief.*  3. How does the existing literature support this proposal?  **4. What is the research question?** |
| ***1. What is the problem being addressed?***  The synoptic overview of the results of the NIHR-funded MERIDIAN study recently reported in The Lancet (1) confirm that the diagnosis of fetal brain abnormalities using antenatal ultrasonography (USS) is difficult and will provide the correct diagnosis in less than 70% of cases. The supplemental technology under study, in utero MR (iuMR) imaging, showed an improvement in diagnostic accuracy of 23%. We have also developed appropriate methods to study diagnostic confidence in such cases (2) and detailed quantatitive and qualitative assessments of pregnant women’s and healthcare professionals opinions of introducing iuMR imaging into the clinical environment (1,3). Ongoing analysis of the MERIDIAN data has looked at the three commonest anatomical subgroups of fetal brain abnormalities (ventriculomegaly, agenesis of the corpus callosum and posterior fossa abnormalities) and the emerging data shows that diagnostic errors on USS occur in both directions with high rates of false positive and false negative findings (4-6). By way of example, in cases of isolated agenesis/hypogenesis of the corpus callosum diagnosed on USS the corpus callosum was normal in 58% of cases but other brain abnormalities, not recognised on USS, were found in 14%. We concluded that iuMR should be offered to all women whose fetus has a brain abnormality suspected on USS.  An important limitation of MERIDIAN is that recruitment was restricted to cases where the USS reported a brain abnormality; we do not know how many fetal brain abnormalities are missed by USS. If iuMR is to demonstrate an improvement, it is most likely to do so in higher risk pregnancies. In this expression of interest we outline a programme of research to evaluate the role of iuMR imaging in pregnant women judged to have an increased risk of having a baby with a brain abnormality. This can come from a number of sources and we will study three groups of fetuses at increased risk:  Work stream 1. A fetus/child with a brain abnormality in an earlier pregnancy and a medical geneticist has judged that there is a risk of recurrence e.g. neural tube defects, lissencephaly and other cortical formation abnormalities.  Work stream 2. A fetus in which there is evidence of maternal Cytomegalovirus (CMV) infection during pregnancy.  Work stream 3. Microcephaly recognised on USS and otherwise not included in group 1) or 2).  Finish with a statement on why this trial is needed now?  *2. Why is the research important in terms of improving the health of the public and/ or to patients and the NHS?*  This research is important to NHS patients on several levels. Most of the brain pathology that will be included in this project has a very high risk of poor neurodevelopmental outcome, to a degree that, if detected on ante-natal imaging, termination of pregnancy would be on the basis of Ground E of the Abortion Act (section 1(1)(d) – substantial risk of serious mental or physical handicap).  True positive – will help patients make informed choice  False positive and false negative results of ante-natal imaging can both have serious effects e.g.   * False positive finding may lead to inappropriate termination of pregnancy leading to considerable psychological trauma to parents and potential litigation * False negative findings may lead to the delivery of an affected child whose parents would otherwise have considered termination of pregnancy. The potential cost to the NHS in terms of litigation is described in the case of Lillywhite & Anor v University College London Hospitals NHS Trust [2005] EWCA Civ 1466 (07 December 2005 and subsequent appeal).   We thinkit is highly likely that fetal maternal centres will offer iuMR imaging to women in high risk groups without a good evidence-base that it is clinically appropriate. The results of this study are highly likely to give a definitive answer to this issue. These situations are also quite common – developmental brain abnormalities occur in approximately 2/1000 pregnacies and many have increased risks of reccurence, primary CMV infection occurs in 1-3% of pregnancies and approximately 50% transmit to the fetus, whilst the proportion of fetuses with microcephaly depends on the definition used as described below.  *3. How does the existing literature support this proposal?*  The original MERIDIAN study provided compelling evidence that iuMR leads to an increased diagnostic accuracy among fetuses in which a brain abnormality has been shown on USS (1). In addition, there are four systematic reviews/meta-analyses that show similar, positive effects of iuMR (7-10). We believe that similar benefits will be found in pregnancies at a high risk of fetal neuropathology when the USS findings are abnormal. Nevertheless, there is currently little published data to judge the use of iuMR imaging in high risk cases when the USS examination is normal as described below.  Work stream 1. Increased risk on the basis of a sibling with a brain abnormality  The applicants group has published what we believe is the only paper on this subject in a retrospective study of 100 fetuses at high risk due to a CNS malformation in an earlier pregnancy (11). The study suffered from several methodological flaws including not being adequetly powered and poor outcome reference data collection but the results of that study provide the only information available to inform the power calculation given below.    Work stream 2. Increased risk on the basis of CMV infection  The literature is sparse. Mallinger and colleagues in 2003 reported 27 fetuses with CMV and only found one case which provided additional information (12) in contrast to a more recent study, Doneda et al in 2010 (13), of 38 fetuses with CMV infection showed that iuMR gave extra information in 18 (47%). Benefits of iuMR have also been described by Picone et al. in at least 6/28 (21%) in 2008 (14). None of these studies were formally powered and we have taken a conservative estimate of 10% improvement to inform our power calculations  Work stream 3. Increased risk on the basis of a microcephaly  A routine part of the prenatal assessment of the fetus during the second trimester anomaly USS is to monitor fetal growth, which includes measurement of the skull dimensions usually by way of head circumference. This allows comparison with reference data from a large number of normal pregnancies in order to identify those fetuses with an abnormally small head size (microcephaly). Identifying these fetuses is important as microcephaly is often associated with other brain abnormalities which may indicate a poor prognosis. The severity of microcephaly has also been shown to correlate with the risk of poor outcome (15,16). Although there is still an increased risk of poor neurodevelopmental outcome when no other structural brain abnormality is present (isolated microcephaly) the risk is reduced, particularly when microcephaly is defined as <2SD below the normative mean (17). Isolated microcephaly can occur due to genetic and chromosomal anomalies, as a consequence of antenatal exposures to infections drugs or chemicals but in many cases the cause is not known (18).  Several studies have demonstrated that iuMR imaging is a valuable adjunct to USS in terms of improvement in diagnostic capability and diagnostic certainty when a structural brain abnormality is suspected in the developing fetus most recently the MERIDIAN study (1). There is a paucity of iuMR studies whose focus is solely to evaluate fetuses with microcephaly, and consequently the potential role of iuMR imaging in this group of patients has not been fully investigated – it is important to note that cases of isolated microcephaly were not eligible for recruitment into MERIDIAN. The MR studies that have been done have focused on comparing the agreement of biometric measurementsbetween USS and iuMR or reporting iuMR biometric referencevalues (19,20).  Whilst skull size is used to diagnose microcephaly it is only a surrogate indicator of brain size as described above the correlation is not perfect (21). Postnatal MR studies have shown that there is a reduction in brain volume in microcephalic infants (22,23), therefore there is the possibility that brain size or more precisely brain volume may be a more accurate indicator of microcephaly and neurodevelopment outcome in fetuses where small head size is a concern.  Any ongoing studies we are aware of?  *4. What is the research question?*  Should iuMR imaging be performed in pregnancies at increased risk of a fetal brain abnormality if the ultrasound examination is normal or shows non-specific features?  Study design: multi-centre, prospective cohort recruiting 850 fetuses from x centres.  Work stream 1. High risk on the basis of a sibling with a brain abnormality  We will enrol a cohort of 200 fetuses that are considered to be “high risk” for having a brain abnormality on genetic grounds, but in whom USS has not detected a structural brain abnormality. Participants will undergo iuMR to assess fetal brain abnormalities. Fetuses will undergo a post-natal imaging assessment (autopsy for non-surviving infants) to determine the ORD, and the percentage of correct diagnoses made by USS and by iuMR will be calculated in relation to these. The difference in percentages will be presented along with its 95% confidence interval and p-value, calculated by the Wilson score interval and McNemar’s paired sample test respectively.  The sample size is justified as follows: the original MERIDIAN study was powered to detect a 10% net increase in the percentage of correct fetal diagnoses (20% where iuMR corrected an inaccurate USS diagnosis and 10% where iuMR differed erroneously from USS). The latter occurred only rarely, with 2/570 (0.4%) instances of iuMR erroneously changing the finding on USS. Assuming iuMR incorrectly finds an abnormality on a negative USS finding in 1% of cases, and that iuMR correctly changes a negative diagnosis in 10% of cases (i.e. a 9% net improvement), we require a total of 139 fetal scans. Assuming ORD is not available in a third of cases (as seen in the primary MERIDIAN analysis), the sample size is inflated to 200. The choice of 10% in keeping with the original MERIDIAN study since this will lead to changes in prognosis and clinical mangagement in at least 5% of cases.  Work stream 2. Increased risk on the basis of CMV infection  We will enrol a cohort of 200 fetuses with confirmed CMV infection but with no fetal brain abnormality detected on USS. The methods and sample justification are identical to workstream 1.  Work stream 3. Increased risk on the basis of a microcephaly  The nature of the research question for workstream 3 differs from 1 and 2. We will assess whether iuMR improves the diagnostic accuracy among fetuses with microcephaly (at least 2SD below normative mean) as the sole USS diagnosis, or with non-specific findings such as VM or enlarged extra-axial CSF spaces., but we hypothesise that the risk of additional diagnoses will depend on the degree of microcephaly. In workstream 3 we will assess the relationship between head size and additional diagnoses, and in so doing the cut-off at which iuMR is likely to lead to an appreciable increase in diagnostic accuracy.  For the purposes of this workstream, cases of microcephaly will be divided into three risk groups (<2 to 2.5SD, <2.5 to 3SD and <3SD below normative mean). We will aim to recruit approximately 450 fetuses in total with at least 90 in the <3SD group. Assuming that the risk in the three subgroups is 1%, 5% and 10% respectively we will have 90% power to detect this association at the two-sided 5% level of significance and will estimate the risk of additional diagnosis to a standard error of <=4% within in each subgroup. |
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| **Scientific Abstract** |
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| The overall results of the MERIDIAN were reported recently in ‘The Lancet’ (1) and show clear benefits in performing in utero MR (iuMR) imaging in cases of brain abnormality suspected on ultrasonography (USS). Specifically, we have shown:   1. An improvement in diagnostic accuracy of 23% in 18-23 week fetuses 2. Statistically significant improvements in all indicators of diagnostic confidence 3. Changes in prognosis in at least 20% of cases 4. iuMR imaging has a high acceptability to pregnant women – 95% said they would have an iuMR study in a future pregnancy if there was a suggestion of a brain abnormality.   We plan to build on the experience of the MERIDIAN study in this proposal by studying fetuses *in utero* who are at an increased risk of a brain abnormality. Our work is directed at the key clinical question ‘should we offer iuMR imaging to women whose fetuses are at an increased risk of having a brain abnormality’. Increased risk for such cases can come from many sources but we will study pregnancies at:  Work stream 1. Increased risk on the basis of a sibling with a brain abnormality  Work stream 2. Increased risk on the basis of maternal CMV infection during pregnancy  Work stream 3. Increased risk on the basis of a microcephaly  All of these conditions are relatively rare and we require a large population in order to perform such a study. The MERIDIAN study was collaboration between 16 regional fetal maternal units in the UK and most of those centres have agreed to recruit into the proposed study and two other large centres have agreed to join. We believe we have the capacity to recruit from 50% of the UK’s population. We will use the experience gained from MERIDIAN (most of the assessment methods will be used unchanged) but we will use more advanced MR methods that we have over the last 8 years, most importantly, 3D-volume imaging and brain volume measurements (24-26).  We predict at the end of the study we will be in a position to judge if iuMR imaging should be offered to pregnant women in the three workstreams described above as part of routine clinical care in the NHS. |

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| **Summary (in plain English)** |
| This proposal describes a programme of work to improve the detection of brain abnormalities in the unborn baby by using MR imaging during pregnancy. The study team previously conducted a study showing clear benefits in performing MR imaging on unborn babies who have a brain abnormality recognised on ultrasound. This led to the correct diagnosis being made in 23% more pregnancies when compared to using ultrasound alone(the current best method of showing brain abnormalities in the unborn baby). Feto-maternal consultants and pregnant women stated this information was important to their counselling and clinical management in a high percentage of cases.  We believe, however, that more women may benefit from this new application of MR imaging, specifically women whose baby is at a high risk of a brain abnormality but whose ultrasound examinations during pregnancy are normal. The fundamental difference between this study and the MERIDIAN study is that the women have to have a NORMAL ultrasound examination to come into the study, whereas the brain of the fetus had to be ABNORMAL on ultrasound to be recruited into MERIDIAN. So, in this proposal we wish to build on the experience gained from the MERIDIAN study and study women whose unborn baby is at an increased risk of a brain abnormality because;   1. A previous baby had a brain abnormality that may also affect the current pregnancy, perhaps from a genetic cause. 2. The pregnant woman develops a CMV (a virus) infection during pregnancy that may be passed on to the unborn baby and cause damage to its brain 3. The unborn baby has a small head size (microcephaly)   Fortunately, all of these situations are quite rare and we will need to recruit from a very large population in order to get sufficient suitable cases, however, the MERIDIAN study showed that this is possible and was a very successful collaboration between 16 regional fetal maternal units providing maternity services to over 28 million women/patients (over 40% of the UK’s population). Most of those centres have agreed to recruit into the proposed study and three other large centres have agreed to join the collaboration and we believe that we will recruit from over half of the UK’s population.  Most of the assessment methods used in MERIDIAN are now tried and tested but we have also developed some new MR methods over the last 8 years, which will allow us to look at the brain of the unborn baby in much greater detail. As a result, we predict that the results of the study willsay if it is valuable to offer MR imaging to pregnant women in the three categories listed above as standard practice in the NHS. |

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| **CLINICAL TRIALS UNIT PARTICIPATION** |

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| **Is a Clinical Trials Unit involved with this research proposal?** | | | Yes | | |
| **Clinical Trials Unit (CTU)** | [**Does the CTU hold a UKCRC registration?**](https://netscc-mis.nihr.ac.uk/mis/Implementation/Modules/Application/ModuleContent.aspx?Config=SubmitOutlineApplication100027Config&Page=CLIENTGWiderContext&ctlPageContent_DPSort_CLIENTGranteeProjectCTUInvolvement=ctlDataList/HoldUKCRCYesNo.Abbr/Ascending&mPageFrameCtl_ctlPageContent_ctlDataList=#mPageFrameCtl_ctlPageContent_ctlDataList) | [**UKCRC Reg. No.**](https://netscc-mis.nihr.ac.uk/mis/Implementation/Modules/Application/ModuleContent.aspx?Config=SubmitOutlineApplication100027Config&Page=CLIENTGWiderContext&ctlPageContent_DPSort_CLIENTGranteeProjectCTUInvolvement=ctlDataList/UKCRCRegistrationNumber/Ascending&mPageFrameCtl_ctlPageContent_ctlDataList=#mPageFrameCtl_ctlPageContent_ctlDataList) | | [**Is the CTU receiving CTU support funding from NIHR?**](https://netscc-mis.nihr.ac.uk/mis/Implementation/Modules/Application/ModuleContent.aspx?Config=SubmitOutlineApplication100027Config&Page=CLIENTGWiderContext&ctlPageContent_DPSort_CLIENTGranteeProjectCTUInvolvement=ctlDataList/ReceivingSupportFundingYesNo.Abbr/Ascending&mPageFrameCtl_ctlPageContent_ctlDataList=#mPageFrameCtl_ctlPageContent_ctlDataList) | |
| Sheffield Clinical Trials Research Unit (CTRU) | Yes | 34 | | Yes | |
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| **If applicable,please describe how you have worked with a Clinical Trials Unit in developing your application and what support they will provide if funding is approved.** | | | | | |
| Sheffield CTRU. have been fully involved with the application inputting to the study design and management, sample size,data analysis and management and coss. CTRU will provide study management, data management and statistical analysis, supported by the senior trials team (all co-applicants. | | | | | |
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| **UPLOADS** | | | | |
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| **Upload name (maximum file size of 2Mb)** | | | | |
| **Flowchart** | | | | |
| **References** | | | | |
| **Cover letter** | | | | |
| **Research CV of Chief Investigator (1 side of A4 only)** | | | | |