Great Ormond Street Hospital for Children NHS Foundation Trust

HTA 14/168/02 - Minimally invasive autopsy for fetuses and children based on a combination of post-mortem MRI and endoscopic autopsy examination; Feasibility study

STAGE 1

Protocol for prospective work undertaken in HTA project 14/168/02

Version 1: 4.1.16

Study title: Personalising examination after death to improve experience for bereaved parents

Principal Researcher: Professor Neil Sebire

STAGE 2

Protocol for retrospective work undertaken in HTA project 14/168/02

Version 1.1: 31 May 2016

Study title: Minimally invasive autopsy for fetuses and children based on a combination of post-mortem MRI and endoscopic autopsy examination: feasibility study (retrospective data analysis)

Principal Researcher: Professor Neil Sebire

NIHR Portfolio registration: 20747

Project protocol
Version 1.1: 31.5.16
Study title: Minimally invasive autopsy for fetuses and children based on a combination of post-mortem MRI and endoscopic autopsy examination: feasibility study
Principal Researcher: Professor Neil Sebire

Aim: To assess patient and public acceptability of minimally invasive autopsy

Principle objectives:

- Assess whether minimally invasive autopsy is preferable to standard methods
- Assess the proportion of patients who would consent to minimally invasive autopsy who currently decline standard autopsy

Secondary objectives:

- Explore whether minimally invasive autopsy is more acceptable to those religious and ethnic groups who are currently likely to decline standard autopsy

Background

Around 1/80 ongoing pregnancies in the United Kingdom (UK) results in either stillbirth, termination following diagnosis of a fetal abnormality or infant death, representing at least 8,000 cases per annum, and there are >500 unexplained infant and childhood deaths annually. Following perinatal, infant or childhood death, post-mortem examination (autopsy) may be required to determine cause of death, to provide recurrence risk, implications for family members, improved counselling and informing early prenatal diagnostic testing in future pregnancies.[1] Without an autopsy, many parents are left without understanding of the disease process related to their child's death. Unfortunately despite these potential benefits, the majority of parents do not find standard traditional autopsy an acceptable approach. In addition, there are a number of ethnic and religious groups for whom invasive autopsy would not be considered.[2,3] The development of an acceptable approach to examination after death would represent a major improvement in patient experience of care, a health priority in the NHS.[4]

Traditional autopsy procedures have hardly changed over centuries, but there is now an opportunity to change the methods used for investigation after death based on new approaches which are more acceptable to patients and the public. Standard autopsy involves a large incision so that organs can be inspected and examined. Currently most parents (around 50% after stillbirth and around 80% after neonatal death) do not consent to traditional autopsy[5,6], largely due to dislike of the invasive process.[7] This is despite evidence that in around 30% of cases, clinically significant additional information is identified at autopsy.[8] The feasibility and effectiveness of non-invasive autopsy (NIA) based on post-mortem MRI examination has been demonstrated but when used alone it is inadequate in

some patient groups in whom tissue sampling is essential for diagnosis.[9] The minimally invasive autopsy (MIA; 'keyhole autopsy') based on post-mortem MRI and endoscopic assisted sampling has been developed, and may be more acceptable to parents than traditional autopsy but currently very little is known about accuracy and acceptability.[10,11] The MIA and NIA approaches have the potential to address sensitivities around organ retention, as well as accommodate the need to respect religious and cultural diversity.[10] Many religious and ethnic groups are not currently served by the NHS in this area, since for them standard autopsy is unacceptable and there is no alternative offered. The emphasis on developing more acceptable alternatives could allow more parents to benefit from gaining information regarding these deaths. MIA/NIA could also have secondary benefits for researchers, policy planners and society, by providing improved information regarding causes of fetal, infant and child deaths as a result of increased uptake.

There are currently no data regarding acceptability of MIA/NIA, but a recent study indicated that almost all parents agree to post-mortem imaging (MRI), even those who refuse autopsy, and among health care professionals MIA was regarded as highly acceptable and it's availability considered beneficial for discussing autopsy with parents.[10,12] If MIA/NIA represents an acceptable alternative to standard autopsy, this will radically change the future approach to investigating such deaths. Our research will therefore address a number of pertinent questions including: 1) whether MIA and/or NIA is more acceptable to parents than standard autopsy methods, 2) how alternate methods of investigating death should fit into existing care pathways, 3) which patient populations these methods are most appropriate for, and 4) how best to offer such a service to groups for whom standard autopsy is never acceptable, including specific ethnic and religious populations.

Methods

Study design

This is a mixed methods study comprising a questionnaire, interviews and focus groups with patients, health professionals and the public. The aim of the questionnaire is to assess motivations for accepting or declining autopsy and measure acceptability of MIA/NIA. The aim of the interviews is to understand and explore in-depth the reasons why patients might accept or decline MIA/NIA and how best to offer such services in clinical practice. The aim of the focus groups is to explore more broadly the acceptability of MIA/NIA among health professionals, patient advocates and minority ethnic and religious groups.

The study design has been developed with an advisory team which includes a Professor of Paediatric Pathology, a Professor of Genetics and Fetal Medicine, a social scientist, a genetic counsellor and patient group representatives from the groups Antenatal Results and Choices (ARC), SANDS– the Stillbirth and Neonatal Death Charity, and the Lullaby Trust who support families suffering from grief and bereavement, in addition to working with the parents PPI group which is part of our NIHR GOSH Biomedical Research Centre. These groups have also been involved in developing the questionnaire and interview/focus group questions to ensure they are appropriate and address relevant issues.

Setting

Parents and health professional recruitment into this study will be from University College London Hospitals Partners (University College London Hospital, Homerton Hospital, Barts Health, West Hertfordshire Hospital, The Royal Free, Chase Farm, Barnet General, Great Ormond Street Hospital) and Leicester (Leicester Royal Infirmary). This will allow recruitment from two geographically and demographically distinct areas in England, including two hospitals with specialist paediatric pathology services and an established post-mortem imaging infrastructure. Recruitment from across these sites will ensure participants with a range of ethnic and religious backgrounds (London - White, Jewish, black African, Eastern European, and Pakistani; and the Midlands - White, Indian Asian and Bangladeshi). We will also recruit members of the public, who may also have experience of being asked to consent to post-mortem examination, through the patient support groups Antenatal Results and Choices (ARC), SANDS and the Lullaby Trust as well as through religious and community centres.

Participants

Questionnaire

For the questionnaire we will recruit patients who have experience of being asked to consent to autopsy following a perinatal, infant or childhood death (<16 years) through NHS services. In addition, parents will be recruited retrospectively via the appropriate parent support groups and websites.

Interviews

A subset of questionnaire responders will be invited to take part in an interview. We will also invite 'key informants' who have specialised knowledge and understanding of ethnic and religious attitudes towards autopsy to take part in interviews. Understanding the views and acceptability of MIA amongst minority ethnic and religious groups is one of the aims of this research. Interview participants will be purposively sampled to cover a range of ethnic and religious groups, ages, experiences (fetal, infant, child death) and views towards standard autopsy and MIA/NIA.

Focus groups

Focus groups will be conducted to collate opinions of MIA/NIA with a range of stakeholders. We will specifically invite advocacy and support groups, ethnic and religious groups, patient advocates, professionals involved in post-mortem services, and commissioners, managers, coroners and members of the public.

Inclusion criteria

- Parents who have been approached about consenting to autopsy following perinatal, infant or childhood death (<16 years).
- Participants (who may at some point have been approached about consenting to autopsy) recruited through the membership of the support groups Antenatal Results and Choices, SANDS and the Lullaby Trust.
- Members of the public from minority ethnic (such as Pakistani, Bangladeshi, Indian Asian) and religious groups (e.g. Muslim, Jewish).
- Members of the public from the White British population (for comparative purposes).
- Other key stakeholders including health professionals involved in post-mortem services, patient advocates, commissioners, managers and coroners.

Exclusion criteria

- Parents who would be significantly negatively impacted from being invited to take part in this study.

Data collection

Questionnaire

A key aim of this study is to assess the opinion of parents who have experienced perinatal, infant or childhood (<16 years) death about the acceptability of MIA/NIA and whether it is considered preferable to standard autopsy. In order to capture parents' motivations and expectations around post-mortem as well as their views towards MIA/NIA, we will recruit this group prospectively, following a bereavement, at the time they are discussing the option of post-mortem with the health professional. Following that discussion (irrespective of whether they accept or decline post-mortem) they will be given a brief introduction about this study (via the same health professional who is discussing the option of post-mortem with them). If they are interested or would like to find out more about this study, the health professional will give them an envelope containing a participant information sheet (PIS) (Participant information sheet v1 – parents) and a paper copy of the questionnaire (Questionnaire v1). The participant can then take the envelope home with them, read the PIS and if they wish to participate, complete the questionnaire and return it in the enclosed freepost envelope at a time of their choosing. Alternatively, parents can choose to complete the questionnaire at the hospital and hand it back to the health professional (we acknowledge that some parents may wish to take part but fill it out quickly and not think about it again). There will also be a link to an online version of the questionnaire if they prefer. We wish to engage as many ethnic groups as possible but recognise that due to the sensitive nature of the subject matter, appropriately translated information is essential. Therefore, we aim to translate the PIS and questionnaire into the five most commonly spoken languages in the United Kingdom (latest Census data; English plus Polish, Punjabi, Urdu, Bengali, Gujarati), which includes >95% of the UK population's main language. These will be made available online as well as in paper form. (We are aware of the issues regarding difficulties with translation, dialects and requirements for participants to be able to read, therefore the main method by which we will capture the views of non-english speaking participants is via specific focus groups).

The questionnaire will be anonymous <u>unless</u> the responder wishes to take part in an interview, in which case they will be asked to leave their name and contact details (see below). However, each questionnaire will have a code on it so that the researcher knows which hospital the participant was recruited from. This is important to enable us to see whether there are different opinions depending on where the consent discussion took place. The questionnaire has been developed by a multidisciplinary team of clinicians and academics and has been reviewed by the advisory group as well as the GOSH PPI group. The questionnaire will be piloted with the first 20 participants who complete it to ensure it is clear and understandable. It will be made clear to all potential participants that they are under no obligation to take part in this study and that they can take part in the study irrespective of whether they agreed to or declined autopsy. In order to mitigate against the risk of causing further distress to parents at this difficult time, the health professional discussing the option of autopsy will only approach those parents they do not perceive will be caused additional

distress by taking part in this study. To determine if the group agreeing to participant is in any obvious way different to those that decline participation we will collect anonymous demographic data (including age, ethnicity and reason for accepting or declining autopsy) for everyone offered autopsy during the study period.

A link to the online version of the questionnaire will be posted on the websites of the support groups ARC, SANDS and the Lullaby Trust who are members of the advisory committee. This is so that members of these support groups (many of whom are likely to have been in the position of being asked about autopsy) and the public, also have an opportunity to put forward their views towards MIA/NIA.

Sample size

Because this is a feasibility study and we have no prior data regarding the likely acceptability of MIA/NIA, we are unable to calculate a sample size required for this questionnaire study. However, we are aiming to recruit 400 questionnaires in order that we have sufficient data to be able to compare across variables. We collected a similar number of questionnaire in a recent study exploring a new genetic technology and were able to compare across groups.[13]

Interviews

At the end of the questionnaire, responders will be asked whether they would be willing to take part in an interview to discuss their views towards MIA/NIA in more depth (Interview questions – parents v1). Those that are interested will be asked to leave their name and contact details so that a researcher can contact them. If the respondent does not wish to take part in an interview then the questionnaire will remain anonymous. Interviews will be arranged at a time and location convenient to the participant, such as the participant's home or in an office at GOSH. Alternatively, if the participant prefers, the interview can be conducted over the telephone. Prior to the interview beginning the participant will be asked if they have any questions, and asked to read and sign the consent form which includes permission to audio record the discussion (Consent form v1). It will be explained that the discussion will be transcribed but that no identifying features will be included on the transcript. Participants will be able to opt out of having the interview recorded if they prefer. To maintain confidentiality, participants will be assigned a pseudonym.

Interview participants will be purposively sampled to ensure a mix in terms of participants that did/did not consent to autopsy; participants that would/would not consent to MIA and/or NIA; reason for autopsy; age; religion; ethnic background and referral hospital. Interviews will explore in-depth their experience about being approached about autopsy; their views on standard methods of autopsy; their views on MIA/NIA; whether these options would be acceptable to them and how health professionals should discuss issues related to investigations after death.

We will also conduct a series of interviews with key informants, religious and/or cultural leaders who have first-hand knowledge of the community and can offer insight into the topic from a religious and cultural perspective (Interview questions – key informants v1). These participants will be recruited through snowball sampling. Potential participants will be emailed/sent a letter inviting them into the study (Participant Information Sheet – key stakeholders). Interviews will take place either at GOSH or a location of the interviewees

preference. Interviews will be audio recorded and transcribed but each participant will be assigned a pseudonym to maintain anonymity.

Sample size

We anticipate we will recruit between 20-40 participants to interview in order that we get a mix of interviewees, but will cease interviews once saturation has been reached.

Focus groups

In order to explore the acceptability of MIA/NIA amongst a wider group of stakeholders, including lay people and specific religious and ethnic groups, we will conduct a number of focus groups. These will be conducted with members of the public from appropriate communities to explore lay perceptions (such as Pakistani, Bangladeshi, Indian Asian) and religious groups (e.g. Muslim, Jewish) (Focus group questions – ethnic and religious groups v1). These will be conducted with appropriate translation and with segregated subgroups as appropriate. In order to compare these perceptions with the dominant White British population, we will also conduct focus groups with this comparative group so that views can be contrasted and compared. Other key stakeholders that we will conduct focus groups with include health professionals involved in post-mortem services, patient advocates, commissioners, managers and coroners (Focus group questions – health professionals v1; Focus group questions – patient advocates v1). They may have very specific views about MIA/NIA that are not relevant or applicable to patients and lay people.

Members of the S. Asian community, Muslim community and Jewish community will be recruited through community centres, temples, women's groups, synagogues and mosques (Poster for focus group v1). Focus groups will be held in appropriate locations (community centres etc) and at appropriate times, taking account of school hours and religious duties. We have been guided in this area by Professor Monica Lackanpaul at UCL who has a particular interest in inequalities in health and developing interventions tailored to the needs of minority ethnic groups. She has experience in recruiting minority ethnic groups into research studies and has offered guidance on design and will continue to do so in this area throughout the study. In order to recruit focus group participants, posters will be placed in strategic locations (such as notice boards) or adverts in newsletters. Potential participants will be asked to contact the researcher who will send the potential participant a PIS (Participant Information Sheet – members of the public v1) and recruit them into a focus group if they would like to take part. Members of the public from the dominant White British population will be recruited through local groups such as nurseries/primary schools or alternatively through a market research group (Poster for focus group v1). Patient advocates will be recruited through ARC, SANDS and the Lullaby Trust (Participant Information Sheet – text for support group website v1). Health professionals and other key stakeholders (commissioners, managers, coroners) will be recruited through the contacts of the advisory team as well as through snowball sampling (Participant Information Sheet – key stakeholders v1).

Overall, the focus groups may be conducted in one of the meeting rooms at GOSH/ICH, or, neutral locations such as hotels or community centres depending on the group. Focus groups will be facilitated by one of the research team who is experienced in this area, with bilingual facilitators from particular ethnic groups as appropriate. Participants will be asked to sign a consent form (Consent form v1) before the discussion begins, in which they agree that the

discussion can be audio-recorded. It will be explained that the discussion will be transcribed but that no identifying features will be included on the transcript. Participants will be offered a £50 honorarium to cover time and travel. Topics of discussion will include why someone might accept or decline an autopsy; why autopsy is considered unacceptable for certain religious/ethnic groups; what participants think about new methods of investigation after death; whether they are acceptable to those religious or ethnic groups that currently decline standard autopsy; and preferred terminology when discussing new methods of investigation after death.

Sample size

We anticipate we will conduct between 6-8 focus groups with between 6-10 participants in each one.

Risks

We acknowledge that the prospective method of recruiting recently bereaved patients into the questionnaire/interview study may cause concern given that they are being asked to take part at what is likely to be a very difficult and sensitive time. However, the recruitment method has been discussed and agreed by an advisory team which includes members of the support groups ARC, SANDS and the Lullaby Trust as well as bereaved parents and the GOSH PPI lead. They have agreed to this prospective approach. The research team considered the option of recruiting patients at a set time period after the consent to autopsy discussion but it was deemed to be even more inappropriate to contact people out of the blue several months after the event when they may be pregnant again, coming to terms with the loss, etc. In addition, some parents find it therapeutic to take part in research which might result in something positive following a negative experience. A recent qualitative study conducted in the UK found that bereaved relatives found taking part in research to be valuable and offered therapeutic benefits. The authors concluded that the need for bereaved relatives to take part in research studies should be encouraged and that ethics committees need to be aware of the potential benefits for bereaved relatives participating in research of this kind.[14]

Moreover, we have used a recruitment method which has been used previously amongst bereaved parents by Breeze et al.[15,16] In their study, women and their partners were asked by the obstetric and midwifery staff if they wished to discuss perinatal post-mortem with a fetal medicine research fellow following late miscarriage, stillbirth or the decision for pregnancy termination for fetal abnormality. Those agreeing to such a discussion (irrespective of whether or not they gave consent for any form of post-mortem) were given an information leaflet about the study and a self-completion questionnaire. Their study received a favourable ethical opinion from the Cambridge Research Ethics Committee (Ref 04/Q0108/185). On the request of the committee, their questionnaire contained questions to assess responders' attitudes to taking part in the research study. Their findings were that 73% of participants stated that completing the questionnaire had helped them feel better about the decision whether or not to consent to post-mortem and none reported any adverse effect of completing the questionnaire.

Finally, we would add that we have experience of performing research with parents at this difficult time, including the MARIAS study, which involved consenting of parents who had experienced sudden and unexpected child deaths for additional research scans prior to an

autopsy. Despite our initial concerns regarding this approach, this resulted in 97% research consent and demonstrated that with empathy and awareness of how to engage families at this difficult time, such studies are possible.[17] The research team also have previous experience in discussing issues surrounding end of life decisions with parents following diagnosis of fetal abnormality and decisions on pregnancy termination and views of parents regarding prenatal testing.[18]

Data analysis

Thematic analysis will be used to analyse interview data and transcribed audio recordings. This involves an iterative process where data are coded, compared, contrasted and refined to generate emergent themes. During this process emerging themes will be worked back into the interview questions to probe in more detail. Interviews/audio recordings will be transcribed verbatim and NVivo 10 (QSR International, Australia) will be used to manage the data and facilitate coding. Coding will be done by at least two independent researchers to provide rigour of analysis.

For the questionnaire, descriptive statistics will be used to describe the socio-demographic characteristics of the sample and the proportion of responders who would accept/decline standard autopsy, MIA and NIA. In addition, we will conduct inferential statistics to examine the associations between being likely to consent to autopsy with participant characteristics.

Dissemination

Through the work described above we will produce;
-a comprehensive report containing the data stated above regarding next steps for MIA/NIA assessment and/or implementation evaluation for less invasive autopsy
-peer reviewed scientific publications
-presentations to scientific meetings, nationally and internationally
-report to be provided to Royal Colleges (RCPCH, RCPath, RCOG)
-Lay report to be provided for stakeholders (ARC, SANDS, LT and others)

Research Team

Prof Neil Sebire (Chief Investigator) is an NIHR Senior Investigator and Internationally recognised expert in fetal and paediatric pathology with particular expertise in infant death investigation and autopsy, and has pioneered development of MIA. He will lead the project ensuring that the outcomes are appropriate.

Prof Lyn Chitty is an NIHR Senior Investigator and expert in fetal medicine and genetics with expertise in managing large NIHR multicentre studies, including evaluation of patient experiences. She is also Clinical Director of the NIHR CRN North Thames and member of the RCOG Fetal Medicine CSG which is supporting this application. She will oversee recruitment.

Dr Owen Arthurs is an NIHR Clinician Scientist Consultant Paediatric Radiologist with expertise in PM imaging who will direct recruitment and PPI aspects.

Prof Guy Rutty, MBE, is a forensic pathologist experienced in PM imaging and will lead Leicester recruitment. He is also Chair of ISFRI the International Forensic Radiology and Imaging Society.

Dr Celine Lewis is a health psychologist with a background in ethics with extensive experience in performing qualitative research in the context of NIHR studies, having carried out the work on patient views of non-invasive prenatal diagnosis, biosample donation and experiences of parents, who is well placed to conduct research on sensitive topics.

Dr Melissa Hill is a research genetic counsellor with experience in researching prenatal diagnosis and other sensitive topics.

Prof Angie Wade is a statistician with a wealth of expertise in planning and analysing complex data regarding paediatric studies including planning large clinical trials.

Susan Tebbs and **Caroline Dore** are experienced members of the UCL Comprehensive Clinical Trials Unit.

Dr Erin Walker is the PPI lead at Great Ormond Street Hospital and is experienced engaging children and parents in research.

Patient group advisors

Jane Fisher is CEO of **ARC**, the UK's largest patient advocacy and support organisation for patients with a diagnosis of fetal abnormality or pregnancy complication.
Charlotte Bevan, Laura Price and Cheryl Titherly are from **SANDS**, the stillbirth and neonatal death charity.
Charlotte Daman Willems, Gabrielle Osrin and Nicola Richardson are from the **Lullaby Trust** who provide support and care for families affected by Sudden Infant Death syndrome.
Sophia Kotzamanis and Alex Mancini are from the support group **Child Bereavement UK** and offer support to families when a baby or child of any age dies.
Morven Shearer and Raffa Tate are bereaved parents who have experience being approached about autopsy

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