Study Title: Next stage in Evidence-based paediatric surgical Treatment Strategies 2 - Hirschsprung’s Disease (NETS2HD): A nationwide cohort study investigating the impact of choice of surgical intervention on core outcomes at six to seven years of age in children with Hirschsprung’s Disease.

Internal Reference Number / Short title: NETS2HD- Six-year outcomes in infants with Hirschsprung’s Disease

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Chief Investigator Signature: Marian Knight

There are no potential conflicts of interest to declare

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.
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1. **SYNOPSIS**

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<th>Next stage in Evidence-based paediatric surgical Treatment Strategies 2: Hirschsprung's Disease (NETS2HD) - A nationwide cohort study assessing core outcomes at six years of age in children with Hirschsprung's Disease.</th>
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<tbody>
<tr>
<td>Internal ref. no. / short title</td>
<td>NETS2HD - Six year outcomes in infants with Hirschsprung’s Disease</td>
</tr>
<tr>
<td>Study Design</td>
<td>National Cohort study gathering data on health and quality of life outcomes using parent and clinician completed questionnaires</td>
</tr>
<tr>
<td>Study Participants</td>
<td>Children diagnosed with Hirschsprung’s Disease between 1st of October 2010, and 31st of March 2012, who were less than six months of age at diagnosis, and whose data were used in the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System Hirschsprung's Disease study</td>
</tr>
<tr>
<td>Planned Sample Size</td>
<td>305</td>
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<tr>
<td>Planned Study Period</td>
<td>01/06/2017-31/05/2018</td>
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**Objectives**

<table>
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<th>Primary</th>
<th>To investigate whether choice of definitive pull-through procedure is associated with differences in core outcomes at six to seven years of age</th>
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<tr>
<td>Secondary</td>
<td>To describe core outcomes at six years of age for a nationwide cohort of infants with Hirschsprung’s Disease. To investigate whether any disease factors, such as length of affected colon, and mode of presentation affect core outcomes at six years of age. To investigate whether pre-operative factors, such as birth-weight and gestational age affect core outcomes at six years of age.</td>
</tr>
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**Outcome Measures**

| Secondary outcomes are the remaining nine outcomes identified in the NETS1HD Core Outcome Set. Faecal incontinence at six years of age. |

2. **ABBREVIATIONS**
3. BACKGROUND AND RATIONALE

Three approaches to the definitive Hirschsprung’s Disease operation now exist; the ‘open approach’ (OA), the ‘laparoscopically-assisted approach’ (LA) [1], and the ‘purely trans-anal approach’ (TA) [2].
There is variation in practice between different surgical centres, and no evidence-based management guidelines exist[3, 4].

Proposed benefits to the laparoscopically assisted approach over the open approach include improved cosmesis, reduced operative time, length of stay, and risk of intra-abdominal adhesions[5-7]. Assessments of benefit for the purely trans-anal approach have mainly been made using short-term markers of success such as operative time, or bowel function prior to the age at which an infant can be expected to be continent [8, 9]. It has been suggested that over the long-term, the purely trans-anal approach may be associated with poorer outcomes than the open or laparoscopically assisted approaches[10-13]. With the trend towards increased utilisation of the purely trans-anal approach[3, 4], it is important that we assess its impact on valid, patient centred outcomes over the longer-term. As there is currently insufficient evidence on which to base a randomised controlled trial, population based cohort studies should instead be performed.

The British Association of Paediatric Surgeons Congenital Anomalies Surveillance System, (BAPS-CASS) is an established scheme through which data have been collected on outcomes in a number of conditions requiring early surgery. This system has been designed to inform evidence-based practice in a setting where recruitment to clinical trials has traditionally been challenging. By assessing the impact of different interventions on outcomes at 28 days of life and again at one year of age, the BAPS-CASS collaboration has published an evolving body of evidence to inform current practice. The impact of early surgery however often lasts throughout a patient’s life, and expansion of the BAPS-CASS framework to incorporate assessment of outcomes in the latter stages of childhood and on into adulthood is essential.

This study will therefore use the national anonymous cohort of infants with Hirschsprung’s Disease identified through BAPS-CASS as the sampling frame to identify patients and seek consent from their parents to gather data on long-term outcomes in the condition.

3.1. Hirschsprung’s Disease

The incidence of Hirschsprung’s Disease is estimated at around 1 in 4500 live births[14]. It is a condition characterised by colonic aganglionosis, where the intestine’s intrinsic nervous system (the myenteric plexus) has failed to fully develop, resulting in the infant being unable to spontaneously open their bowels. Varying amounts of the bowel can be affected, ranging from the classic ‘short segment’ affecting only the rectum and sigmoid colon, to total colonic Hirschsprung’s Disease affecting the entirety of the colon. Prognosis is generally considered to be better for those with shorter affected segments of bowel[15].

There are classically three modes of presentation for infants with Hirschsprung’s Disease. Neonatal presenters are those who present shortly after birth with delayed passage of meconium, abdominal distension and vomiting. Chronic presenters are those who present at a later age with symptoms of chronic constipation. Enterocolitis presenters are then those who present in either age group with
abdominal distension, fever, and diarrhoea secondary to bacterial translocation occurring as a result of the functional obstruction caused by the aganglionic segment of bowel[16]. Initial treatment of Hirschsprung’s disease always involves decompression of the obstructed bowel, usually with rectal washouts. For infants presenting with enterocolitis, antibiotics and intravenous fluid resuscitation are needed in addition to rectal washouts.

Definitive treatment of Hirschsprung’s Disease however almost always requires operative intervention. Since the first successful surgical treatment of an infant with Hirschsprung’s Disease[17], there has been significant evolution in the management strategies used. In uncomplicated infants, there has been a progression towards performing the repair as a single-stage, minimally invasive procedure[3, 7]. Three main approaches to the repair now exist: the ‘open approach’ (OA), the ‘laparoscopically assisted approach’ (LA) [18], and the ‘purely trans-anal approach’ (TA)[19]. Three main anastomotic techniques also exist, the Swenson [17], where an oblique anastomosis is formed between the ganglionic colon and aganglionic rectal remnant, the Duhamel [20], where an end-side anastomosis between ganglionic colon and rectal remnant is preceded by a retro-rectal dissection, and finally, the Soave [21], where colonic dissection proceeds in a sub-serosal plane prior to prolapsing of the ganglionic colon through the remaining rectal muscular cuff and anastomosis to the anus. There is currently wide variation in practice between different surgical centres [3, 4].

All three anastomotic techniques, as well as all three approaches to the procedure are in common use. Proposed benefits to LA over OA are that it reduces the risk of forming intra-abdominal adhesions, improves cosmesis, and reduces operative time, length of stay and financial cost [5-7]. It is suggested that TA further improves these outcomes[8, 22]. However, long-term benefits to TA are less clear, with higher long-term rates of faecal incontinence suggested[10, 11]. This is however, still debated [12, 13].

A further proposed drawback to TA is the inability to accurately identify the transition point between ganglionic and aganglionic bowel prior to starting the rectal dissection[7]. With ten per-cent of infants having no radiologically identified transition zone, and approximately eight per-cent having a transition zone identified operatively that is proximal to that suggested on pre-operative imaging[23], there is a significant risk of attempting TA on infants with a proximal transition zone (long-segment Hirschsprung’s Disease). It has been suggested that infants with a proximal transition zone should not undergo TA, as their outcomes are proposed to be better if other approaches are used[24, 25].

Although the vast majority of infants will have their definitive Hirschsprung’s ‘pull-through’ performed as a one-stage operation, there are still some who will undergo a staged procedure. This involves formation of a defunctioning loop enterostomy in order to decompress the bowel, followed by latter pull-through procedure, and then reversal of the stoma. Some surgeons employ the staged procedure as their standard operation, whilst some will use it only in infants who are unwell or who have significant intestinal dilatation.

Post-operatively, most infants will be started early on enteral feeds without the need for intravenous nutrition, and most will be discharged within a week of the operation[26]. Long-term outcomes however
are very variable. Complications include ongoing constipation, long-term incontinence, recurrent enterocolitis, adhesional small bowel obstruction, and need for further operations. The impact of the choice of early surgical intervention can therefore be long lasting.

### 3.2. Long-term outcomes

Whilst paediatric surgeons know that infants with Hirschsprung’s Disease frequently have difficulties over the longer–term, most research to date has focussed on short-term outcome measures, hospital metrics or surrogate markers of success[27]. There are many reasons for the short-term focus, but primarily it is due to the fact that Hirschsprung’s Disease has a low incidence, making it impossible for a single centre study to recruit sufficient infants to answer clinically relevant questions over a sensible period of time. Most studies therefore either represent small, but contemporaneous cohorts of patients, or larger, but historical cohorts, collected over time-periods where there have been multiple changes in practice[27]. The retrospective nature of the majority of these studies[28] means that limited data-points are available to researchers, and hence analysis focuses on those that are easily identified from case records, as opposed to those which are relevant to patients, their families, or service provision. Two recently conducted systematic reviews comparing the purely trans-anal pull-through with the laparoscopically assisted pull through identified that there is insufficient high quality data to make any meaningful comment on whether there is benefit to one or other intervention over the longer term[26, 27].

### 4. OBJECTIVES AND OUTCOME MEASURES

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<td>The primary outcome will be faecal incontinence, defined as per the NETS\textsuperscript{1HD} core outcome set as “involuntary passage of faecal matter in an inappropriate place”. Severity will be graded using a modification of the Krickenberg criteria.</td>
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<tr>
<td>To investigate whether choice of definitive pull-through procedure affects core outcomes at six to seven years of age</td>
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<tr>
<td><strong>Secondary Objectives</strong></td>
<td>Secondary outcomes will be the remaining nine outcomes in the NETS\textsuperscript{1HD} core outcome set.</td>
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<td>Secondary objectives are to describe core outcomes at six years of age in infants with</td>
<td>These are:</td>
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<td></td>
<td>- Mortality, with cause classified as due to</td>
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<td></td>
<td>o Complications of treatment, excluding Hirschsprung’s</td>
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Next stage in Evidence-based paediatric surgical Treatment Strategies 2 - Hirschsprung’s Disease (NETS2H): A nationwide cohort study investigating the impact of choice of surgical intervention on core outcomes at six to seven years of age in children with Hirschsprung's Disease.

| Hirschsprung’s Disease, and investigate whether any of the following factors affect core outcomes at six years of age in infants with Hirschsprung’s Disease? |
|-----------------|-----------------|
| • Length of affected bowel |
| • How they presented at first diagnosis |
| • Whether a stoma (a piece of bowel pulled out through the abdominal wall to relieve pressure on the gut) was created before their definitive operation |
| Associated Enterocolitis (HAE) |
| o HAE |
| o An associated anomaly or |
| o Other |
| • Voluntary bowel movements without need for enemas, or rectal or colonic irrigation |
| • Psychological stress and quality of life for the individual with Hirschsprung’s Disease, as measured using the PedsQL (standard validated instrument) |
| • Urinary incontinence that is constant, causing social problems, or requiring catheterisation. |
| • Bowel function as measured by the Paediatric Incontinence and Constipation Score (PICS) |
| • Unplanned re-operation. Unplanned is defined as any procedure not considered part of routine post-intervention practice for the definitive operation the child underwent. The scope of included procedures is limited to any procedure performed as a direct result of the diagnosis or treatment of the child's Hirschsprung's Disease, or any episode of general anaesthesia that is required as a direct result of the diagnosis or treatment of the child’s Hirschsprung’s Disease, regardless of whether or not an operative procedure is undertaken (e.g. Examination under anaesthesia, or manual evacuation). |
| • Need for a permanent stoma as a direct result of the diagnosis or treatment of Hirschsprung's Disease, including where the decision for a stoma has been made out of patient preference or for continence management. Permanent is defined as any stoma which was created without the intention of reversing it. |
| • Diagnosis of HAE where a decision was made to admit and instigate treatment, or where a score of 10 or more was achieved on Pastor et al's Delphi score for HAE[29]. |

5. STUDY DESIGN

5.1. Summary

This will be a prospective, nationwide cohort study investigating the impact of choice of surgical intervention on core outcomes at six to seven years of age in an already established cohort of 305 infants with HD. There will be two arms to the study, a parent reported outcomes arm, and a clinician reported outcomes arm. Anonymous data only will be collected from clinicians. Results will inform management guidelines for infants with HD. See attached file Study flow diagram for overview of study processes.
5.2. Study Size

The study size is governed by the size of the cohort of infants with Hirschsprung’s Disease previously identified through BAPS-CASS and will thus include up to 305 children and their parents.

5.3. Costs and Resources

Benjamin Allin, a NETS2HD researcher, has a personal grant from the National Institute for Heath Research as part of a Doctoral Research Fellowship. This will fund the principal research staff and resources.

5.4. Project Management

Day-to-day management of the project will be carried out by a Management Group consisting of the Chief Investigator (Professor Marian Knight), Dr Benjamin Allin, the Project Co-ordinator, the Data Manager, the Project Programmer, the Statistician and other external members as considered necessary for the project.

Oversight of the studies direction and implementation will be maintained by the Study Steering Committee, which will comprise Professor Marian Knight, Dr Benjamin Allin, Professor Maria Quigley, Mr Timothy Bradnock (Consultant Surgeon), Mr Gregor Walker (Consultant Surgeon), Mr Simon Kenny (Consultant Surgeon), Ms Gemma Jordan (Parent Representative), and Ms Rebecca Craven (Parent Representative).

5.5. Public Participation

The research questions and design of this study has been informed through consultation and collaboration with a parental advisory group containing families of children requiring early surgery. The outcomes to be investigated have been identified through a robust Delphi process involving key stakeholder groups, including people with Hirschsprung’s Disease, and parents of children with Hirschsprung’s Disease. Parents of children with Hirschsprung’s Disease, people with Hirschsprung’s Disease, and representatives of the Hirschsprung’s and Motility Disorders Support Network have been involved in development of the study materials and methodology, in particular, the participant information leaflet, consent form and data collection form, and the recruitment and consenting process. Two parents of children with Hirschsprung’s Disease have been appointed to the Study Steering Committee.
6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Children will be eligible to take part in the study if they were previously reported anonymously to the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS) as having been diagnosed with Hirschsprung’s Disease at less than six months of age, between the 1st of October 2010 and 31st of March 2012. Records of eligible children held by the BAPS-CASS data collection centres will be used to identify these infants. There are 305 children in this cohort. Infants who have died prior to six years of age will not be included in the parent reported outcomes arm of the study.

6.2. Inclusion Criteria

Any infant who:

- Was diagnosed with Hirschsprung’s Disease in the UK and Ireland between October 2010 and March 2012.
- Was six months of age or less at the time of diagnosis
- Was reported as part of the BAPS-CASS Hirschsprung’s Disease study

6.3. Exclusion Criteria

- Children not meeting the inclusion criteria.
- Children who meet the inclusion criteria, but who died prior to turning six years of age will not be included in the parent reported outcomes arm of the study.

6.4. Recruitment

Sharing information with parents of potentially eligible participants

Based upon feedback from a Parent Advisory Group established by the National Perinatal Epidemiology Unit, information relating to the existence of the NETS2HD study will be shared with parents of potentially eligible children, through trusted sources, prior to formal eligibility screening or approach for participation in the study. The intention of sharing information relating to the existence of the study in an ad hoc manner through trusted sources is to reassure parents that their child’s treating hospital is
involved in the study, and that the hospital, and relevant parent support groups endorse the study’s conduct. This information will be shared in the following five ways:

- A child’s main point of contact with their treating hospital is through their specialist colorectal nurse. These nurses will be given information about the NETS 2HD study, and asked to explain its presence to parents of children who may be eligible to participate. They will not be involved in seeking consent for sharing of contact details, or seeking consent to participate in the study. Nurses will be given a short form parent information leaflet to share with parents (see attached file PIS Short form V1).
- Print and/or electronic posters will be displayed in the outpatient departments and paediatric surgical wards of participating hospitals (see attached file Hospital poster V2)
- A summary information leaflet for families of potentially eligible infants will be available in the outpatient departments and paediatric surgical wards of participating hospitals. This will be the same short form parent information leaflet given to parents of potentially eligible infants by the specialist colorectal nurses.
- The NETS 2HD website
- Websites for the Hirschsprung’s and Motility Disorders Support Network, the CHAMPS Appeal, and the Breakaway foundation.

**Eligibility screening and initial contact**

This will be a National Institute for Health Research (NIHR) portfolio study, and therefore eligible for NIHR Clinical Research Network (CRN) support. NIHR CRN research nurses, and members of the child’s clinical team will use hospitals’ BAPS-CASS registers to identify infants who meet the inclusion and exclusion criteria. If there is insufficient capacity for participant identification centres to identify infants using only these staff, then support will be provided by Dr Benjamin Allin, the NETS 2HD researcher who is working under the auspices of a research passport. All participant identification will take place from the physical building of the child’s initial reporting hospital, and will be supervised by the site lead (a consultant paediatric surgeon). These same staff members will use the NHS Digital (England and Wales), Community Health Index (Scotland), HSCN (Northern Ireland) and hospital records to confirm a child’s survival status. An application has been made to the Confidentiality Advisory Group for approval to use members of staff outside of the clinical team for eligibility screening (see section 11.7 for more details).

Initial contact with parents of children who are potentially eligible for inclusion in the NETS 2HD study will be made by either an NIHR CRN research nurse working at the child’s reporting hospital, or a member of the child’s usual clinical team. Where there is insufficient capacity for the NIHR CRN research nurse or a member of the child’s clinical team to make the initial contact, this will be done by Dr Benjamin Allin. All contact between these members of the study team (including Dr Benjamin Allin), and the parents of potentially eligible children will be made from the child’s treating hospital, and will be made under the supervision of the site investigator. First contact will be made by telephone, unless contact cannot be made on three occasions, when a letter will be sent. This first contact will be used for the purposes of explaining the study and seeking consent for continued sharing of the child’s contact details outside of
their usual clinical team. It will not be used for seeking consent to participate in the study. Only parents of children who are still alive will be contacted. Verbal consent for on-going sharing of contact details will be recorded in writing by the member of staff obtaining consent.

If parents verbally consent to their contact details being shared with staff in the NPEU for the purposes of contacting them regarding participation in the NETS\(^{2HD}\) study, then the child’s name and NHS number, and parental telephone number and address will be sent in an encrypted file via secure transfer to staff in the NPEU where they will be entered into an encrypted database on secure NPEU servers. The child will be assigned a NETS2HD case ID number.

6.5. Consent to participate

Following consent for continued sharing of their contact details, parents will be sent either electronically (if they indicate this is their preference, and provide a valid email address), or via mail, a study pack containing:

- Invitation letter
- Patient information leaflet
- Contact details for NETS\(^{2HD}\) study staff
- Consent form

Parents will be given the opportunity to discuss the study further via telephone directly with research staff prior to giving consent to participate if they wish. In order to answer any questions they may have, research staff based in the National Perinatal Epidemiology Unit will contact parents two and four weeks after receipt of the pack if they have not yet indicated whether they wish to participate. Consent to participate can be indicated through completion of either the paper or electronic consent forms. Parents of eligible children can indicate they do not wish to participate by returning a blank consent form in the freepost envelope, informing study staff during telephone contact, or by simply not completing any of the study documentation. It will be made clear to parents in the study materials that non-participation will not affect the care their child receives, and that they need not give a reason for choosing to not participate. Parents will be asked whether they consent to being contacted in the future with regards to their child’s data being used in a research database. This will be recorded and their contact details will be used accordingly, either only for discussion of the NETS\(^{2HD}\) study, or for future contact in regards to development of a Hirschsprung’s Disease research database.

6.6. Requirements of study participants
Participation in the study will require parents of eligible children to complete one study questionnaire which will be sent to them on their child’s sixth birthday or the date of consent to participate, whichever is the later. Two weeks after receipt of the study questionnaire, parents will be contacted by research staff in the NPEU if they have not completed the questionnaire, or indicated that they wish to withdraw from the study. This process will be repeated at four weeks post receipt of the questionnaire.

Please see section nine relating to data management for further information relating to data collection and storage procedures. The parental questionnaire can be found in attached file Parental DCF.

6.7. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
  - Withdrawal of Consent
- Loss to follow up

The reason for withdrawal will be recorded in the CRF.

6.8. Definition of End of Study

Data will be collected from 01/06/2017-31/05/2018. At the time of data collection, infants will be six to seven years of age, with the last infant turning six prior to the 31st of March 2018. The additional three months of data collection from 31st of March to 31st of June will allow time for consent of the last infants, abstraction of their data, and chasing of any queries.

7. STATISTICS AND ANALYSIS

The primary outcome measure for this study is faecal incontinence. This will be defined as per the NETS1HD Core Outcome Set as "Involuntary passage of faecal matter in an inappropriate place". Severity of faecal incontinence will be graded using a modified version of the Krickenbeck classification – Grade 1 – occasional (once to twice per week), with or without ensuing social problems, Grade 2 – every day but without social problems, and Grade 3 – constant, with social problems.

Secondary outcomes are the remaining outcomes from the NETS1HD Core Outcome Set. These are:
Next stage in Evidence-based paediatric surgical Treatment Strategies 2 - Hirschsprung's Disease (NETS2HD): A nationwide cohort study investigating the impact of choice of surgical intervention on core outcomes at six to seven years of age in children with Hirschsprung's Disease.

- Mortality, with cause classified as due to
  - Complications of treatment, excluding Hirschsprung’s Associated Enterocolitis (HAE)
  - HAE
  - An associated anomaly or
  - Other
- Voluntary bowel movements without need for enemas, or rectal or colonic irrigation
- Psychological stress and quality of life for the individual with Hirschsprung's Disease, as measured using the PedsQL (standard validated instrument)
- Urinary incontinence that is constant, causing social problems, or requiring catheterisation.
- Bowel function as measured by the Paediatric Incontinence and Constipation Score (PICS)
- Unplanned re-operation. Unplanned is defined as any procedure not considered part of routine post-intervention practice for the definitive operation the child underwent. The scope of included procedures is limited to any procedure performed as a direct result of the diagnosis or treatment of the child's Hirschsprung's Disease, or any episode of general anaesthesia that is required as a direct result of the diagnosis or treatment of the child’s Hirschsprung’s Disease, regardless of whether or not an operative procedure is undertaken (e.g. Examination under anaesthesia, or manual evacuation).
- Need for a permanent stoma as a direct result of the diagnosis or treatment of Hirschsprung's Disease, including where the decision for a stoma has been made out of patient preference or for continence management. Permanent is defined as any stoma which was created without the intention of reversing it.
- Diagnosis of HAE where a decision was made to admit and instigate treatment, or where a score of 10 or more was achieved on Pastor et al's Delphi score for HAE[29].

Descriptive information will be presented for key birth demographics. Proportions and 95% confidence intervals will be calculated for the cohort as a whole, and for each of the operative groups for each of the following core outcomes.

- Faecal incontinence
- Mortality
- Voluntary bowel movements without need for enemas or rectal or colonic washouts
- Urinary incontinence
- Unplanned re-operation
- Permanent stoma
- Hirschsprung's associated enterocolitis

Medians and interquartile ranges will be calculated for the cohort as a whole and for each operative group for each of the following core outcomes:

- Quality of life, as measured by the PedsQL score
- Bowel function, as measured by the PICS score
As a causal relationship is being investigated between choice of definitive procedure and faecal incontinence at 6 years of age, a regression analysis model will be built based upon prior knowledge of likely confounding factors. A Direct Acyclic Graph (DAG) (see attached file daggity-model-6.pdf) was developed using Daggity[30] in order to identify factors that should be adjusted for in this model. Based upon the results of the DAG, the following factors will be adjusted for:

- Birthweight
- Age at presentation with Hirschsprung's Disease
- Presence of enterocolitis at first presentation
- Development of pre-operative enterocolitis
- Pre-operative stoma formation
- Weight at operation
- Method of rectal dissection
- Length of affected segment of colon

7.1. The Number of Participants

There are 305 infants in the original BAPS-CASS Hirschsprung’s Disease cohort. These infants will form the study sample size.

Assuming an incidence of faecal incontinence of 35% in infants undergoing LA[31], with 43% of infants undergoing the LA, and 15% TA, this study would have 80% power at the 5% level of significance to detect a relative risk of 1.8 or above, or 0.35 or below when comparing to infants with HD undergoing TA.

8. DATA MANAGEMENT

8.1. Access to Data

Personal data will only be accessible by members of the NETS2HD study team with a legitimate need to contact participants. Responsible members of the University of Oxford or NHS Trusts may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations.

8.2. Data Recording and Record Keeping

Data entry
Clinician reported outcomes will be entered directly into OpenClinica. Parent reported data will either be directly entered into OpenClinica using the Participate expansion, or will be recorded on a paper data collection form, dependent on parental preference. Where a paper data collection form has been used, this will be returned to staff at the NPEU, where data will be double entered into OpenClinica. Pre-specified acceptable data entries and ranges will be used to identify the input of potentially incorrectly entered data.

**Data collection - Clinician Reported Outcomes Arm**

NIHR CRN research nurses and members of the child’s usual clinical team will be responsible for extraction of data from existing hospital records, including clinic letters, operative notes and radiological investigations. All data extraction will take place from the physical building of the child’s initial reporting hospital, and will be supervised by the site lead. Anonymous data will be directly entered into OpenClinica hosted on secure NPEU servers, and will be associated with the child’s BAPS-CASS case ID.

**Data collection - Parent Reported Outcomes Arm**

On their child’s sixth birthday, or the date of consent to participate, whichever is later, parents will be sent a paper data collection form, or link to an electronic data collection form according to their preference. Where they opt for an electronic form, they will enter data directly into OpenClinica on the secure NPEU servers. Where they opt for a paper data collection form, these will be returned to the NPEU, where they will be double entered in the secure database by NETS2HD study staff. No participant identifiable data will be collected on the data collection forms. Outcomes will be reported using the child’s NETS2HD case ID. No participant identifiable information will be stored in the outcomes database.

**Linkage of clinician and parent reported data**

To achieve the primary objective of the study, it is essential that parent and clinician reported outcomes can be linked to data relating to this cohort of children that were collected by the BAPS-CASS Hirschsprung’s Disease studies when the children were 28 days of age and one year of age. Achieving this requires linking a child’s BAPS-CASS case ID to their NETS2HD case ID. Therefore, after consent has been obtained for participation in the NETS2HD study, the NIHR CRN research nurse based in the child’s reporting hospital will be asked to transfer to staff in the NPEU the BAPS-CASS case ID that is associated with a child’s NHS number. This transfer will be done in an encrypted file via secure transfer system. Staff in the NPEU will add the BAPS-CASS case ID to the child’s existing registration record containing their name, NHS number, parental contact details, and NETS2HD case ID. This information will all be stored on the NPEU secure servers in a database separate from any clinical information.
Data Storage

Personal data provided directly by parents will be entered onto a secure area of the National Perinatal Epidemiology Unit (NPEU) computer system. This will be stored separately from the information provided in the questionnaires. All analysis will take place on fully anonymised datasets only. The security of the data will be maintained by storage on a secure NPEU network accessible only by the key researchers and responsible members of the University of Oxford who may require access to data to ensure compliance with regulations.

Completed paper questionnaires will be stored in locked filing cabinets and, once entered onto a database, compliance will be maintained by storage on a secure NPEU network, accessible only by the key researchers and responsible members of the University of Oxford who may require access to data to ensure compliance with regulations.

Personal data will have been provided by parents with consent on the basis that we may contact them regarding use of their child's data in development of a Hirschsprung's disease research database.

We will not retain any personal data for parents who have chosen not to consent to participation or have withdrawn from the study.

All data will be stored in a study specific database hosted on the secure servers of the National Perinatal Epidemiology Unit, with security maintained through implementation of National Perinatal Epidemiology Unit standard operating procedures., specifically:

Physical security:

Physical access to the building is controlled by swipe card and a manned reception for visitors. Further swipe access is required to access the NPEU section of the building. Access for visitors is via the NPEU reception and visitors are allocated a visitor badge.

Paper records containing sensitive and/or personal data are kept in locked filing cabinets in offices dedicated for a given research project; these offices are kept locked when vacant.

Virtual security:

Any personal or sensitive digital data, such as patient identifiable data, is kept on the NPEU’s encrypted network drive. This drive is controlled by eDirectory and access permissions are granted to data for identified, authorised and authenticated users. The NPEU adopts a policy where no sensitive or personal data leaves the unit on removable devices unless consultation has been had with the unit’s Director and would only be approved for exceptional circumstances where the data needs to be transferred and an alternative secure electronic transfer mechanism cannot be enabled.
All security is supported by the NPEU policies and these are regularly reviewed and audited in accordance to the NHS Information Governance Toolkit (IGT). Information Security is discussed at every monthly senior management group meeting and is an agenda item for the NPEU tri-annual staff meeting, where the latest updates and vulnerabilities are reported and staff training is provided. Random checks can be carried out by the Head of IT and Information Security at any time.

The NPEU has been awarded level 3 status with 100% score on the NHS IG Toolkit (EE133863-8J017-NPEU). The NHS IGT aligns itself to the controls of ISO27001 and ISO27002. The NPEU has policies to support the NPEU’s operations in a safe, secure and controlled environment. Policies are reviewed biennially and distributed to staff by an electronic system (PRISMS) which can, if required, test users on their knowledge for a given policy and/or SOP. The NPEU adopts a risk management and mitigation approach.

NHS IG Toolkit: EE133863-8J017-NPEU; version 13, level 3 with a score of 100% with an improvement plan in place.

Uni Ox Data protection registration number: Z575783X

Data availability, timeline of use, and removal

Once parental contact details have been obtained by a National Institute for Health Research (NIHR) Clinical Research Network (CRN) research nurse, reporting clinician, or Dr Benjamin Allin, these will be kept securely within the reporting hospital. Only the child’s NHS number, name date of definitive operation or stoma formation if definitive procedure has not been performed, and parent’s names and telephone numbers will be available to people outside of the clinical team (NETS2HD study team) prior to consent being obtained.

First attempt at contact via telephone with the parents of eligible children will be made within 72 hours of obtaining the contact details. A further two attempts at contact will be made within one week of obtaining the contact details. If no contact is made, an attempt will be made to make contact in written format within two weeks of obtaining contact details. Each of these attempts at contact will be made in order to obtain consent to continued sharing of contact details with members of the NETS2HD study team. If consent is given it will be recorded in writing by the team member who made contact with the parents. A lack of response from parents within a month of posting of the written communication will be assumed to indicate they do not give their consent for on-going sharing of their contact details. In this scenario, or where consent is not given for sharing of contact details following contact with the recruiting member of staff, all contact details will be removed from the local records, and replaced with a record indicating that consent to sharing of contact details has not been obtained.

Where consent to sharing of contact details is given, these details will be shared with NETS2HD research staff in the NPEU who will send a participant information pack to parents of the eligible child. This pack will contain an invitation letter, patient information leaflet, contact details for NETS2HD study staff and a
consent form. If no indication has been given by parents of whether they wish to participate at two weeks and four weeks after receipt of the participant information pack, they will be contacted by study staff to ascertain whether they wish to participate. If consent has not been given for participation within two months of posting of the study information pack, all contact details will be removed from the database held in the NPEU, and replaced with a record indicating that consent to participate was not obtained.

Through using the above methods to obtain consent, and removal of contact details where consent has not been obtained, the NETS<sup>2HD</sup> study will move towards a situation where there is no longer any patient identifiable data being used without consent. The longest time-period that patient identifiable data may be held without explicit consent is 14 weeks. This would be for an infant whose parents were contacted in writing two weeks after the initial attempt at telephone contact, and who then gave consent to sharing of contact details one month later, but who did not then respond to any of the attempts to obtain consent to participate in the study, leading to removal of their contact details two months after posting of the study information pack.
9. QUALITY ASSURANCE PROCEDURES

The day-to-day management of the study will be undertaken by the study management group, which comprises the study researcher, Programme Manager, Study Programmer and Senior investigator.

Overall conduct of the study will be overseen by the Study Steering Committee, which comprises the researcher and senior investigator in addition to three consultant paediatric surgeons and two parents of children with Hirschsprung’s Disease. The steering committee will meet three monthly throughout the design, implementation and analysis of the study, and will be in contact electronically and via telephone more frequently as required. They will monitor recruitment, scrutinise acceptability of the study design, and analyse any adverse feedback from participants or those who dissent to participate in the study.

Progress of the study will also be monitored in the weekly meetings between Professor Marian Knight and Dr Benjamin Allin that form the supervision meetings for Dr Allin that are incorporated into the Doctoral Research Fellowship training and supervision program. Similarly, the study progress will be monitored at the monthly supervision meetings that include Professor Jenny Kurinczuk as well as Professor Marian Knight and Dr Benjamin Allin.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1. Declaration of Helsinki
The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

10.2. Guidelines for Good Clinical Practice
The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

10.3. Approvals
The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the sponsor, an appropriate Research Ethics Committee (REC), HRA and host institution(s) for written approval. Approval is also being sought from the Confidentiality Advisory Group.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.
10.4. Reporting
The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

10.5. Participant Confidentiality

The study staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by a participant ID number on all study documents.

Screening, handling and erasure of identifiable personal information of potentially eligible children will only be undertaken in the manner described. Any contact details or participant identifiable information we receive will be stored securely, separate from the research information. All analysis will take place on fully anonymised datasets only.

Completed paper questionnaires will be stored in locked filling cabinets and, once entered onto a database; the security of the data will be maintained by storage on a secure University network accessible only by the key researchers and responsible members of the University of Oxford who may require access to data to ensure compliance with regulations. Access by any other individuals for the purposes of any other study will only be allowed after review by the NETS\textsuperscript{2HD} Steering Committee and further reference to a Research Ethics Committee.

It is possible that direct quotes from free text areas of the questionnaire may be used in publications related to the questionnaire study. No such quotes will be able to be traced to any individual.

The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

10.6. Expenses and Benefits

There are no intended payments or other benefits to participants.

10.7. Justification for eligibility screening by members of staff outside of the usual clinical team

Only anonymous data were collected for the BAPS-CASS study (Ethics Ref: 12/SC/0416), and therefore only the sites which collected the data, and not researchers have access to children’s and parent’s contact details. We conducted a previous study (AIMESGS, Ethics Reference Number 14/LO/1949) in
Next stage in Evidence-based paediatric surgical Treatment Strategies 2 - Hirschsprung's Disease (NETS2HD): A nationwide cohort study investigating the impact of choice of surgical intervention on core outcomes at six to seven years of age in children with Hirschsprung's Disease.

which we asked clinicians at sites to confirm eligibility and then post out long-term follow-up questionnaires to parents of children with a different condition, whose anonymous data had also been included in a previous BAPS-CASS study. Only 50% of sites managed to identify eligible children and post out the questionnaires due to issues with staff capacity, and only 10% of questionnaires were returned by parents. At one site where parents were contacted personally by the research team by telephone, response rates were higher. Reasons for failure of this study to recruit have been investigated in detail with reporting clinicians, and also with members of the parent advisory group. The reasons for failure were broken down into two broad areas:

1. Insufficient time for clinical staff to identify eligible children, post study materials to them and contact them to ensure receipt and understanding of materials.
2. Parents feeling disconnected from the study due to a lack of recent contact with healthcare professionals, and lack of information about the study/opportunity to discuss the study prior to receiving the questionnaire.

The recruitment and consenting process used for the NETS2HD study has therefore been developed based upon this feedback, with the following changes suggested:

1. Use of research nurses and where necessary, Dr Benjamin Allin, the NETS2HD study researcher in addition to reporting clinicians to identify eligible children. This will reduce the workload on busy clinicians, and ensure the study can be successfully carried out even in departments where there are insufficient clinicians to make identification of eligible children feasible.
2. First contact with parents of eligible children being made via telephone as opposed to mailed information in order to allow discussion of the study prior to study materials being received by parents.
3. First contact with parents of eligible children simply being to obtain consent to continued sharing of their contact details, as opposed to being to obtain consent for participation in the study.
4. Providing information about the NETS2HD study at participating hospitals, to ensure that parents of eligible children are aware it is taking place, and that their hospital is taking part. This will also prompt parents to ask for more information from their clinicians if they believe their child may be eligible to participate.

Based upon this analysis of the limitations of the AIMESGS study, we propose that initial contact with children who are potentially eligible for inclusion in the NETS2HD study will be made by either a National Institute for Health Research (NIHR) Clinical Research Network (CRN) research nurse working at the child’s treating hospital, or a member of the child’s usual clinical team. Where there is insufficient capacity for the NIHR CRN research nurse or a member of the child’s clinical team to make the initial contact, we propose that this will be done by Dr Benjamin Allin, the NETS2HD researcher, working under the auspices of a research passport, from the relevant site. All contact between these members of the
Next stage in Evidence-based paediatric surgical Treatment Strategies 2 - Hirschsprung’s Disease (NETS2HD): A nationwide cohort study investigating the impact of choice of surgical intervention on core outcomes at six to seven years of age in children with Hirschsprung’s Disease.

study team, including Dr Benjamin Allin, and the parents of potentially eligible children will be made from the child’s treating hospital, and will be made under the supervision of the site investigator. First contact will be made by telephone, unless contact cannot be made on three occasions, when a letter will be sent. This first contact will be used for the purposes of explaining the study and seeking consent for continued use of the child’s contact details outside of their usual clinical team. It will not be used for seeking consent to participate in the study.

If Dr Benjamin Allin is required to assist with identification of eligible children, he will only have access to that information required to identify the child, confirm eligibility and contact their parents. This information will be limited to the child’s NHS number, name, date of definitive operation or stoma formation if definitive procedure has not been performed, and parent’s names and telephone numbers. Site investigators will be appointed in each participating hospital, and will have responsibility for ensuring that only essential data are accessed. All identification of potentially eligible children will take place at the recruiting hospital.

This method of first contact has been developed with the close involvement of parent groups, and they reported that sharing of the above details with a research nurse and/or Dr Benjamin Allin working within the above framework was a step they were happy to take if it improved the chances of the study achieving its objectives. Quotes from parents include:

“As a parent I don’t think I would mind if you had access to my contact details, I think people have a general assumption that clinicians will treat personal information with respect. I’m not sure they necessarily worry about the distinction between hospitals as long as it is explained why it is necessary.”

And

“As a parent I don't have concerns about confidential contact information being passed outside our immediate clinical team”.

And

“The main thing is that you get a good response rate and that there's adequate resources to follow up with parents and give them an opportunity to ask questions”.

11. FINANCE AND INSURANCE

11.1. Funding
This study is funded by the National Institute for Health Research (NIHR) as part of Doctoral Research Fellowship awarded to Mr Benjamin Allin.

11.2. Insurance

The University of Oxford maintains Public Liability and Professional Liability insurance which will operate in this respect.

12. PUBLICATION POLICY

The findings of this study will be presented at specialist conferences, such as the BAPS Annual Congress. Resulting work will also be submitted for publication in peer-reviewed journals. Findings will also be fed back to a parental advisory group and thence, to the relevant patient and parent groups.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute for Health Research (NIHR). Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.
13. REFERENCES


Next stage in Evidence-based paediatric surgical Treatment Strategies 2 - Hirschsprung’s Disease (NETS2ND): A nationwide cohort study investigating the impact of choice of surgical intervention on core outcomes at six to seven years of age in children with Hirschsprung’s Disease.


Next stage in Evidence-based paediatric surgical Treatment Strategies 2 - Hirschsprung's Disease (NETS2HD): A nationwide cohort study investigating the impact of choice of surgical intervention on core outcomes at six to seven years of age in children with Hirschsprung's Disease.

Next stage in Evidence-based paediatric surgical Treatment Strategies 2 - Hirschsprung's Disease (NETS<sup>2HD</sup>): A nationwide cohort study investigating the impact of choice of surgical intervention on core outcomes at six to seven years of age in children with Hirschsprung's Disease.

14. APPENDIX A: STUDY FLOW CHART

See file Study Flow Diagram V2.pptx
15. APPENDIX C: AMENDMENT HISTORY

<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Protocol Version No.</th>
<th>Date issued</th>
<th>Author(s) of changes</th>
<th>Details of Changes made</th>
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List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC submission.