CSOR Programme: Approved Protocols Document

Using stated-preferences methods to develop a summary metric to determine successful treatment of children with a surgical condition: a study protocol

Oliver Rivero-Arias[1], John Buckell[2], Benjamin Allin[1], Benjamin M Craig[3], Goher Ayman[1] and Marian Knight[1] on behalf of the CSOR Collaborative Group

1. National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
2. Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK
3. Department of Economics, University of South Florida, CMC206A, 4202 E. Fowler Avenue, Tampa, FL 33620, USA

Corresponding author:
Associate Professor Oliver Rivero-Arias
National Perinatal Epidemiology Unit
Nuffield Department of Population Health
Old Road Campus
University of Oxford
OX3 7LF

Abstract

Introduction: Wide variation in the management of key paediatric surgical conditions in the UK has likely resulted in outcomes for some children being worse than they could be. Consequently, it is important to reduce unwarranted variation. However, major barriers to this are the inability to detect differences between observed and expected hospital outcomes based upon the case-mix of the children they have treated, and the inability to detect variation in significant outcomes between hospitals. This study proposes to develop a summary metric to determine what represents successful treatment of children with surgical conditions. A stated-preference study has been designed to estimate the value key stakeholders place on different elements of the outcomes for a child with a surgical condition.

Methods and analysis: Preferences from parents, individuals treated for surgical conditions as infants/children, health care professionals and members of the public will be elicited using paired comparisons and kaizen tasks. A descriptive framework consisting of seven attributes representing types of operations, infections treated in hospital, quality of life and survival was identified. An experimental design has been completed using a D-efficient design with overlap in three attributes and excluding implausible combinations. All participants will be presented with an additional choice task including a palliative scenario that will be used as an anchor. The survey will be administered online. Primary analysis will estimate a multinomial logit model to understand the strengths of preferences associated to attributes for each type of participant and elicitation method. A traffic light system to determine what combination of attributes and levels represent a successful or unsuccessful treatment will be created.

Dissemination: We will disseminate all of our results in peer-review publications and scientific presentations. Findings will be additionally disseminated through relevant charities and support groups, professional organisations and via social media and through a project-specific website.

Strengths and limitations of this study

- To our knowledge, this is the first research study attempting to estimate a summary metric to determine what outcomes represent a successful treatment in children with a surgical condition, facilitating comparisons of hospitals' observed outcomes against their expected outcomes, and comparison of outcomes between hospitals.
- Preference data from two different elicitation techniques, paired comparisons and a novel kaizen task, will be collected contributing to the knowledge-base of the latter for future studies.
- Preference data from different stakeholders relevant to the decision context will be available to estimate the final summary metric.
- Given that children with surgical conditions are relatively few in number, data collection may present challenges, in particular for the identification of parents and health care professionals, which will be mitigated using a thorough recruitment strategy.

1 Introduction

Around half a million children need surgery in England and Wales every year [1]. The 2011 National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) review of children's surgery concluded that outcomes were not appropriate and challenges in the surgical decision-making process were noted as one reason for outcomes being worse than expected [2]. These challenges reflect variation in the management of key conditions leading to variation in outcomes [3-10]. Significant, unwarranted variation in the management of conditions inevitably exposes children to poorer outcomes, but can also affect the wellbeing and quality of life of carers [11]. Reducing this unwarranted variation is possible, but complicated by three key barriers: 1) an inability to detect variation in significant outcomes, 2) a lack of evidence-based management guidelines and 3) slow uptake of published guidance. The NIHR funded study "Improving unwarranted variation in outcomes of children's surgery through a new Children's Surgery Outcome Reporting system using routinely available data (CSOR)" investigates whether one unified system is capable of addressing these three issues and therefore reducing unwarranted variation in surgical care. This protocol paper describes the study design of one of the CSOR sub-studies, tackling the first barrier.

National data are needed to understand outcome variation of children's surgeries across centres. Current evidence is limited by a lack of parent-reported outcomes and long-term outcome data; and poor coverage of centre-specific management assessments [12]. The gold standard approach for comparing outcomes of interest to patients between centres within a jurisdiction is to use a core outcome set (COS) [13]. Several COS have recently been developed that are relevant to children with a surgical condition [7, 14-16], which have presented opportunities to improve the measurement of outcomes of paediatric surgery. Whilst the nature of paediatric surgical conditions suggests that many outcomes within a COS will be specific to that condition, some universality exists, with several outcomes being repeated across the identified paediatric surgical core outcome sets. These common outcomes could be compared across conditions to understand between-centre variation. To make such comparison meaningful, a summary metric that categorises a child's outcome into, for instance, `successful` or `unsuccessful` from a combination of common core outcomes is needed. The aim of this study is to develop an algorithm to assist in defining this summary metric, and therefore

determining what constitutes successful treatment of children with a surgical condition across a variety of conditions.

Whether a certain combination of common core outcomes across conditions indicates a successful or unsuccessful treatment depends on the value that relevant stakeholders place on the different elements of the core outcomes. Economists employ preference elicitation techniques to determine such values [17]. Stated preference techniques such as discrete choice experiments (DCE) are well-suited to understand the value of potential combinations of core outcomes of paediatric surgery [18]. A DCE is an experiment with choice tasks that elicit preferences indicating how individuals value attributes of alternatives in a decision scenario [18]. The value of a scenario depends on the levels associated to attributes, which are the characteristics of health, treatments or health care services being evaluated [18]. During a DCE, participants are presented with a number of scenarios and are asked to choose their preferred option, trading off among the attributes. DCEs can take different formats, but *paired comparisons*, where the participant is presented with two or more scenarios and asked to choose one, are most widely used [19]. Other alternatives to paired comparisons exist including best-worst scaling and more recently kaizen tasks [20, 21]. Participants' choices in stated preferences exercises are analysed using discrete choice models, where choices are associated with combinations of attributes and levels to understand participants' preferences (i.e., their relative importance).

This is a protocol for a stated-preference study designed to estimate the value key stakeholders place on different combinations of health and care outcomes following treatment of a child with a surgical condition. Stakeholders will be presented with a series of paired comparisons and novel kaizen tasks to elicit their preferences. The final product of the collected data will be an algorithm to determine whether the treatment of a child with a surgical condition has been "successful" or "unsuccessful". The use of stakeholder preferences to help in health care decision-making by policymakers has increased considerably across most developed jurisdictions [19]. This has been accompanied by best practice guidance for developing such studies, applied herein [22-25].

1.1 Aims

To understand how parents, guardians and health care professionals caring for children with a surgical condition, individuals treated for surgical conditions as children, and members of the general public value common health and care outcomes following treatment of a child with a surgical condition. Specifically:

A. To estimate the relative importance of key health outcomes following treatment for a surgical condition in childhood for multiple conditions using a paired comparison and a novel kaizen task.
B. To compare preferences between the two sources of preference data and type of participant in the context of children with a surgical condition.
C. To estimate an algorithm using weights derived from the relative importance estimates in A to derive a summary metric that categorises outcomes following surgery in childhood into "successful" or "unsuccessful" outcome.

2 Methods and analysis

2.1 Overview of the framework for the stated-preference study

Figure 1 describes the framework and different phases that will be followed to conduct this study. This protocol describes the following sections: 1) identification and description, 2) experimental design, 3) survey instrument, and 4) statistical analysis.

2.2 Identification and description

2.2.1 Decision model and descriptive framework

We have followed the most recent guidance on formative research for the identification of attributes and levels for the descriptive system used in this study [25]. Our decision problem explores how to best conceptualise what constitutes a more successful outcome following treatment for a surgical condition in childhood from the values that relevant stakeholders place on key core outcomes across paediatric surgical conditions. Our decision model hypothesises that a successful treatment for a child with a surgical condition can be represented by a combination of characteristics or attributes. In this

study, we define attributes as core health outcomes included in available COSs relevant to paediatric surgery. The attributes and associated levels that describe potential outcomes following treatment define our descriptive framework. We used literature reviews, interviews with parents and paediatric surgeons, and group discussions with our Parent Advisory Group (PAG) to determine the descriptive system for the final survey instrument. Our PAG consists of over 100 parents and family of children who have undergone early surgery for conditions including Hirschsprung's disease, gastroschisis, exomphalos, short bowel and necrotising enterocolitis.

An initial list of conceptual attributes were identified through a review of published COS relevant to paediatric surgery. Relevant COS have been developed for children with Hirschsprung's disease, gastroschisis and appendicitis, as well as for children receiving neonatal care in a high-income setting [7, 14-16]. Each of these COS were developed using a combination of literature reviews, an online Delphi process, and consensus meetings, and included in their stakeholder groups, clinicians, allied health professionals, parents, and children or adults previously treated for the target condition. We also conducted focussed discussions with our PAG who had the opportunity to comment on the COS identified in the literature review. The core outcomes identified in the above mentioned conditions are presented in Table 1.

An iterative process to the identification of attributes was followed. In a first step, conducted by the clinical team (BA, MK), overlap in outcomes of importance was identified between the four COS. Each COS also identified outcomes that were relevant only to the condition of interest, and not represented in the other COSs. In a second step, we reviewed these condition-specific outcomes with our PAG in order to determine how best to represent them in the descriptive system. The group concluded that these condition-specific outcomes were highly likely to impact the child's overall quality of life and would therefore be adequately represented through an overarching attribute of quality of life. Three outcome categories including survival, adverse events, and quality of life were common to all four relevant COSs and therefore selected as the initial set of attributes for the descriptive system. Similar outcomes have also been identified as important in other developed paediatric COS [26, 27]. The specific adverse events identified from each COS were also discussed with our PAG and the CSOR paediatric surgeons in a group discussion. The PAG and surgeons agreed that the main adverse

events were better summarised as operations, and hospitalisations due to significant infections. Therefore, four core attributes were identified at the end of the second step. A description of each attribute is given next:

1. **Operations**

Most surgical conditions are treated with one or more operations. Some operations that a child might undergo will be planned at the beginning of the child's treatment, whilst some will be emergency, or unplanned operations. The complexity of each operation also varies, from minor operations, such as draining an abscess (a pocket of pus under the skin), to more major operations, such as removing sections of intestine (bowel or gut). For the purpose of the preference study, the number of operations will be presented within four different attributes according to type of operation.

2. **Whether the child has an infection treated in hospital after their operation**

Each of the COSs identified as relevant to paediatric surgery include condition-specific significant infective complications, such as enterocolitis and intra-abdominal abscess. Some also include a more generalised measure of significant infection, *sepsis.* For the purposes of the preference study, the infective complications included in each COS will be represented by the attribute infections treated in hospital, and the levels will define the frequency of infections.

3. **The child's quality of life**

Each of the COSs included the outcome quality of life, whilst some also specifically included outcomes relating to psychological wellbeing. There are multiple instruments to measure quality of life in children, but they have not been validated in children with a surgical condition. These tools generally describe multiple domains, including social functioning, physical functioning, and psychological wellbeing, with their output generally reported in a continuous manner. However, for the purposes of the paired comparisons, quality of life will be categorised as good, fair or poor. The impact of key condition-specific outcomes such as faecal incontinence, need for parenteral nutrition, and liver disease will be reflected in the child's overall quality of life.

4. **How long the child survives after their diagnosis**

Although death is relatively uncommon following most surgery in childhood, it is such a significant outcome that all four COSs relating directly to childhood surgery, and the majority of paediatric COSs

include it. For the purposes of the paired comparisons, this outcome will be presented positively as survival.

The identification of the attribute levels also employed an iterative process. Firstly, we reviewed the epidemiological data available for each of the attributes to guide the range that could be presented to participants. Existing large-scale cohort studies describing the outcomes for children with any of the six conditions to be covered in the CSOR programme were reviewed [4, 6, 8, 9, 28-37]. A researcher (BA) extracted point estimates and associated measures of uncertainty for each of the attributes. In discussions with two other researchers (OR-A, BC) initial deterministic ordinal levels for each attribute were developed. The selection of levels considered the potential participant cognitive burden and the ability to test appropriate functional forms hypothesis (e.g., linear, quadratic) for quantitative attributes. This initial list of ordinal levels was discussed with paediatric surgeons in a group meeting to ensure their clinical appropriateness and suggest changes to the wording. The language used to describe the levels was refined further following review by members of the PAG. Finally, we conducted three think aloud exercises with different parents who completed a mock choice task of the survey instrument with two of the researchers (OR-A, JB). Parents were given the opportunity during these interviews to comment on the wording used for the attributes and associated levels. The proposed attributes and attribute levels are described in the descriptive framework in Table 2.

2.2.2 Elicitation task and format

Two elicitation formats will be used in this study to estimate preferences: a paired comparison and a kaizen task. Each paired comparison will include two scenarios describing combinations of treatment outcomes of a child with a surgical condition without an opt-out option. An example is presented in Supplementary material 1. This type of choice task is the most widely used format in health preference research [19] and has been used previously to elicit preferences for outcomes of surgery [38-40].

Recent work has reported that valuation can be problematic in the context of child health [41, 42]. Eliciting values to inform decision making at the start of life or early childhood requires stakeholders to

complete tasks from someone else's point of view. There is some evidence that when the tasks in an elicitation exercise refer to someone else's instead of their own preferences, individuals find the exercise strenuous. This is accentuated when the perspective is that of a new-born or a young individual [41]. In a paired comparison, it is easy to understand that choosing between two undesirable outcomes of paediatric surgery could be distressing to stakeholders. Moreover, members of the general public may find it both distressing and unfamiliar as they find it difficult to relate to the decision context [43]. This in turn can affect the preferences elicited in paired comparisons.

In addition to the paired comparisons in this study, we will therefore also administer a series of kaizen tasks to participants (supplementary information 1). Each kaizen task begins with a paired comparison between a single profile and a palliative one (i.e. no operations and no infections, but the child has fair health and dies within one month). Next, the respondent makes three improvements to the single profiles. After these improvements, the respondent completes a final paired comparison between the improved profile and a palliative one. Respondents may find the task of improving a child's health to be more engaging than choosing between two diverse outcomes.

2.3 Experimental design

A preliminary experimental design has been completed for both elicitation exercises using a three-step approach: 1) generation of a design for the paired comparison task and 2) selection of pairs for the first and third part of the kaizen task and 3) selection of profiles for the second part of the kaizen task.

Our preliminary design has employed a *D-efficient* design to identify the combination of pairs to present in the paired comparison [18]. This is a procedure for generating choice tasks (for respondents) in a way that maximises the statistical efficiency of the choice models that will be estimated. Several restrictions were imposed including "overlaps" in three attributes to reduce cognitive burden (similar attribute levels between pairs) and implausible combinations of outcomes. The latter combinations were identified by the CSOR surgical team and included:

a. Reject scenarios in which quality of life is good, the child survived for less than one year, and the child underwent many operations

b. Reject scenarios in which the child underwent some minor operations, but no major operations, and survived for less than 20 years

c. Reject scenarios in which the child underwent fewer than six minor operations, no major operations, and quality of life is low

d. Reject scenarios in which quality of life is good, the child survived for less than six months, and the child underwent major operations

A candidate-set was created including these restrictions and used as the initial candidates in Ngene [44]. We generated a preliminary design with 45 choice tasks divided into five blocks to which participants will be randomly allocated i.e. nine choice tasks in each block. Participants will be randomised to one of these five blocks and the order of the pair in each choice task will also be randomised.

An additional choice task was added to all blocks which serves as an “anchor”. This anchor was a palliative profile defined as having no operations, no infections, fair quality of life and a survival of one month. This anchor will be used to facilitate comparisons between paired comparison and kaizen responses and also when developing the final algorithm for CSOR. The experimental design is presented in supplementary material 2.

The experimental design for the kaizen task was constructed directly from the pairs in supplementary material 2. Given each pair, an initial profile of the kaizen task was constructed from the worst attributes found in the pair. Likewise, the four possible improvements were defined to be the best attributes found in the pair. Therefore, the preference path captured by the kaizen task should agree with the paired comparison response (i.e. the path passes through profile chosen in the paired comparison before passing through the profile not chosen in the paired comparison).

2.4 Survey instrument

The survey will be administered online and will be programmed in Oxford University servers with an open source platform. The survey will consist of an initial participant information and consent form, followed by a general welcome, three screening questions, an introduction to the research question

and description of attributes (provided in both written and short video formats). For each attribute, respondents will answer warm-up tasks to give their view on the attribute for a hypothetical condition (see supplementary material 1). This will be followed by the preference elicitations starting with the 10 paired comparisons and then the three kaizen tasks. For both tasks, participants will have the opportunity to complete a practice question. At the end of the elicitation tasks, participants will be asked three debriefing questions covering which exercise they found easier to complete, prefer to complete and easier to understand. Finally, a set of demographic questions will be collected including experience with neonatal/childhood surgical conditions, employment status and education qualifications. For health care professionals we will also ask their job title and level of professional experience with neonatal/childhood surgical conditions.

A preliminary mock survey has been completed and is presented in supplementary material 1. In developing the instrument, preliminary testing was undertaken to maximise user understanding as described in section 2.2.1.

2.5 Statistical evaluation

2.5.1 Data collection, recruitment strategy and sampling

The survey instrument will be completed by 1) a sample of parents of children with a surgical condition, 2) participants who had treatment for a surgical condition as a baby or a child, 3) health professionals caring for those who undergo surgery in childhood and 4) members of the general public. Main data collection will commence in October 2021.

We will first collect preferences from the first three groups as funding has been secured and ethical approval has been obtained. Recruitment materials will be distributed via existing contacts e.g. by our PAG, by the project's 'experts by experience', and by the project's healthcare professional team members; registers and mailing lists of support groups, charities and professional groups/bodies; and open advertising through support groups, charities and professional groups/bodies' communication channels e.g. Twitter, Facebook, e-newsletters, and websites. Distribution to health professionals will be via professional bodies. We will also include information on our project website and Twitter account, and advertise via Facebook to share the opportunity as widely as possible. These

recruitment strategies have been successfully used in previous quantitative and qualitative studies [7, 14, 45-47].

We will use an online panel company to invite adult members of the general public to complete the survey. We will use quotas and a target recruitment strategy to ensure the sample is representative of the UK general population in terms of gender, age, social grade and nation.

In this study we aim to collect 200 responses from parents and individuals with a surgical condition and 200 responses from health care professionals (total of 400) over a three-month period. We are also aiming to collect 400 responses from members of the general public. This is based on typical sample sizes in the health literature and on simple minimum sample size principles [48]. Since there are no prior studies, it is not possible to obtain prior values for accurate power calculations. However, we will conduct a pilot study of around 80 individuals to assess whether our choice models will have sufficient power to detect significant differences.

The pilot study will also be used to assess the feasibility of the survey instrument in terms of finding programming errors and the process of data capture. Participants will all be recruited from the UK but if we encounter issues with recruitment in this setting, preferences from participants in high-income Western countries will also be collected.

2.5.2 Data analysis

In a primary analyses, response data will be analysed using a multinomial logistic model with individual-clustered standard errors. A heteroskedastic multinomial logit will investigate the impact of survey completion time on preferences. Latent class models will assess deterministic (individual characteristics) and random preference heterogeneity.

We will test the following hypotheses:

1. Coefficients are logically consistent and with expected directions.
2. The coefficient for the anchor scenario is negative.

3. Decreasing marginal utility for quantitative attributes i.e. larger utility decrements associated to movements from level 0 to level 1 than movements from level 3 to level 4.

4. Survival matters more if child lives in good quality of life and survival matters less if child lives in poor quality of life.

5. Reductions in major planned or emergency operations matter more than reductions in minor or emergency operations.

6. We will observe differences among preferences from the different types of participants (e.g. parents versus health care professionals) but not necessarily between elicitation tasks.

Each type of participant (parents, people who were treated for a surgical condition, health care professionals and members of the general public) will have completed the paired comparison and kaizen tasks. Therefore, eight sets of preference data will be available for analysis. We will compare preferences between types of respondent within each elicitation tasks using two approaches. First, latent scale values will be rescaled using the coefficient for the anchor scenario and predicted choice probabilities for types of respondent compared using mean square and absolute errors. Second, we will examine the relative attribute importance (RAI) scores by attribute. This involves estimating the utility range for each attribute and applying an attribute-based normalisation to enable comparisons [49]. A similar approach will be used to compare preferences between elicitation tasks.

The decision about which preferences to use in the final algorithm for CSOR will be made by the CSOR Co-investigator Group based on the results of the statistical analysis, feedback from participants, and the face validity of the preferences obtained.

For the final selected model with rescaled coefficients, we will predict the distribution of utilities of all possible combinations of attribute and levels. This distribution will be used to determine the likelihood of a combination to be considered successful or unsuccessful using a traffic light system: green area (high chance to be successful), amber area (uncertainty about success) and red area (not successful). The external validity of this algorithm will be evaluated in a separate study.

This study is expected to be completed by December 2022.

2.6 Ethics and dissemination

2.6.1 Ethical considerations

Ethics approval to conduct this study to administer the survey to parents, individuals who had treatment for a surgical condition as a baby or a child and health care professionals caring for children with a surgical condition has been obtained from the Medical Sciences Inter-Divisional Research Ethics Committee (IDREC) at the University of Oxford (R59631/RE001-03). Informed consent will be obtained for all participants at the start of the survey.

2.6.2 Dissemination

We will disseminate all of our results in peer-review publications and scientific presentations. A lay summary of the findings will be created using our PAG and circulated to parent support networks and the British Association of Paediatric Surgeons, via social media and on the project website.

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Footnotes

Author's contributions: OR-A and MK developed the original idea for the study; OR-A, JB, BC, BA and MK were responsible for the study design. OR-A, JB, BA and GA conducted the formative research component informing the development of attributes and levels for the descriptive system. JB, BC and OR-A carried out the experimental design. OR-A and BC implemented the online survey instrument. OR-A drafted the manuscript; all authors revised and approved the final manuscript.

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Figure 1: A framework for discrete choice experiments

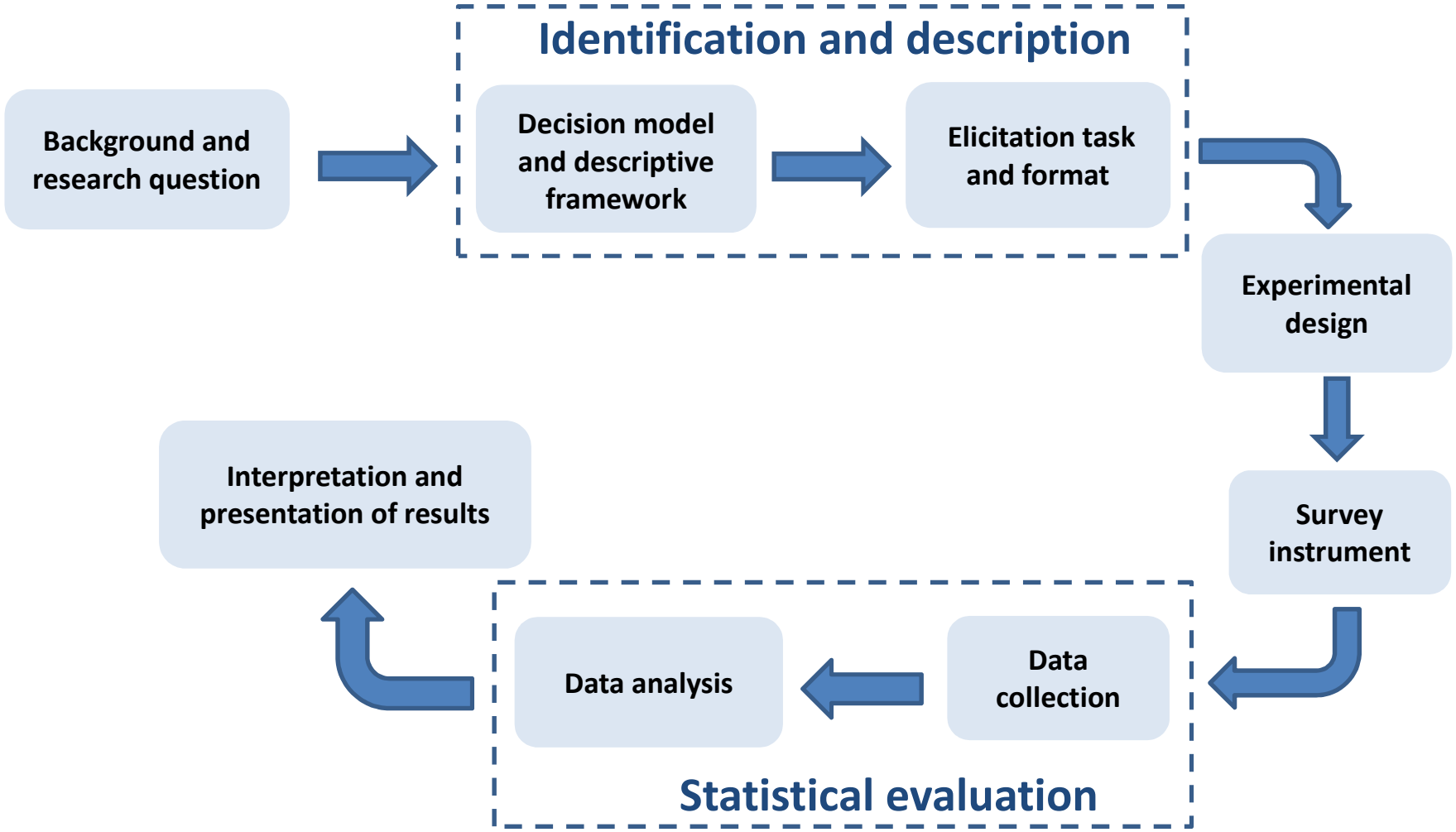

Table 1: Summary of identified core outcomes in neonatal conditions

Category	Core outcome	Included in core outcome set?			
		Hirschsprung's Disease	Gastroschisis	Neonatal care	Appendicitis
Survival	Survival	x	x	x	x
Quality of life	Quality of life	x	x	x	x
	Psychological stress	x			x
	Time away from full activity				x
Adverse events	Unplanned reoperation	x			x
	Number of operations		x		
	Severe gastrointestinal complication		x		
	Retinopathy of prematurity			x	
	Chronic lung disease			x	
	Bowel obstruction				x
	Readmission				x
	Length of hospital stay				x
	Significant infection		x	x	
	Hirschsprung's Associated Enterocolitis	x			
	Necrotising enterocolitis			x	
	Wound infection				x
	Wound complication				x
	Intra-abdominal abscess				x
Condition specific	Faecal incontinence	x			
	Bowel function score	x			
	Voluntary bowel movements	x			
	Urinary incontinence	x			
	Permanent stoma	x			
	Growth		x		
	Time on parenteral nutrition		x		
	Liver disease		x		
	Brain injury on imaging			x	
	Motor/cognitive/visual/hearing ability			x	
	Antibiotic failure				x
	Negative appendicectomy				x
	Recurrent appendicitis				x

Table 2: Study descriptive framework

Attributes	**Attribute Levels**
P*lanned major* operations related to the condition	- No planned major operations - One planned major operation - Two planned major operations - Six planned major operations
P*lanned minor* operations related to the condition	- No planned minor operations - One planned minor operation - Two planned minor operations - Six planned minor operations
U*nplanned major* operations related to the condition	- No unplanned major operations - One unplanned major operation - Two unplanned major operations - Six unplanned major operations
Infections treated in hospital	- No infections treated in hospital - One infection treated in hospital - Two infections treated in hospital - Six infections treated in hospital
Child's quality of life	- Good quality of life - Fair quality of life - Poor quality of life
How long the child survived after their diagnosis	- More than twenty years, without any expectation that their surgical condition would shorten their life expectancy - Twenty years - Five years - One year - Six months - One month

Study Title: The Children's Surgery Outcome Reporting Research Database

Internal Reference Number / Short title: CSOR Research Database

Ethics Ref: TBC

IRAS Project ID: TBC 302622

Date and Version No: Version 1.0, 9th August 2022

Chief Investigator: Professor Marian Knight, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford

Investigators: Professor Simon Kenny, Alder Hey Children's Hospital

Mr Benjamin Allin, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford

Associate Professor Nigel Hall, University of Southampton

Dr Lisa Hinton, University of Cambridge

Mr Nicholas Lansdale, Royal Manchester Children's Hospital

Ms Anna Long, Cambridge University Hospitals NHS Foundation Trust

Mr Charles Opondo, London School of Hygiene and Tropical Medicine

Associate Professor Oliver Rivero-Arias, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford

Ms Joanne Shepherd, Parent

Data Controller University of Oxford

Data Custodian Dr Michael Lay
Clinical Trials Service Unit
Richard Doll Building, Old Road Campus
Roosevelt Drive, Headington, Oxford
OX3 7LF
michael.lay@ndph.ox.ac.uk

Information Guardian	Professor Marian Knight, University of Oxford
Caldicott Guardian	Dr Alastair Moore Acting Caldicott Guardian Level 3, Academic Centre John Radcliffe Hospital Headley Way Headington Oxford OX3 9DU caldicott.guardian@ouh.nhs.uk
Sponsor:	University of Oxford Research Governance, Ethics and Assurance Joint Research Office 1st Floor Boundary Brook House Churchill Drive, Headington, Oxford OX3 7LQ ctrg@admin.ox.ac.uk +44 (0) 1865 289885
Funder:	National Institute for Health Research
Chief Investigator Signature:	The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

The study team have no conflicts of interest to declare

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1. KEY CONTACTS

Chief Investigator	Professor Marian Knight, marian.knight@npeu.ox.ac.uk, 01865289727
Sponsor	University of Oxford Research Governance, Ethics & Assurance (RGEA)Joint Research Office 1st Floor Boundary Brook House Churchill Drive, Headington, Oxford OX3 7LQ ctrg@admin.ox.ac.uk +44 (0) 1865 616480
Funder(s)	National Institute for Health Research
Statistician	Mr Charles Opondo, Charles.opondo@npeu.ox.ac.uk
Committees	CSOR Research Database Steering Committee, Chair Professor Marian Knight, marian.knight@npeu.ox.ac.uk, 01865289727

2. LAY SUMMARY

There is currently significant variation in the way children with a range of surgical conditions are managed. Examples of variation include the age or weight at which a planned operation is carried out, the type of operation a child gets, and how quickly they are allowed to start feeding after an operation. At the moment, it is not clear which elements of variation affect how successful a child's treatment is, and which elements do not. The aim of the Children's Surgery Outcome Reporting (CSOR) Research Database is to combine information from three different sources in order to help clinicians understand how successfully their hospitals are treating children with a range of surgical conditions. The three sources of information are: information collected directly from the child's health record; information from nationally held routinely collected sources of data; and information collected from the child's parents.

In order to reliably understand what the best treatments are, it is important that information is collected about as large and representative a sample of children as possible. If information is only collected about a few children being treated, the results may be misleading. Therefore, the first two sources of information (that from the child's health record and that from nationally held routinely collected sources of data) will be collected about all eligible children without seeking consent from their parents. This collection and utilisation is conducted under Confidentiality Advisory Group (CAG) section 251 approvals in England [insert CAG reference] and equivalent Public Benefit and Privacy Panel for Health and Social Care (PBPP) approvals in Scotland [insert PBPP reference] under the legal principle of conducting research in the public interest. CAG and PBPP are special approvals given to use confidential patient information in a way that is in the public interest but cannot be carried out if consent is sought. Parents of all eligible children will however also be invited to provide information relating to their child's quality of life (the third source of data we are collecting and linking), as it is known that this is very important in deciding how successful a child's treatment has been. When children turn 16 years of age, they will be asked to confirm whether they wish to continue providing quality of life data. Information we collect about a child's quality of life will be linked to the health information about the child, in order to build a complete picture of how successfully they were treated in hospital. The data collected in the CSOR Research Database will be used to provide hospitals with feedback on how successfully they are treating children. Additionally, independent researchers will be able to apply to use the data to answer clinically important questions. All analyses will be carried out on pseudonymised data, and no children will be identifiable from the information that is analysed.

Periodically, an evaluation exercise will take place to determine whether running the CSOR Research Database and providing feedback of information to hospitals is helping to improve how successfully children with a range of surgical conditions are being treated. This process will involve a combination of data analysis and also interviews with parents and clinicians. Approvals for the full scope of this process evaluation will be submitted in an amendment to the REC application.

3. SYNOPSIS

Study Title	The Children's Surgery Outcome Reporting research database
Internal ref. no. / short title	CSOR research database
Study Participants	Children diagnosed with any of the following six conditions: 1. Hirschsprung's disease 2. Oesophageal atresia 3. Gastroschisis 4. Necrotising enterocolitis 5. Posterior urethral valves 6. Congenital diaphragmatic hernia and admitted to any of the participating sites
Sample Size	1000
Planned Approval period	01 September 2022 - 30 April 2025

4. ABBREVIATIONS

CI	Chief Investigator
CAG	Confidentiality Advisory Group
CDH	Congenital Diaphragmatic Hernia
CHI	Community Health Index Number
CRF	Case Report Form
CSOR	Children's Surgery Outcome Reporting
DCE	Discrete Choice Experiment
EOR	Electronic Operative Record
EPR	Electronic Patient Record
GCP	Good Clinical Practice
GP	General Practitioner
HD	Hirschsprung's disease
HEI	Hospital Episodes Information
HES	Hospital Episodes Statistics
HRA	Health Research Authority
HSCN	Health and Social Care Network
ISD	Information Services Division
ICF	Informed Consent Form
NEC	Necrotising Enterocolitis
NHS	National Health Service
OA	Oesophageal Atresia
PBPP	Public Benefit and Privacy Panel for Health and Social Care in Scotland
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PUV	Posterior Urethral Valves
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RES	Research Ethics Service
RGEA	Research Governance, Ethics & Assurance Team
SEFT	Secure Electronic File Transfer
SEIQoL-DW	Schedule for the Evaluation of the Individual Quality of Life-Direct Weighting

SMR	Scottish Morbidity Record
SOP	Standard Operating Procedure
SUS	Secondary Uses Service
UDH	University Data Holding

5. BACKGROUND AND RATIONALE

In England and Scotland there are currently 24 Trusts/Health Boards commissioned to provide *specialised surgery in children* (Appendix B). *Specialised surgery in children* includes:

1. Management of rare surgical conditions in children
2. Provision of specified specialised surgical procedures during childhood
3. Surgery in neonates
4. Surgical management or procedures for more common paediatric surgical conditions when a child requires specialist pre-operative, anaesthetic or post-operative care (Simple surgical procedures in children with complex medical needs).

Many of the conditions falling under the remit of *specialised surgery in children* commissioning affect only a few hundred children in England and Scotland each year, and what little is known about these children's long-term health and wellbeing suggests that even after treatment, they have significant ongoing healthcare needs[1-7]. Widespread variation in management of children with these conditions currently occurs[1-6], but due to the rarity of the conditions, it has not to date been possible to identify how much of this variation is unwarranted or associated with variation in outcome. To identify unwarranted variation in management and outcome between centres providing *specialised surgery in children* it is necessary to develop mechanisms that will:

1. Collect accurate, unbiased data about children treated in individual centres
2. Combine data from children with different conditions in a way that enables meaningful outcomes analysis
3. Enable adjustment for case-mix factors affecting centres' outcomes

The CSOR research database will be established at the University of Oxford to collect the data required for identifying unwarranted variation in management and outcome between centres providing specialised surgery in children. The database will act as a repository for specific data items from three sources of data relating to children with a condition falling under the remit of *specialised surgery in children* commissioning. These three sources of data are:

1. Data collected in hospitals' electronic patient record systems, including through the use of standardised, structured, electronic operative records
2. Hospital Episodes Information including Hospital Episodes Statistics (HES), Secondary Uses Services (SUS) data, and Scottish Morbidity Record (SMR) data.
3. Data collected annually from the child or their parent/guardian about the child's quality of life

Amalgamation of data collected from these three sources will enable accurate understanding of the characteristics of the child (for example their disease severity) that may affect their outcome, elements of the child's management that may affect their outcome, and whether the outcome of the child's treatment should be considered as successful or unsuccessful at defined time-points. Case reporting and clinical data collection processes will be automated to maximise case ascertainment and prevent an additional burden being placed on clinicians' time. These are both

factors that have limited success of previous attempts at collecting data relating to children treated for surgical conditions[1-12].

In order to reliably determine whether unwarranted variation and management exists, it is essential to collect health data on all children born with any of the conditions included in CSOR. If data on any children are missing, whether hospitals are treating children successfully cannot be robustly compared. For this reason, we have obtained special permission through the Confidentiality Advisory Group at the Health Research Authority in England [insert CAG reference number] and the equivalent Public Benefit and Privacy Panel for Health and Social Care (PBPP) approvals in Scotland [insert PBPP reference] for participants to be consented by members of the research team, not the clinical team, and to collect health information about all eligible babies without seeking consent, under the legal principle of conducting research in the public interest.

6. OBJECTIVES

6.1. Primary objective:

To establish a research database comprising three linked sources of data about children with specific surgical conditions that will provide a valuable resource for identifying unwarranted variation in practice and for the conduct of approved research.

6.2. Secondary objective:

To assess whether feedback to hospitals of data from the CSOR Research Database has an impact on outcomes. This assessment will take place in a five yearly process evaluation. An overview of this has been included within this protocol and associated REC/CAG application, but approvals for the full scope of the evaluation will be handled in a subsequent amendment. Please see the section 9.16 for more detail about the process evaluation study.

7. GOVERNANCE

The CSOR Research Database will be governed by Nuffield Department of Population Health policies and procedures. Access will be provided to research data for research projects by bona fide researchers. Requests for sharing of pseudonymised data will be considered by the CSOR Research Database Steering Committee. The CSOR database is held in the University of Oxford. Ultimate responsibility for governance and management of the CSOR Research Database is held by the Nuffield Department of Population Health Information Systems and Governance Officer and for access decisions is held by designated CSOR Research Database Steering Committee staff. The database is held in the University of Oxford and the Chief Investigator (CI) is Professor Marian Knight. Full details of the governance procedures for access to the data in the CSOR Research Database are given in the attached Data Access Policy. Key points include:

7.1. Requests for anonymised research data

- Researchers must complete the data access request form and specify the required data fields
- The CSOR Research Database staff will confirm requesters' research capacity/bona fides
- Responsibility for decisions on access to CSOR data is held by designated CSOR Research Database Steering Committee members
- Sharing of data with researchers will be subject to the agreements outlined in the attached CSOR data access agreement form/policy
- All data provided to researchers will be anonymised. Datasets are provided using project-specific CSOR IDs so that each dataset provided cannot be linked to any other by recipients.
- Data released are at the minimum possible level of detail to minimise risk of reidentification (e.g. year of birth, rather than full date of birth).

7.2. Requests for data for re-contact about other studies

- Responsibility for decisions on access to CSOR Research Database participants who have consented to contact about future research studies is held by designated CSOR Research Database Steering Committee members.
- The CSOR Research Database staff will confirm requesters' research capacity/bona fides and researchers must register their study online. To be considered, studies need to:
    - Have finalised a protocol and gained research ethical approval,
    - Have achieved full funding or have proof there will be funding contingent on CSOR Research Database approval
    - Fall within the remit of the CSOR Research Database as detailed in the CSOR Research Database data access request form/policy.
- Potentially suitable participants for studies that apply to the CSOR Research Database will be identified by algorithms within the CSOR Research Database using criteria provided in the application.
- When a participant is identified as potentially suitable for a study, an invitation email (or letter, if the parent does not use email) will be distributed to the parents/guardians of the identified participant. This invitation will contain the contact details of the recruiting researcher, so parents/guardians can contact them if they wish to take part in the research. No identifiable personal data will be shared with an external body without clear consent to do so from the individual.
- Sharing of data with researchers will be subject to the agreements outlined in the attached CSOR Research Database data access agreement form.

8. PURPOSE OF DATABASE

8.1. Overview of design

The CSOR system will comprise one data holding (University) and a separate data processing server (NHS).

8.1.1. University Data Holding:

This will be an SQL database held on a dedicated secure server at the University of Oxford, and subject to Nuffield Department of Population Health Governance policies. The University data holding will be comprised of five separate tables. There will be a primary key: Foreign key relationship between the tables, with the parent and survey tables being linked with a one: many relationship.

The five tables are:

1. **Centre** – This table will comprise data relating to the data collection centres and the reporting clinicians in that site. Identifiable.
2. **Participants** – This table will comprise data relating to parents of potentially eligible children and those children. The data collected will include personal information of the child, such as NHS/CHI number, name and date of birth, and personal information (name) and contact details (phone number, address and email address) of the child's parent or guardian. These data will either be entered directly into the database by site staff using a web/app based portal, or will be collected via HES/EPR, and transferred as per section 9.5. Identifiable.
3. **Parent** – This table will serve as an editable copy of the participant table. This will allow updating of parent information by members of the research team, whilst maintaining integrity of the originally entered data. Identifiable.
4. **Survey** – This table will comprise The Schedule for the Evaluation of Individual Quality of Life – Direct Weighting (SEIQoL-DW) data entered by parents. Pseudonymised.
5. **Health** – This table will comprise pseudonymised data exported from the NHS data processing servers.

8.1.2. NHS data processing server:

The NHS data processing server will act as the server within the secure HSCN network on which linkage and pseudonymisation/encryption of identifiable data will occur prior to export to the Health table of the University Data Holding.

8.2. Database description

8.2.1. Overview of data held

The CSOR database will hold data relating to children treated for necrotising enterocolitis (NEC), Hirschsprung's disease (HD), gastroschisis, posterior urethral valves (PUV), congenital diaphragmatic hernia (CDH) and oesophageal atresia (OA) in any of the participating sites from the date of inception of the database onwards. This is anticipated to represent approximately 325 new infants per year.

8.2.2. Summary of data variables held

University Data Holding, Centre Table:

1. Centre ID
2. Centre Name
3. Centre Address
4. Status of data collection centres
5. Names and job titles of reporting surgeons
6. Contact email address for each surgeon
7. Withdrawn date
8. Start date

University Data Holding, Participant Table:

1. CSOR ID
2. Centre ID
3. Child's NHS/CHI number
4. Child's name
5. Child's surgical condition
6. Child's date of birth
7. Child's address
8. Parent/Guardians name
9. Parent/Guardian's telephone number
10. Parent email address
11. Name of clinician registering the child
12. Email address of clinician registering the child
13. Date case registered
14. Confirmed case indicator

University Data Holding, Parent Table:

1. SEIQoL-DW Form ID
2. CSOR ID
3. Child's name
4. Child's surgical condition
5. Parent email address
6. Child's date of birth
7. Child's address
8. Parent's phone number
9. Date consent obtained to retain contact variables for the purposes of collecting annual quality of life data
10. Variable indicating whether consent has been obtained for contact about future studies
11. Date last data collection form completed,
12. Age of child when last data collection form completed

13. Date next data collection form due
14. Age of child when next data collection form due
15. Date and time SMS reminders sent
16. Date and time and email reminders sent
17. Data and time of telephone reminders
18. Number of consecutive data collection forms not completed,
19. Variable to flag parents for SMS, email, and postal notification of impending withdrawal from study
20. Variable to flag loss to follow-up/withdrawal from study

University Data Holding, Survey Table

1. Survey ID
2. SEIQoL-DW Form ID
3. Survey Token
4. Token valid until
5. Sent date
6. [SubmittedDate]
7. Relationship of person completing the questionnaire to the child
8. SEIQol-DW Questions
    a. [ImportantAspect1]
    b. [ImportantAspect2]
    c. [ImportantAspect3]
    d. [ImportantAspect4]
    e. [ImportantAspect5]
    f. [RateYourChild1]
    g. [RateYourChild2]
    h. [RateYourChild3]
    i. [RateYourChild4]
    j. [RateYourChild5]
    k. [OverallQualityOfLife]
    l. [QualityOfLife1]
    m. [QualityOfLife2]
    n. [QualityOfLife3]
    o. [QualityOfLife4]
    p. [QualityOfLife5]

University Data Holding, Health Table:

1. Child's CSOR ID,
2. Condition specific, case-mix adjustment and outcome data points as described in the attached CSOR Data Dictionary

NHS Data Processing Server:

1. Raw Comma Separate Values (CSV) files containing
    a. Baseline Data
    b. HES/SUS/SMR Case Data
    c. Outcomes Data
2. Central Case List containing NHS Number, Date of Birth, CSOR IDs and case confirmation attribute
3. Encryption key

8.2.3. Review of collected data

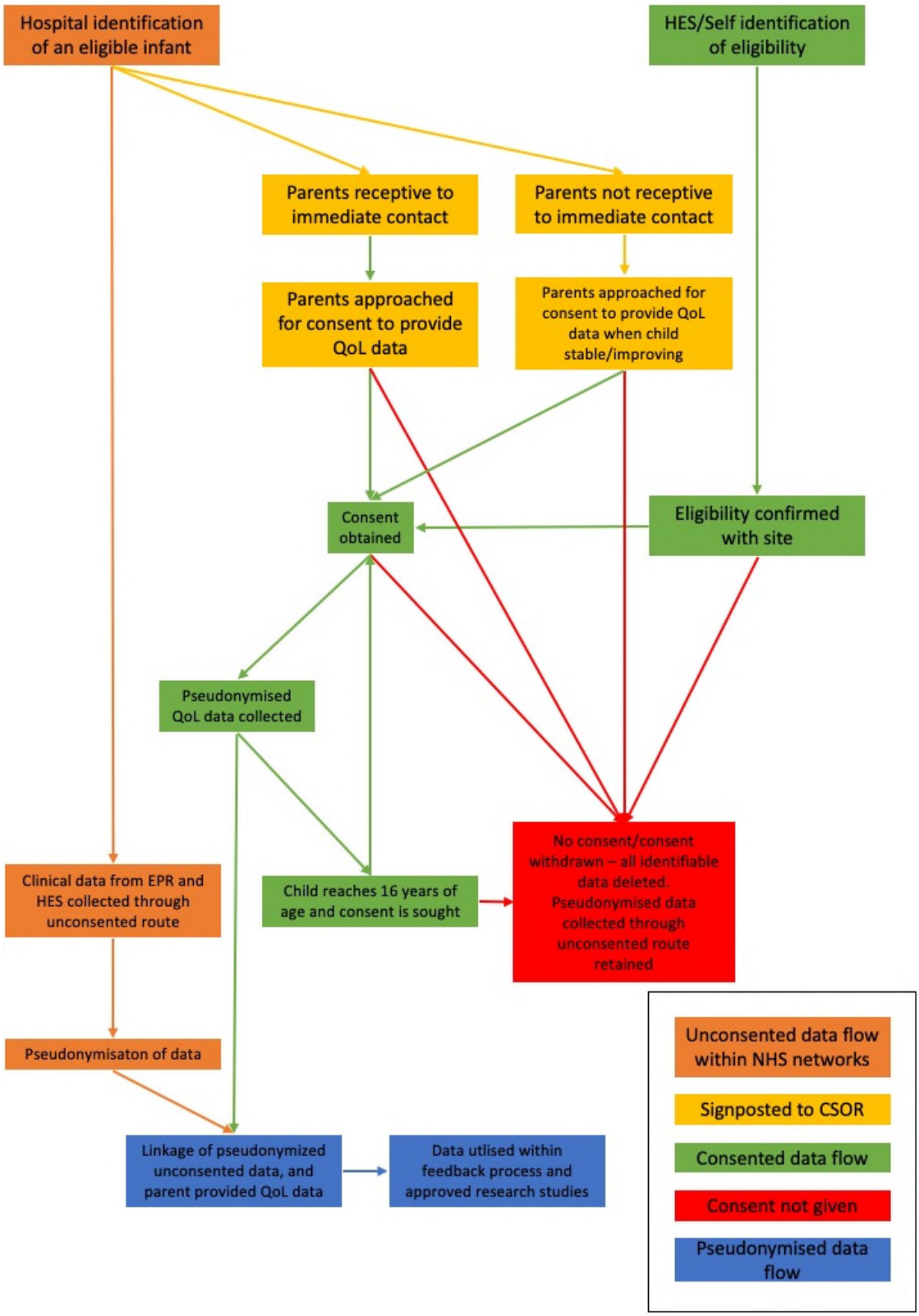
At each meeting of the CSOR Research Database Steering Committee, the data that are received and retained will be reviewed to ensure that they remain the minimum required to achieve the aims of the CSOR Research Database. Following approval from the CSOR Research Database Steering Committee, the Data Dictionary will be updated as required and circulated to data collection centres.

8.3. Eligibility for inclusion

All children who are treated for oesophageal atresia, PUV, gastroschisis, HD, NEC, or CDH in one of the participating data collection centres after the inception of the CSOR database will be eligible for inclusion in the database.

9. PROCEDURES

Figure 1 – CSOR Research Database Participation Pathway



9.1. Case identification

Cases will be identified through four routes:

1. Completion of a relevant structured electronic operative record by surgeons at any of the participating data collection centres, resulting in an EPR 'flag' highlighting that infant's data for extraction.
2. Presence of a relevant problem/diagnosis code on an infant's EPR, resulting in creation of an EPR 'flag' highlighting the infant's data for extraction.
3. A monthly extract of Hospital Episodes Information from HES/SUS/SMR, providing identifiers for all children treated in any of the participating data collection centres over the past month who have a diagnostic or operation code pertaining to one of the CSOR conditions. Subject to confirmation of eligibility by the relevant data collection centre. Appropriate identifiers (e.g. NHS/CHI number, and date of birth) will be shared with data collection centre staff to enable confirmation of eligibility.
4. Parental self-registration through the CSOR parent portal. Subject to confirmation of eligibility by the relevant data collection centre. Appropriate identifiers (e.g. NHS/CHI number, name, and date of birth) will be shared with data collection centre staff to enable confirmation of eligibility.

Data relating to all eligible infants will be collected through the unconsented data collection route (section 9.2). In addition, consent will be sought from parents of eligible infants to provide data relating to their child's quality of life and linkage of these data to that which has been collected through the unconsented data collection route.

9.2. Unconsented data collection

On a monthly basis, relevant data for eligible infants, as described in the CSOR Data Dictionary, will be extracted from each hospital's EPR system and on a quarterly basis from HES/SUS/SMR. These data will be linked and pseudonymised on the NHS Data Processing Server at Oxford University Hospitals NHS Foundation Trust. Following pseudonymisation, these data will be exported to the Health Table in the University Data Holding. These data will be collected without the requirement for consent following Confidentiality Advisory Group Section 251 approvals in England, and equivalent PBPP approvals in Scotland, under the legal principle of conducting research in the public interest.

9.3. Consent – signposting to CSOR Research Database

At the time of identification of an eligible infant, local staff will signpost the infant's parents to the existence of the CSOR Research Database. Materials including a list of talking points for data collection centre staff, posters, videos, the participant information leaflet, and an 'Introduction to the CSOR Research Database' sheet have been developed to aid this process. No consent, either for sharing of contact details, or for participation in the CSOR Research Database will be sought by data collection centre staff. This is because, feedback from our Parent Advisory Group, which consists of parents of children who have had early surgery, as well as charity/support group

representatives, highlighted that during the period in which parents first found out about their child's diagnosis, most would want to know that the CSOR Research Database existed, but that some would find it difficult to take in a large amount of information about it in one go. Working with the parental advisory group, the Introduction to the CSOR Research Database sheet was therefore designed to be used to give information to parents where data collection centre staff felt the parents would want to know more about the existence of the CSOR Research Database, but where they were likely to not be able to take in large amount of information due to the severity of their child's illness. It is intended that this information sheet would be supplemented with the full participant information leaflet at a point where the parents were more readily able to take in the full study information required to give informed consent to participate. Consent would then be sought to participate as per sections 9.6 and 9.7. See section 9.9 for the justification of the consent process being used.

9.4. Consent - retrieving contact details for eligible parents

Local staff will provide the central CSOR Research Database team with contact details for the parents of eligible infants via direct entry into the University Data Holding Participant table using a web-based interface. In the same process, local staff will also indicate whether the parents are likely to be receptive at that point to discussion of providing parent reported quality of life data for the child.

9.5. Discrepancy resolution and case ascertainment checking

On a monthly basis, NHS/CHI number, name, date of birth, primary condition, parental names, telephone numbers, email addresses, postal address, date of admission and treating hospital will be extracted from each hospital's EPR system for all eligible children. The same data will be extracted from HES/SUS/SMR for all infants with a diagnostic or operation code relating to one of the target conditions and who were treated in one of the participating hospitals in the past month. These data will remain within the NHS HSCN, and in an automated process, will be cross-checked against one another, and against the identifiers and contact details of children whose data are already held in the database. Where discrepancies are identified, the NHS number and date of birth of discrepant cases will be securely transferred in encrypted format via Rest API/https from the NHS Data Processing Server to the Parent/Participant tables of the UDH. Local data collection centre staff will be contacted and asked to confirm as necessary an infant's eligibility, their correct contact details, whether the child's parents are likely to be receptive at that point to discussion of providing parent reported quality of life data for the child, and whether or not the child's parents had previously received information about the existence of the CSOR research database. Following confirmation that contact details are correct and correspond to an eligible infant, the parental contact details will be retrieved from the NHS Data Processing Server and transferred to the Participant/Parent Tables of the University Data Holding in encrypted format via Rest API/https. Where local staff indicate that the parents have previously been informed about the existence of the CSOR research database, the standard consent process will be followed (see sections 9.6 and 9.7). Where data collection centre staff indicate that parents have not previously been informed about the existence of the CSOR research database, the CSOR

Research Database team will send the parents the introduction to CSOR leaflet, with the standard consent process beginning one week later (see sections 9.6 and 9.7). Where data collection centre staff indicate that an identified child is not eligible to participate, all details of that child will be removed from the UDH, and the NHS Data Processing Server, except for the child's NHS number and date of birth which will be retained in the NHS Data Processing Server for the purposes of preventing further review of the child's eligibility should their details be received from HES/EPR again.

9.6. Consent – Participants identified by data collection centres/national data

When registering a child, if data collection centre staff indicate that parents are likely to be receptive at that point to discussion of providing parent reported quality of life data for their child, then parents will be sent links to the CSOR Participant Information Leaflet (PIL) and Consent Form in electronic (text and email) and written format. Consent will be taken through an online form, with parents receiving information on how to contact appropriate research staff if they have questions or wish to discuss further. This approach to consent is being taken, as opposed to an active consenting by a member of the research team, as the study is low risk, involving data collection with no intervention or alteration to patient care. Parents will be emailed a copy of the completed consent form for their records. Consent will be sought to:

- Contact them for the purposes of obtaining annual quality of life data relating to their child and linking this data to clinical data obtained from data collection centres' EPR systems.
- Review relevant sources (e.g. the NHS spine) for the purposes of ensuring contact details are kept up to date, and preventing contact with parents if their child has died
- Contact them about participation in future studies

Where an eligible child has been identified and it has been indicated that currently the parents are unlikely to be receptive to discussions about providing parent reported quality of life data, the identifying data collection centre will be contacted one week after identification of the infant, and monthly thereafter, to report whether the infant's clinical condition is improving, unchanged, or deteriorating. If the infant's condition is unchanged or improving, the parents will be sent the links to the PIL and consent form.

If parents have have not submitted a consent form (either consenting, or actively opting out of the study), reminders will be sent 7 days, 28 days, 6 months and one-year after the PIL and consent form were sent. At 7 days, reminders will be sent via text and email. At the remainder of the time points, consent information will also be sent via post, and attempts to contact will be made via telephone. Prior to contact being attempted at 28 days, 6 months and one year, sources will be reviewed to ensure that the infant has not died. No contact will be made with parents of children who have died.

If no response is received within one month of the one-year reminder, the infant's and parent's identifiable data will be removed entirely from the University Data Holding. Any pseudonymised data that is held within the Health Table of the University Data Holding will be retained.

This approach has been developed following focus group work with parents of children with surgical conditions, and subsequent review and discussion of the approach and consent process with a Parent Advisory Group established at the National Perinatal Epidemiology Unit, University of Oxford. The group felt that the approach of chasing consent four times was an appropriate balance between ensuring that those who wanted to participate were given sufficient opportunity to do so, whilst those who did not were not overly burdened. Their feedback also determined the time points to use for chasing up consent and the methods we will use to contact parents. The parents explained that the lives of parents of children with surgical conditions were usually busy and often chaotic, and therefore not responding to a request to participate in research such as the CSOR Research Database was usually due to having forgotten to reply rather than actively deciding not to participate.

9.7. Consent – Self-Identification

Parents who have seen the CSOR Research Database advertised, believe their child is eligible, and wish to participate will be able to review the PIL and consent to provide parent reported quality of life data to the CSOR Research Database by visiting the CSOR website and Parent Portal. Self-registration will trigger a process of eligibility confirmation with data collection centre staff in the child's treating data collection centre. Where children are found to not be eligible to participate, their parents will be informed, and all data relating them will be securely deleted.

9.8. Collection of parent data

Two routes of collecting parent data will be used:

Timed data collection:

Within a month of a child reaching 28 days of age, or within a month of consenting to participate, whichever is later, parents will be contacted via email and text message and be provided with a link to complete a CSOR quality of life survey. Data will be entered via the secure CSOR parent portal. This process will be repeated at six months of age, and then annually within a month of the child's birthday. Along with each annual survey request, participants will be sent a birthday card. Reminders to complete the survey will be sent 7 days, 14 days and 21 days after the initial link was sent. At 7 and 14 days the reminders will be sent via text and email. At 21 days the reminder will additionally be sent to the parents' postal address and attempts at contact via telephone will be made. If a postal reminder is sent, parents will be asked to confirm that their contact details are up to date. With each reminder, parents will be given the option to opt out of the study if they wish to do so.

Ad hoc data collection:

Parents will additionally be able to provide data on an ad hoc basis, using a link generated through entry of their email into the CSOR Research Database parent portal. Where emails are registered within the CSOR Research Database, a link will be sent to the registered email address.

In order to facilitate ad hoc data collection, particularly for parents of children who have limited access to the internet, tablet devices will be provided on the neonatal wards, paediatric wards and outpatient departments of participating data collection centres, from which parents of eligible children can access the CSOR parent portal.

9.9. Rationale for data collection and parental consenting processes (Rationale for a Confidentiality Advisory Group application)

In order to fulfil the aims and objectives of the CSOR Research Database, it is necessary to collect two sets of information without prior consent from parents. Approvals from the Confidentiality Advisory Group and the Public Benefit and Privacy Panel for Health and Social Care in Scotland have therefore been sought. The two areas of data that will be received without consent are:

1) Research data from hospitals and national sources

2) Parental contact details for the purposes of obtaining consent to provide quality of life data to the CSOR research database

9.9.1. Research Data from Hospitals:

In order to reliably ascertain whether there is unwarranted variation in management and outcome between participating hospitals, it is essential that data are collected for a complete cohort of children at each data collection centre. In order to ensure this, the data that will be extracted from participating hospitals' Electronic Patient Record Systems, and the data that will be collected from National Hospital Episodes Information (HES/SUS/ISD/SMR), will be collected without consent. This approach is necessary for two reasons:

1) It strengthens stakeholder trust in the results of the analysis, as by ensuring data are collected for a complete set of infants, it removes the possibility that a high performing centres results are achieved through ‘gaming the system’, i.e. by seeking consent to provide data from parents of children with worse outcomes.
2) It maximises the completeness of the dataset, thereby ensuring that any recommendations are based upon valid, unbiased analyses

Over more than a decade of running the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System studies, in which similar data were used without consent, no complaints have been received. This includes in the situations where parents have later been contacted in relation to participation in other studies, and informed at that time that their child's data have previously been used without consent.

9.9.2. Parental contact details:

In order to maximise the benefit of the CSOR research database, it is essential that quality of life data are obtained from the largest possible sample of parents, as these data are integral to understanding how successful treatments have been. In order to ensure this, the central research team will receive contact details for parents of eligible children without consent. These details will be received in order to allow them to obtain consent from parents to participate in the CSOR research database. Contact details will be received both from direct entry by data collection centre staff, and also using automated routes from EPR systems and HES/SUS/ISD/SMR This approach is necessary for X reasons:

1) Recent paediatric surgical studies have shown that reliance on hospital staff to supply contact details for the purposes of obtaining consent results in approximately 30% of the eligible population not being approached for consent, as hospital staff have been unable to supply their contact details. This is most commonly down to a lack of time to identify the relevant contact details.
2) Members of the parental advisory group have stated that whilst they want to receive information about the existence of studies from their hospital, which will be achieved through the use of posters, and the CSOR introduction leaflet, they want the information required for consent to be provided by those who know most about the study and are best placed to answer any questions. The central research team have the most knowledge about the study and therefore will coordinate the approach for consent.
3) Hospital staff frequently do not have sufficient time to concentrate on consenting parents for participation in research. Therefore, if the consent process is co-ordinated by data collection centre staff rather than centrally, it is likely that parents who are interested in participating would not be approached to participate due to a lack of staff time.
4) By co-ordinating the consent process centrally, using automated systems that remove the need for clinician entered data, it is possible to ensure that there is a standardised process in place across the board. This therefore again removes the possibility of the system being 'gamed', and enhances stakeholder trust in the results of analyses.

In previous paediatric surgical studies where parents have been approached for consent without prior knowledge that their contact details have been shared with researchers, this has resulted in high consent rates. In a recent paediatric surgical study in which approximately 190 parents were approached by a research team without prior consent, no complaints were received about the fact that their contact details had been shared outside of their usual clinical team without prior consent.

In the CSOR Research Database, the obtained contact details will be utilised to seek consent from parents of eligible infants to provide data relating to their child's quality of life and linkage of these data to that which have been collected through the unconsented data collection route.

The contact and consent pathway that is being utilised has been based upon the results of extensive focus group work with parents of children with surgical conditions, and work with the

parental advisory group established by the National Perinatal Epidemiology Unit, which consists of over 100 parents of children with surgical conditions, charities, and support groups. The designed pathway was felt by them to achieve the appropriate balance between maximising recruitment and protecting participants privacy and information.

9.10. Removal of free text identifiable data

The SEIQoL-DW questionnaire that parents will complete requires in part on entry of free text by parents. It is possible that parents will enter identifiable information, for example the child's name, or their surgeon's name in this free text. All identifiers will be removed from the stored free text using widely available software, e.g. NLM scrubber.

9.11. Collection of data from children

From the time their child turns 10 years of age, participating parents will be sent information about the CSOR Research Database in a format that they can use to explain the study to their child. If they believe that their child is old enough to understand the questions being asked in the annual questionnaires, they will be given the opportunity for both themselves and the child to complete separate questionnaires. These materials will be submitted for REC approval by amendment closer to the relevant time.

9.12. Duration of participation

Assuming ongoing funding for the database, parents will be contacted annually to complete a CSOR data collection form up until their child's 16th birthday. However, at their child's 10th birthday, they will also be provided with information about the CSOR database in a format which is understandable to children. Parents will be asked to discuss this information with their child at the point at which they feel the child is able to understand what is being undertaken in the CSOR programme, and can use and weigh this information in reaching a decision about whether they would like information provided about themselves to the CSOR database (i.e. they have attained Gillick Competence). In line with HRA guidance, from 16 years of age, it will be presumed that the young person is capable of giving consent on their own behalf. Therefore, unless the child's parent/guardian indicates that the child lacks capacity to consent and there is an alternative arrangement for consenting in place, at this stage, consent will be sought from the young person for their ongoing participation in the CSOR Research Database. If consent is not received at this stage, then reminders will be sent as per the initial parental consenting process. If consent is not received from the young person, then their participation in the CSOR programme will terminate at that point.

9.13. Discontinuation/withdrawal

Parents will be given information on how to withdraw from the CSOR Database in the PIL. Details of what will happen to data if they choose to withdraw from the CSOR database is also outlined

in the CSOR Privacy Notice, a link to which is included in the PIL (a printed copy can also be requested).

Based upon feedback from our parent advisory group, and the results of extensive focus group work with parents of children who have undergone early surgery, parents will not be deemed to have withdrawn from the study through non-completion of questionnaires until they have missed five in a row. Prior to participants being withdrawn through non-completion of questionnaires, their parents will be sent an electronic electronic and paper version of the same information, explaining that they will shortly be withdrawn from the study, and asking them to get in touch if they wish to continue participation.

Either through directed withdrawal, or withdrawal through non-completion of the parent questionnaires, withdrawal will mean that the CSOR Research Database would no longer contact the participant but would retain and use information previously provided and would continue to utilise additional pseudonymised data received through the unconsented data collection route. This collection and utilisation would continue under CAG section 251 approvals in England and equivalent Public Benefit and Privacy Panel for Health and Social Care (PBPP) approvals in Scotland, without the requirement for consent under the legal principle of conducting research in the public interest. Participating data collection centres will screen all potential participants against the National Data Opt-Out to ensure no data is transferred to the CSOR database in these cases. In all situations where consent is withdrawn, all identifiable data would be permanently removed from the CSOR Research Database.

9.14. Safeguarding

Incidental findings are unlikely, but if any arise and raise significant concerns regarding safeguarding of the participants, then confidential advice will be sought from, and steps taken as required to notify, the relevant authority or care provider.

9.15. Data feedback interface and facilitated feedback model

Participating data collection centres will be able to access high level summaries of their data through an interactive web-based dashboard and accompanying facilitated feedback model. The experience-based co-design approaches developed by Robert & Bate[13] and used previously by the Health Experiences Research Group at the University of Oxford (lead Dr Lisa Hinton) in several projects including work in adult intensive care[14] will be adapted to develop the interface. Existing interfaces, including those developed by specialised services quality dashboards will be reviewed with focus groups of relevant clinicians, managers, commissioners and parents to understand which aspects work well and which require improvement. This information will be used to co-design a web-based interface allowing trusts to access their outcomes data and compare this to national benchmarks. Development of this interface will be an iterative process, bringing in parent perspectives, and integrating feedback from clinical and non-clinical staff within trusts. A facilitated feedback model incorporating a peer review process along the lines of the Royal College of Paediatrics and Child Health Diabetes Quality Programme – Peer Review (https://www.rcpch.ac.uk/work-we-do/quality-improvement-patient-safety/diabetes-quality-

programme/peer-review) will be developed to help trusts interrogate and understand their own data.

9.16. Process evaluation

In order to understand the impact of implementing the CSOR Research Database and feedback mechanism, a process evaluation will be conducted once data flows have been established for a minimum of three months in at least three participating data collection centres, and then repeated on a five yearly basis thereafter to understand the ongoing impact of the programme. This process is summarised below, however, the details of the evaluation will be handled within a later amendment.

For the initial process evaluation, a controlled before after study will be conducted. Data will be collected from a minimum of four participating data collection centres for a minimum of 3 months duration in order to collect baseline outcomes data and allow refinement of the case mix adjustment model. After a minimum of three months of data collection, the CSOR web interface and facilitated feedback model will then be introduced in half of the data collection centres for whom a minimum of three months baseline data have been collected. A further 6 months' data will be collected prior to implementation of the CSOR web interface and facilitated feedback model in the remaining data collection centres. Following the six months of data collection, a theory-driven process evaluation involving parents, clinicians and service managers will be undertaken to identify whether there was a positive change in attitudes and practice following implementation of the CSOR Research Database and feedback mechanism in participating data collection centres. Pre and post implementation outcomes data will also be compared in the control and intervention data collection centres to investigate whether a positive increase in the ratio of observed to expected successfully treated children was seen post implementation of the CSOR Research Database. It is anticipated that given the relatively short duration of this pilot programme, the low case numbers, and the time it will take for the impact of changing practices to be seen, it may not be possible to show improvement in this measure with statistical significance at the initial process evaluation. However, at the subsequent five yearly process evaluations, it is anticipated that sufficient data will have been collected to show statistical benefit to the CSOR Research Database.

10. STATISTICS AND ANALYSIS

10.1. Summary

It is anticipated that there will be approximately 325 infants added to the database each year. The database will be used for a variety of studies relating to children with surgical conditions. The database will also be used for recruitment to future studies. Where data requests are judged inappropriate, these will not be approved.

10.2. Principal analysis

Using numbers and proportions of those with complete data, the characteristics of infants treated in each participating data collection centre and the management strategies utilised will be described. The mean difference between a hospital's observed Treatment Success Score and their expected Treatment Success Score will also be calculated and described.

The Treatment Success Score is a score that is calculated based upon an algorithm derived from the CSOR Discrete Choice Experiment (DCE). The score takes account of the number and types of operations a child has undergone, the number of times they've been treated in hospital for an infection related to their surgical condition, their quality of life, and the length of time they have survived. The maximum score an infant can obtain is 1, which would be obtained if they underwent no operations, developed no infections, had a good quality of life, and were still alive at the outcome reporting time point. A score of 0 corresponds to an infant having an outcome considered by DCE participants to be as successful as palliation, whilst negative scores correspond to outcomes that were considered by DCE participants to be worse than palliation. An observed Treatment Success Score will be calculated for each infant based upon the outcomes data collected in the CSOR Research Database. The expected Treatment Success Score will be calculated for each infant utilising the case-mix adjustment data collected in the CSOR Research Database, and through application of a previously developed Treatment Success Score prediction model. This prediction model has will be developed based upon existing observational data and will be refined after each additional 100 cases are added to the CSOR Research Database.

10.3. Procedure for Accounting for Missing, Unused, and Spurious Data.

The ranges and distributions of quantitative variables will be examined to identify extreme or unlikely values; these will be removed from further analyses. A complete case analysis will be conducted if less than 10% of observations have missing data on at least one variable included in the case-mix adjusted model of expected outcomes. However, if more than 10% of infants have missing data on key variables, multiple imputation with chained equations of the missing values following best practice guidance will be conducted if appropriate for the pattern of missingness to assess the robustness of conclusions derived from the model based on complete cases.

11. DATA MANAGEMENT

The plans for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

11.1. The research database:

The CSOR Research Database will be held on servers on the University of Oxford and Oxford University Hospitals NHS Foundation Trust networks as described in Section 8.2, and in line with the information security and governance policies of these institutions. Documentation of the database holdings, processing of the data and data provided to requesters is the responsibility of the CI and the CSOR Research Database Administrator.

11.2. Network security

A software firewall on the host and hardware firewalls at the perimeter will provide network security. Access is limited to the IP range of University clients.

Network security will include strong encryption of data during its passage from OUH to the University of Oxford. Log on security will use industry standard authentication methods, with passwords stored and validated by OUH IT infrastructure. Access to the database itself will be restricted using role-based active directory controls.

All computers and virtual machines used by the research database team to access CSOR data will be password protected at turn on. All members of the CSOR research database team other than the patient representative(s) have NHS contracts or honorary contracts and are bound by NHS confidentiality policy and disciplinary procedures.

11.3. Server security

Physical access to servers is limited. The XNAT server has nightly security patches. Unneeded services are disabled. Logs are monitored and daily summaries are emailed to system admin.

11.4. Desktop security:

Desktop access to the CSOR Research Database is granted via virtual machine.

11.5. Data provided to requesters:

When data are requested and approved by the designated CSOR Research Database Steering Committee Staff,anonymised data tables (CSV files) will be accessed by researchers as per the CSOR Research Database Data Access Policy. Only processed data will be provided, such that there is no onward sharing of raw HES/SUS/SMR or hospital data.

11.6. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

11.7. Data Recording and Record Keeping

11.7.1. Data collection and transfer

Unconsented data will be extracted monthly, directly from hospitals EPR systems in CSV format, and transferred to the NHS Data Processing Server at OUH NHS Foundation Trust using SFTP within the secure HSCN. Unconsented HES/SUS/SMR data will be manually downloaded monthly

in CSV format from the NHS Digital Secure Electronic File Transfer environment directly onto the NHS data processing servers at OUH NHS Foundation Trust. Parent reported quality of life data will be entered directly into the Survey Table of the University Data Holding, using the CSOR Research Database Parent Portal. Data will be transferred from the NHS Data Processing Servers at OUH NHS Foundation Trust to the Health Table of the University Data Holding in CSV format via Rest API/https.

11.7.2. Data retention

- Unprocessed CSVs containing clinical information transferred from hospitals will be retained on the NHS Data Processing Servers at OUH NHS Foundation Trust for 3 years from the point of receipt.
- Data entered into the participant questionnaires will be retained for 60 years.
- Parental contact details will be retained in the Participant and Parent tables of the University Data Holding on the Nuffield Department of Population Health (University of Oxford) secure servers until the child consent process is completed following the child's 16th birthday. This will be completed at the latest by 1 month after the child's 17th birthday. Contact details for participants consented at age 16 will be retained in the Parent table of the University Data Holding on the Nuffield Department of Population Health (University of Oxford) secure servers for a period of 44 years (until the participants 60th birthday).Pseudonymised data contained within the Health Table of the University Data Holding will be retained for 60 years
- Where consent is not received from parents, all identifiable data will be removed within 13 months of being received.

12. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. All CSOR staff (including those in organisations other than the university of Oxford and Oxford University Hospitals NHS Foundation Trust) handling CSOR data will be trained in the principles of information governance and security, the Data Protection Act 2018 and the UK General Data Protection Regulation (UK GDPR). All researchers requesting access to CSOR Research Database Data or Participant contact details will be required to meet the same standards.

12.1. Study Committees

12.1.1. CSOR Research Database Steering Committee

The Steering Committee will meet six monthly with a remit to review and amend as necessary the data being collected, review applications for use of the pseudonymised research data, review the results of any completed process evaluations, including expansion to additional conditions or data collection centres, and ensure that the CSOR Research Database continues to meet its primary objective. The core membership of the Steering Committee will comprise the CI, the CSOR

Research Database programme manager, the CSOR Research Database statistician, one additional member of the central CSOR Research Database study team, and a representative of OUH NHS Foundation Trust. Additional members of the Steering Committee will then include two paediatric surgeons from participating data collection centres, one non-surgeon clinical staff from participating data collection centres, one independent clinician, a representative each of the British Association of Paediatric Surgeons, the Royal College of Paediatrics and Child Health and the Royal College of Surgeons, and two parents of children who have been treated for surgical conditions. Non-core membership will be on a rotating basis with members serving a maximum of 3 years on the committee.

12.1.2. CSOR Research Database Management Group

The Management Group will meet monthly with a remit to ensure the smooth day to day running of the CSOR Research Database. The Management Group will consist of the core members of the Steering Committee plus the CSOR Research Database programmer, and any additional project specific staff required for delivery of key components of the CSOR Research Database.

13. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. the consent process) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form.

14. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor will be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving Research Ethics Committee (REC) and the relevant NHS host organisation within seven calendar days.

Suspected personal data breaches must be reported immediately to the University of Oxford’s Data Breach Team: data.breach@admin.ox.ac.uk .

IT security related incidents (e.g. malware, hacks) to be reported to the University of Oxford’s Information Security Team: oxcert@it.ox.ac.uk .

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Participant confidentiality

The CSOR Research Database staff will ensure that the participants' anonymity is maintained. All documents will be stored securely and only accessible by CSOR Research Database staff and authorised personnel. The project will comply with the Data Protection Act, which requires data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. All CSOR Research Database staff handling CSOR Research Database data will be trained in the principles of Information Governance, the Data Protection Act 2018 and the UK General Data Protection Regulation (GDPR).

15.2. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC, host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

15.3. Declaration of Helsinki

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

15.4. Guidelines for Good Clinical Practice

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

15.5. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate REC, Confidentiality Advisory Group at the Health Research Authority in England and Privacy Panel for Health and Social Care (PBPP) in Scotland, and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.6. Transparency in Research

Research findings will be published and promoted on the CSOR Research Database website and National Perinatal Epidemiology Unit news feeds and social media channels. Parents and relatives of participants will be invited to an annual event (Parental Advisory Group) where the results of research using the CSOR Research Database, ongoing studies and plans for new studies will be presented and invited for feedback. Participants will also be asked if they would like to receive an annual newsletter with updates. Results will be submitted for presentation at appropriate congresses and for publication in appropriate peer reviewed journals. In line with the funder requirements, manuscripts arising from analyses carried out by the CSOR Research Database team will be made open access. Results of analyses carried out by the CSOR Research Database team will also feed into public facing dashboards akin to those created for children's heart surgery (https://www.childrensheartsurgery.info).

CSOR is registered on the Research Registry, where all registration details are publically available: https://www.researchregistry.com/browse-the-registry#home/registrationdetails/6025433fa415e9001b06ad55/

16. FINANCE AND INSURANCE

16.1. Funding

The CSOR Research Database is funded by the National Institute for Health Research (NIHR) Health Services and Delivery Research programme, grant number NIHR127844.

16.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

16.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

17. PUBLICATION POLICY

17.1. Publications by the CSOR Research Team

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 NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

17.2. Publications by other bona fide researchers utilising anonymised CSOR Research Database data or following contact with CSOR Research Database participants

As per the CSOR Research Database Data Access Policy, the following will apply to publications arising from third party researchers.

- Any publications resulting from the analysis of CSOR Research Database research data (or through contact of CSOR Research database participants) must acknowledge the CSOR Research Database and the National Perinatal Epidemiology Unit (see below)
- Any publications resulting from the analysis of the CSOR Research Database research data (or through contact of CSOR Research database participants) must cite the CSOR Research Database protocol paper
- A copy of or electronic link to any publication utilising the CSOR Research Database research data (or through contact of CSOR Research database participants) must be sent to CSOR@npeu.ox.ac.uk within three months of the publication date.

To acknowledge CSOR Research Database Research Data (or contact of CSOR Research database participants), the following phrase must be included in the acknowledgements:

"This work was conducted using data from the CSOR Research Database, supported by the NIHR Health Services and Delivery Research programme. The views expressed here are those of the authors and not those of the NHS, the NIHR or Department of Health. For more information about the CSOR Research Database, visit npeu.ox.ac.uk/csor."

18. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

19. ARCHIVING

Contact details will have been provided by parents with consent on the basis that we may contact them regarding future research and that we may invite them to participate in future studies. No contact will be made with parents without this being part of a study that has been subject to approval by a research ethics committee. We will not retain any contact details for parents who have chosen not to consent to participation or have withdrawn from the study. All data will be stored within a study specific database hosted on the NDPH secure servers. Parental contact details (with consent), and pseudonymised study data will be retained for minimum periods as described in section 11.7.2. All data will be stored, handled and destroyed in line with standard University of Oxford policies (https://researchdata.ox.ac.uk/university-of-oxford-policy-on-the-management-of-data-supporting-research-outputs/).

20. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / HRA submission.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).

21. APPENDIX B: LIST OF HOSPITALS COMMISSIONED TO PROVIDE SPECIALISED SURGERY IN CHILDREN IN ENGLAND AND SCOTLAND

- Addenbrooke's hospital, Cambridge
- Alder Hey Children's Hospital, Liverpool
- Birmingham Children's Hospital
- Bristol Royal Hospital for Children
- Chelsea & Westminster Hospital, London
- The Evelina Children's Hospital, London
- Great North Children's Hospital (Royal Victoria Infirmary, Newcastle)
- Great Ormond Street Hospital for Sick Children, London
- Hull Royal Infirmary
- Jenny Lind Children's Hospital (Norfolk & Norwich University Hospital),
- King's College Hospital, London
- Leicester Children's Hospital (Leicester Royal Infirmary)
- Leeds Children's Hospital (Leeds General Infirmary)
- Nottingham Children's Hospital (Queen's Medical Centre)
- Oxford Children's Hospital (John Radcliffe Hospital)
- Royal Aberdeen Children's Hospital
- Royal Alexandra Children's Hospital, Brighton & Sussex
- Royal Manchester Children's Hospital
- The Royal Hospital for Children Glasgow (Glasgow Royal Hospital for Sick Children),
- The Royal Hospital for Sick Children Edinburgh (Edinburgh Royal Hospital for Sick Children)
- The Royal London Hospital
- Sheffield Children's Hospital
- St George's Hospital, London
- Southampton Children's Hospital

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