Improving outcomes in paediatric surgery through the development and implementation of core outcome sets – the NETS studies

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This thesis is dedicated to my grandpa Philip, who passed away just before it was finished. He was a passionate believer in just getting on with life, doing what was right, and trying to make things better for others. He ensured that everything in this thesis passed the grandparent test, and couldn't wait to come back to Oxford to celebrate it being finished. His passion, kindness and love will be missed.

This thesis represents the culmination of six years work, over which time I have been patiently taught and supported by many wonderful people. My supervisors, Marian Knight and Jenny Kurinczuk have offered expertise and insight, but have also dedicated endless hours to mentoring me as I navigated the murky waters of surgical academia.

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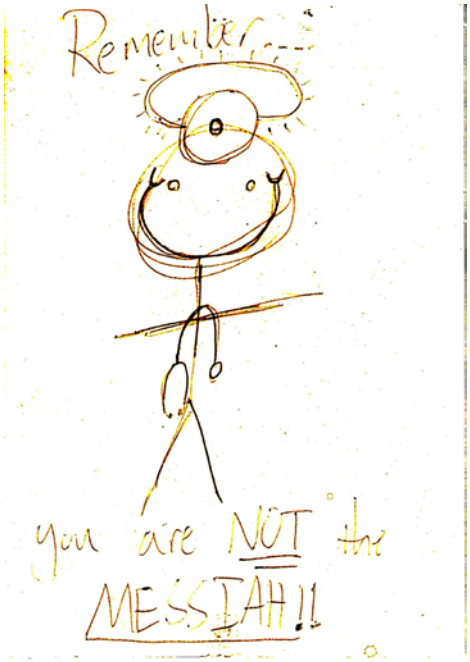
Finally, without the love of my wife, Jess, none of this would have been possible, and I will always be glad we spent a cold January night dancing and laughing together all those years ago.



Abstract

Background

Gold-standard medical practice involves utilising high quality evidence to support clinicians, patients, and their families in identifying the optimal treatment pathway for a particular individual. Currently, there is insufficient high quality evidence to allow paediatric surgeons, who are responsible for the care of children requiring surgical intervention from birth through to sixteen years of age, to deliver such gold-standard practice. Developing and utilising core outcome sets in research has been proposed as one method through which the quality of the paediatric surgical evidence-base can be improved.

Thesis aim

The overall aim of this thesis was to investigate whether outcomes in paediatric surgery can be improved through the development and use of core outcome sets.

Methods

Core outcome sets were developed for two exemplar paediatric surgical conditions, Hirschsprung's disease, where the infant's intestines do not function properly, and gastroschisis, where the infant is born with the intestines outside of the body. The same methodology, consisting of a systematic review, a three-phase Delphi process, a consensus meeting, and a measurement meeting was used for development of each core outcome set. Key stakeholders, including patients, parents of affected children, and clinicians, were involved in each development process.

Subsequently, a joint British Isles-Canadian population-based cohort study was undertaken to investigate the effect of three key treatment modalities; silo repair; operative primary fascial closure; and ward-based reduction; on short-term core outcomes for infants born with gastroschisis. A British-Isles-wide cohort study was also undertaken to describe core outcomes at primary school age for children born with Hirschsprung's disease. The latter study involved collection of parent reported outcomes as well as data from clinicians.

Findings

The developed Hirschsprung's disease core outcome set consisted of ten outcomes identified as important by key stakeholders; death, faecal incontinence, bowel function score, unplanned reoperation, voluntary bowel movements, urinary incontinence, psychological stress, quality of life, permanent stoma, and Hirschsprung's Associated Enterocolitis. Eight outcomes were included in the gastroschisis core outcome set; death, sepsis, growth, number of operations, severe gastrointestinal complication, time on parenteral nutrition, liver disease and quality of life.

In infants born with gastroschisis who had no features of significant bowel injury at birth, the cohort study demonstrated that in comparison to operative primary fascial closure, the use of silo repair was associated with approximately a 75% reduction in the incidence of severe gastrointestinal complications in the first 28 days of life, but at the expense of a 40% increase in number of operations, a doubling in the risk of

experiencing one or more infection, and potentially a small increase in number of days on which parenteral nutrition was received over the same period of time.

Lower than anticipated data return rates limited the certainty with which conclusions could be drawn from the Hirschsprung's disease study. Nevertheless, there was sufficient evidence to suggest that approximately 60% of children with Hirschsprung's disease are not continent of faeces at five to seven years of age, 45% have undergone at least one unplanned reoperation, and 11% are incontinent of urine. There is also some limited evidence to suggest that one operation used for treating children with Hirschsprung's disease, the Swenson procedure, is associated with a greater incidence of unplanned reoperations than the other main surgical treatments of Hirschsprung's disease, the Soave repair and the Duhamel repair.

Conclusions

It is possible, in a practical and expeditious way, to develop core outcome sets for paediatric surgical conditions. It is also possible to use those core outcome sets in large-scale observational studies to address clinically important questions. Results of such studies can be used to improve the care of children undergoing early surgery. The conclusion of this thesis is therefore that developing and implementing the use of core outcome sets ***can*** improve outcomes in paediatric surgery.

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List of abbreviations

BAPS	British Association of Paediatric Surgeons
BAPS-CASS	British Association of Paediatric Surgeons Congenital Anomalies Surveillance System
CAPSNet	Canadian Pediatric Surgery Network
COMET	Core Outcome Measures in Effectiveness Trials
COS	Core Outcome Set
EUPSA	European Paediatric Surgeons' Association
GPS	Gastroschisis Prognostic Score
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAE	Hirschsprung's Associated Enterocolitis
HR	Hazard Ratio
HRA	Health Research Authority
HD	Hirschsprung's disease
IDEAL	Idea Development Exploration Assessment Long-term outcomes
IQR	Inter-quartile Range
IRR	Incidence Rate Ratio
MiCARE	Maternal Infant Care institute
NCEPOD	National Confidential Enquiry into Patient Outcomes and Death
NEC	Necrotising Enterocolitis
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NPEU	National Perinatal Epidemiology Unit
OPFC	Operative Primary Fascial Closure
ORBIT	Outcome Reporting Bias in Trials
OR	Odds Ratio
PICS	Paediatric Incontinence and Constipation Score
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomised Controlled Trial
SMG	Study Management Group
SR	Silo placement with staged reduction and delayed closure (Silo Repair)
UKPCG	United Kingdom Paediatric Colorectal Group
VON	Vermont Oxford Network
VPN	Virtual Private Network
WBR	Ward-based reduction with sutureless closure
WHO	World Health Organisation
95% CI	95% Confidence Interval

Chapter One

A pathway to evidence-based practice

1.1. Decision-making in paediatric surgery

Paediatric surgeons are responsible for the care of children requiring surgical intervention from birth through to sixteen years of age. They represent one of the last true general surgical specialties, managing both congenital and acquired conditions, performing emergent and routine operations, and treating diseases of many different organ systems, including the respiratory tract, gastrointestinal tract and the renal tract. At present, there is little sub-specialisation within paediatric surgery, and as such, although the breadth of conditions each surgeon manages will be wide, the rarity of many of the treated conditions means that the individual surgeon will only treat a handful of children with each condition per year.

In situations such as this, where individual experience of a condition is naturally limited, it is only by drawing upon collective experience in the form of high-quality research, national guidelines, and standardised management protocols, that optimum patient care can be delivered. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) review of organisational and clinical aspects of children's surgery has highlighted specifically how difficulties with decision making are impacting outcomes for infants with Necrotising Enterocolitis (NEC), a key paediatric surgical condition(1). The enquiry identified that improving the evidence-base supporting management of these infants was going to be key to improving decision making, and ultimately outcomes. This is likely to be true across the breadth of paediatric surgery, where the evidence-base to support clinical practice is universally limited(2).

To date, robust paediatric surgical research has primarily been conducted by three groups, the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS), the Vermont Oxford Network (VON) and the Canadian Pediatric Surgery Network (CAPSNet). These groups have used population based cohort studies in the UK, USA and Canada to study a range of conditions including Hirschsprung's disease (HD)(3), gastroschisis(4, 5), NEC(6), congenital diaphragmatic hernia(7), and oesophageal atresia(8). However, despite there being examples such as these of good practice in paediatric surgical research, in 2013, over 80% of published paediatric surgical research consisted of either single patient case studies (35%), or retrospective case series (47%)(2). At present, it is therefore neither possible to reliably use the existing evidence-base to develop robust management guidelines, nor to inform the design of randomised controlled trials (RCTs), which could, following their completion, be used to develop such guidelines.

1.2. The IDEAL Collaboration

Between 2007 and 2009, a group of researchers, methodologists and surgeons were brought together by Professor Jonathan Meakins at Balliol college, Oxford, in order to identify some of the barriers holding back development of high-quality surgical research(9). The outputs of this group have been formalised as part of the IDEAL collaboration, with the centrepiece being the IDEAL framework for assessment of surgical innovations(10). This framework describes five stages in the assessment of surgical innovations, from their initial development through to long-term assessments of safety and efficacy(10-13). At each stage, recommendations are

made for the types of study design that should be used, the types of outcomes that should be investigated, and the outputs that can be expected(10) (Figure 1).

Currently, a large proportion of paediatric surgical research focuses on stages 1 (Idea) and 2a (Development), where novel techniques are described in a handful of patients as a proof of concept or as a mechanism for demonstrating technical success. However, despite the limited evidence of efficacy or superiority over existing techniques that can be obtained using the study designs employed at these stages of assessment, the results of these studies are often portrayed in the paediatric surgical literature as sufficient to allow widespread dissemination of a technique or innovation. Few innovations therefore are ever assessed in stages 2b (Exploration), 3 (Assessment), or 4 (Long-term study) of the IDEAL framework, where comparison of efficacy is made against existing treatments, and long-term assessments of safety are conducted(2). If a robust evidence-base is to be developed in paediatric surgery, it is essential that studies appropriate for assessment of innovations at stages 2b-4 of the IDEAL pathway are carried out. Broadly, these will consist of large-scale, multi-centre observational studies, registry-based studies, and RCTs.

Figure 1: The IDEAL Framework

Stage	**1** **Idea**	**2a** **Development**	**2b** **Exploration**	**3** **Assessment**	**4** **Long-term study**
Purpose of stage	Proof of concept	Development of technique	Learning	Assessment of outcomes	Surveillance
Output and outcomes	Descriptive, demonstrating technical success or failure	Descriptive, demonstrating safety of technique	Comparative, usually short-term outcomes	Comparative, usually medium-term outcomes.	Assessment of regional variation; Quality assurance; Identifying rare events.
Design	Structured case reports	Prospective development studies	Research databases Explanatory or feasibility RCT	RCT	Registry Routine databases

At present, RCTs are rarely performed in paediatric surgical conditions. This is due to two factors. Firstly, a lack of understanding of which patient factors affect outcome, and which will therefore affect inclusion and stratification criteria for a trial, and secondly, a lack of surgeon willingness to randomise infants because of their individual belief in the merits of a particular treatment strategy, or the feeling that through their involvement in an operation, they hold personal responsibility for a patient's outcome(9). Most interventions for paediatric surgical conditions therefore require as a first step, assessment at stage 2b of the IDEAL framework using large-scale, multi-centre, observational studies.

1.3. Limitations of the paediatric surgical evidence-base

There are very few paediatric surgical studies conducted that are large enough or sufficiently well designed to allow conclusions about the way in which infants should be managed to be drawn from their results (2, 14, 15). In HD and gastroschisis, systematic reviews have attempted to address the limitations imposed by the size of the primary studies through the use of meta-analysis (16-19). However, they have been unable to do so because the methodological limitations of the primary evidence-base are so significant that meta-analyses cannot be performed.

In addition to the limitations of size and type of study design, the HD and gastroschisis systematic reviews identified two further issues that the authors believed were preventing identification of gold-standard interventions. These were firstly, the failure of primary studies to clearly define and describe their study populations, and secondly, the presence of significant heterogeneity in the choice of

outcomes reported by primary studies (16, 19). Both of these limitations require addressing in order to develop a robust paediatric surgical evidence base.

However, in order to seek homogeneity in the populations of infants that are studied, it is first important to identify the patient factors that affect outcome, and in order to identify those factors, it is necessary to first define which outcomes are important. Identifying outcomes that are useful in defining success of treatment of a particular condition, and hence of interest to those designing studies, is therefore the logical place to start in order to improve the quality of paediatric surgical research. Identifying such outcomes will inform the development of large-scale observational studies to assess innovations at stage 2b (Exploration) of the IDEAL framework, and these studies will in turn address the issues that are currently preventing conduct of RCTs. Eventually, enough high quality RCTs will have been conducted to allow their synthesis in systematic reviews and meta-analyses, upon which truly robust management guidelines can be based.

1.4. Heterogeneity in choice of reported outcomes

Heterogeneity in the choice of outcomes reported by studies suggests that different authors are attempting to answer the same question through the investigation and reporting of different groups of outcomes. Such heterogeneity limits clinical research in three ways(20). The primary concern is that the wide range of outcomes being investigated indicates that there is no agreement on which outcomes are important in defining treatment success and which are therefore relevant to patients and

clinical practice(21). This implies that there will be studies whose results, although methodologically robust, are not of any use in helping patients or clinicians choose between different treatment options, as they do not report outcomes that are relevant to clinical decision-making. An example of this is in research comparing surgical interventions for the treatment of HD, where a systematic review highlighted that primary studies frequently investigated hospital metrics such as operative time, and surrogate markers of success such as bowel function at an age before which continence could be expected, as opposed to investigating outcomes such as long-term continence or constipation, which are known to affect patient quality of life and school performance (16, 22). A systematic review looking at outcome selection in neonatal trials similarly found that outcomes were frequently selected based upon feasibility of data collection as opposed to their importance to key stakeholders(23).

The presence of significant heterogeneity in the choice of reported outcomes also makes it difficult to determine how researchers have chosen the outcomes they report in published manuscripts. In conditions where there are a small number of outcomes that are universally accepted as being necessary to define treatment success, there is a necessity for researchers to robustly justify their decisions when not reporting one of these outcomes. However, for conditions where there are a wide-range of outcomes investigated, and none are universally accepted as important, there is less pressure on researchers to justify their outcome selection. It therefore becomes difficult to ascertain whether researchers have chosen to investigate and report specific outcomes *a priori*, or whether the reported outcomes

are only a selection of those that were investigated in the study. In research areas where there is significant heterogeneity in the choice of reported outcomes, it is therefore very difficult to identify whether and where reporting bias is occurring. This problem has been highlighted in several recent studies(24-27), including that by Kirkham et al, who demonstrated that over 30% of RCTs included in Cochrane systematic reviews either did not publish at all, or did not fully publish the results for their identified primary outcome measure(28).

Finally, significant heterogeneity in the choice of reported outcomes weakens clinical research by making it difficult, or in some cases impossible, to perform meta-analyses(29). In paediatric surgical conditions, where the vast majority of studies have a low number of participants, this is a particular problem(2), since meta-analysis is essential to detect significant differences between treatments. The identified potential for reporting bias, combined with lack of patient relevance, and the fact that chance and confounding are highly likely to be impacting the results of many paediatric surgical studies (2) is significantly limiting the ability of the existing evidence base to help guide clinical management (19, 20, 30).

1.5. Core Outcome Sets

Core outcome sets (COSs) are proposed as a method for reducing heterogeneity in researchers choices of reported outcomes, and hence as a method for increasing patient relevance of research, reducing the risk of reporting bias, and enabling meta-analysis(20). COSs are groups of agreed, standardised outcomes that should, at a

minimum, be reported in every study falling within the scope of the COS(20, 30). The scope of a COS could be specific for a select group of treatments for a single condition, for example surgical interventions for the treatment of peri-anal fistulae in Crohn's disease, or broad for an entire population of patients, for example, babies admitted for neonatal intensive care. The use of COSs in clinical trials is often now a pre-requisite for obtaining funding, and as such, they are becoming more frequently adopted by researchers as the starting point for identifying trial outcomes(31). In conditions where they have been in use for a significant period of time, they have been shown to reduce heterogeneity in the choice of reported outcomes(32). Ultimately, utilising COSs makes research more patient centred, more reliable and more comparable, leading to an increased opportunity for clinicians to make evidence-based decisions relating to the care they offer patients.

COSs are often developed in multiple stages, which can include the use of literature reviews, focus groups, surveys, structured interviews, consensus meetings, a Delphi process(33, 34), or a combination of these techniques. A Delphi process is a multi-staged process in which key stakeholders are guided, through feedback on other participant's opinions, towards consensus on a question of importance. The Delphi process has been used to successfully develop COSs in multiple medical and surgical conditions, including asthma(33), otitis media in children with cleft palate(35), and colorectal cancer(36). Whatever the methodology used, the end result of developing a COS should be identification of a small group of robustly defined outcomes that are widely accepted by key stakeholders as important.

1.6. OMERACT Filter 2.0

In 2004, the Outcome Measures in Rheumatology (OMERACT) Filter 2.0 was developed as a conceptual framework to help ensure that outcomes selected for inclusion in rheumatological COSs covered the breadth of what is measurable within a trial(37). This framework consisted of four core areas, Death, Life Impact, Pathophysiological Manifestations and Resource Utilisation, and it was suggested that outcomes from each of these core areas should be represented within a COS. Additionally, in order to ensure that a COS represented both the benefits and harms of an intervention, it was recommended that outcomes describing adverse events were conceptualised as lying within one of the four core areas, but upon production of the COS, labelled clearly as adverse event outcomes. Whilst it was developed specifically for use in rheumatological COS development, the OMERACT Filter 2.0 is equally applicable to COSs developed for other health conditions.

1.7. Benefits and limitations of utilising core outcome sets

It is only once a COS has been widely used in well-designed research that its potential for improving clinical outcomes can be realised. In paediatric surgery, where adoption of new research methodology has traditionally been slow, such implementation of COSs is likely to be difficult.

Demonstrating that COSs can be used in a practical manner to answer relevant questions would both highlight their potential for helping drive improvements in clinical outcomes, and also help to maintain engagement of the paediatric surgical

community. If engagement could be maintained and such potential for benefit could be demonstrated, it would likely ease uptake of COSs in future research. As it is currently necessary for many paediatric surgical interventions to be assessed at stage 2b (Exploration) of the IDEAL framework, and for patient characteristics affecting outcomes in many conditions to be defined, the most appropriate study design in which to demonstrate such potential would be a large-scale observational study.

In a recent series of articles in The Lancet, Chalmers et al elegantly described how currently, there is significant waste in biomedical research(38-41). Two factors contributing to this waste were under-utilisation of existing data, leading to unnecessary, and sometimes unhelpful, repetition of work, and an inappropriate focus of studies on extreme, random findings instead of on specific, defined analyses. COSs can clearly be used to help focus the analysis of prospectively designed studies. However, what is less clear is whether they can also help focus secondary analyses, or whether the specific nature of outcomes included in a COS would render existing data unusable. Within paediatric surgery, where research funding is scarce, it is important that any new methodological interventions do not lead to increases in waste of resources. Therefore, assessment of the benefit of COSs must be made both in a prospectively designed observational study, but also in a secondary analysis of existing, high quality data.

COSs have never previously been developed for paediatric surgical conditions, and whilst there are therefore many conditions for which they could be developed, in

order to clearly demonstrate their benefit to the wider community, it is essential that the first conditions they are developed for meet certain criteria. An ideal condition would be one in which there are multiple interventions in use that currently require assessment at stage 2b of the IDEAL framework, and which could plausibly be assessed at stage 3 using an RCT once patient populations have been clearly defined and surgeons have been convinced that equipoise exists between the interventions. Two conditions that meet these criteria are HD and gastroschisis. Frequent use of multiple interventions for both conditions has been demonstrated across the UK(3, 4), and systematic reviews have highlighted that these commonly used interventions currently require assessment at stage 2b of the IDEAL framework(16-19). Additionally, gastroschisis is a condition in which two large, prospectively established, databases exist. These databases would therefore also allow investigation of whether a COS could be utilised in a meaningful secondary analysis.

1.8. Hirschsprung's disease and gastroschisis

Affecting approximately 1.8 per 10,000(3), and 1 per 3000(4) live-births in the British Isles respectively, HD and gastroschisis are two of the more common neonatal conditions managed by paediatric surgeons. Currently, the incidence of gastroschisis is increasing(42).

In infants with HD, the primary problem is failure of the intrinsic intestinal parasympathetic ganglia to develop in utero (aganglionosis), resulting in

presentation shortly after birth, with symptoms of intestinal obstruction(3, 43). A subset of infants will also present with Hirschsprung's Associated Enterocolitis (HAE), a condition in which translocation of bacteria has occurred across the intestinal mucosa, resulting in sepsis and offensive diarrhoea in addition to the symptoms of intestinal obstruction. Surgery in the neonatal period or early infancy is required to remove the affected section of intestine, and anastomose the remnant to the anus(44-46).

Gastroschisis is characterised by herniation of the abdominal organs through a defect in the infant's abdominal wall. As with HD, infants with gastroschisis require surgery to correct the underlying defect. However, in contrast to infants with HD, for infants with gastroschisis, this surgery is normally undertaken in the first few days of life, as opposed to the first few weeks or months of life.

Mortality from both gastroschisis and HD is now relatively low(3, 5). However, the little literature that exists, suggests that there is still a relatively significant long-term burden of morbidity associated with each(5, 47, 48). There is also wide variation in the way that both conditions are currently managed, and no robust, evidence-based guidelines exist to help surgical decision-making(4, 49, 50).

Chapter Two

Aims, objectives, and research questions

2.1. Introduction

It is clear from the evidence discussed in Chapter One that improving outcomes for children who undergo early surgery requires wholesale change to the way paediatric surgical research is conducted. The logical place to begin in making this change is with the development and implementation of COSs. However, until the potential for using COSs to improve outcomes is demonstrated in practice, and weighed up against the potential limitations of their use, the extent to which they can be of benefit in paediatric surgery will remain poorly understood.

2.2. Research aim and objectives

The overall aim of this research was to investigate whether it was possible to improve outcomes in paediatric surgery by developing COSs and implementing their use in large-scale, observational studies. HD and gastroschisis were used as illustrative conditions in which to develop the methodology and infrastructure required to achieve this aim. Two distinct groups of objectives were addressed.

2.2.1. Objectives group one: Core outcome set development

The first group of objectives related to development of HD and gastroschisis COSs, and were to:

1. Investigate which outcomes are deemed most important by key stakeholders in defining the overall success of treatment of infants with HD;

2. Investigate which outcomes are deemed most important by key stakeholders in defining the overall success of treatment of infants who were born with gastroschisis; and
3. Investigate how important outcomes should be defined, and when they should be measured.

2.2.2. Objectives group two: Demonstrating improvement in outcomes

It is not possible in the three-year period of this thesis work to definitively demonstrate that utilising paediatric surgical COSs in research improves clinical outcomes. However, it is possible, to demonstrate the feasibility of utilising COSs in paediatric surgical studies where the overall aim is to provide new knowledge that can be used to help deliver high quality care. Such a demonstration would indicate that it is also feasible for COSs to be utilised widely in paediatric surgical research. Based on existing evidence(1, 32, 51), it is hypothesised that such widespread utilisation would eventually result in improvements in paediatric surgical outcomes.

Feasibility of using COSs in paediatric surgical research was determined by investigating if it was possible to address six specific clinically relevant objectives using studies in which outcomes had been selected based upon the developed HD and gastroschisis COSs. These six objectives were to:

1. Investigate which characteristics affected the health and wellbeing of infants treated for gastroschisis in the British Isles and Canada between 2005 and 2017;

2. Investigate whether the operative strategy used to treat children born with gastroschisis in the British Isles and Canada between 2005 and 2017 affected their health and wellbeing;
3. Investigate whether the management strategies and outcomes for children treated for gastroschisis in the British Isles between 2005 and 2008 differed from those treated in Canada between 2005 and 2017;
4. Describe the health and wellbeing at five to seven years of age of children treated for HD in the British Isles between October 2010 and October 2012;
5. Investigate which characteristics were associated with variation in the health and wellbeing at five to seven years of age of children treated for HD in the British Isles between 2010 and 2012; and
6. Investigate whether the rectal dissection technique used to treat children with HD in the British Isles between 2010 and 2012 affected their health and wellbeing at five to seven years of age.

2.3. Component studies and structure of the thesis

The analytical chapters three to five address the thesis aims and objectives using two consensus-based studies, a bi-national cohort study, and a British Isles-wide cohort study. Each of the component studies was part of the *Next stage in Evidence-based paediatric surgical Treatment Strategies (NETS)* programme, a National Institute for Health Research (NIHR) funded fellowship programme. The four component studies were:

- **The NETS^{1HD} study:** Development of a core outcome set for assessing surgical interventions in Hirschsprung's disease (Chapter Three)
- **The NETS^{1G} study:** Development of a core outcome set for assessing surgical interventions in gastroschisis (Chapter Three)
- **The NETS^{2G} study:** A bi-national cohort study investigating the patient and operative factors that affect core outcomes at 28 days of age in infants born with gastroschisis (Chapter Four)
- **The NETS^{2HD} study:** A national cohort study assessing the impact of choice of surgical intervention on core outcomes at five to seven years of age in children with Hirschsprung's disease (Chapter Five)

Chapter Three

Development of Hirschsprung's disease and gastroschisis core outcome sets

3.1. Background

3.1.1. Development of core outcome sets

Many research funders, journal editors, regulatory bodies, research organisations and clinical guideline development groups now recognise the development and implementation of the use of COSs as being integral to improving quality and reducing waste in medical research. Such organisations include the NIHR, the Horizon 2020 programme, the Health Research Authority (HRA), the European Medicines Agency, the National Institute for Health and Care Excellence (NICE), and the 79 women's and newborn health journals that are members of the CROWN-initiative (http://www.crown-initiative.org). In 2010, the Core Outcome Measures in Effectiveness Trials (COMET) initiative (http://www.comet-initiative.org) was established to bring together parties who were interested in developing and implementing the use of COSs, and has since become the standard bearer for ensuring that COSs are developed and implemented in a scientifically rigorous manner.

There are multiple consensus methods that can be used for developing COSs, including expert panels (52), structured interviews(53), nominal group technique(54), focus groups(55) and the Delphi process(56). Each has their pros and cons, and the way in which any of them are designed has the potential to influence the consensus that is achieved at the end of the process(57). However, the method that is currently most prevalent is the Delphi process(34, 58). Broadly, a Delphi process involves asking respondents to complete sequential questionnaires with

group opinion fed back to individual participants in between completion of the questionnaires.

3.1.2. Advantages and disadvantages of Delphi methodology

Using Delphi methodology has several advantages over other forms of attaining consensus. Primarily, it removes the influence that 'big characters', or 'loud voices' can have on the group consensus. By anonymising all responses, each respondent's views are placed on an equal footing, thereby removing the pressure that individuals may feel to fall in line with the views of those who are perceived to be established experts or who have dominant personalities. Use of Delphi methodology, particularly when delivered in an electronic format also makes it easier to conduct international consensus development processes, as it removes the need for participants to be present in the same location at the same time as one another. Unlike many other consensus methods, the data collected from a Delphi process are quantitative as opposed to qualitative, thereby allowing consensus decisions to be supported by robustly defined results.

Whilst most groups recommend the use of a Delphi process for development of COSs, there are limitations to the methodology. Critics suggest that the methods used for data collection, whereby participants are usually asked to rate outcomes using a Likert scale, allows all those involved to quickly, and without having to justify it, express an opinion in relation to the importance of all items within the questionnaires(59). This raises the concern that participants may express an opinion without giving the outcome due consideration, thereby reducing the validity of the

collected data. It has also been proposed that consensus is overestimated through use of a Delphi process, and that the results at least partially represent moulding of participants' opinions to the average view, as opposed to attainment of genuine consensus(60).

3.1.3. Inclusion of the 'personal experience' viewpoint

In 2011, Sinha et al published an article defining the areas that are most likely to affect the results of Delphi processes used for the development of COSs(34). Their article was based upon the results of a systematic review of 15 studies that had used a Delphi process to develop COSs, and they supplemented this review with the results of a series of studies demonstrating the impact that different methodological decisions could make to the Delphi results. The clearest recommendation from this work is that it is essential to retain throughout the Delphi process the opinions of people with personal experience of the target condition. The importance of retaining this group of participants is due to the fact that outcomes that are of importance to clinicians and researchers are often different to those of importance to patients and carers(61, 62). Methods that have been suggested for improving retention of participants, particularly those who may feel they have a minority view, include the use of a pre-Delphi registration site for recruitment, and the displaying of messages throughout the Delphi process that reinforce the importance of collecting views from all groups of participants throughout the entirety of the process(63, 64).

3.1.4. Combining different viewpoints

It is recognised that the way in which the views of different groups of participants are combined can greatly influence the results of a Delphi process(20). If the process is conducted with multiple stakeholder groups combined into one heterogeneous panel, then where there is variation in the number of participants in different groups, the views of smaller groups are likely to be overwhelmed. Separating these groups into different panels helps to preserve the opinions of minority groups, but potentially gives undue weight to the opinions of a few people in a minority group. There is currently no guidance on exactly how to handle the views of different stakeholder groups, and different studies have approached the issue in different ways. Some researchers have elected to analyse the results of different stakeholder groups separately throughout the entire development process, resulting in creation of multiple COSs that are then compared and combined(36, 65). Others have taken the decision to analyse and feed back the results of stakeholder groups separately throughout the Delphi process, and then identify important outcomes based upon the number of stakeholder groups that prioritised them(66).

3.1.5. Defining consensus

Regardless of the way data are combined from different panels, the way in which consensus is defined will significantly affect the outcomes that are identified for inclusion in a COS(20). Following completion of the Delphi process, McNair et al(36) and Egan et al(67) opted to hold face-to-face meetings with stakeholders during which they discussed the results of the Delphi process and gave stakeholders the

opportunity to vote outcomes 'in' or 'out' of the COS. Those outcomes where a pre-defined proportion of participants voted them 'in' to the COS were deemed to have met consensus for inclusion. Potter et al(65) also presented the results of the Delphi process to stakeholders at a face-to-face consensus meeting, but instead of offering participants a simple 'in' or 'out' vote gave them the opportunity to again score outcomes using the nine-point Likert scale used during the Delphi process. Those outcomes then reaching a pre-defined threshold of scores were considered to have met consensus for inclusion in the COS. The COMET initiative have proposed that a threshold of ≥70% participants scoring an outcome 7-9 and <15% scoring it 1-3 on a 9 point Likert scale could be used to define an outcome as having met consensus for inclusion in the COS(20).

3.1.6. Defining and measuring the core outcomes

Prior to use of a COS in a measurement of effectiveness study it is essential that the outcomes have been robustly defined, measurement tools have been identified for each outcome, and that time-points for measurement of the outcomes have been set. This process requires an initial review of the literature to identify existing measurement tools, followed by the use of consensus methods such as expert focus groups(68) to identify the tool which most truthfully measures an outcome, most reliably discriminates between different states of the outcome, and can most feasibly be utilised in future research(37).

3.2. Objectives and research questions

There were two global objectives to the work presented in this chapter:

1. To develop a Hirschsprung's disease COS and a gastroschisis COS
2. To identify methodological issues associated with development of paediatric surgical COSs

Six specific research questions were addressed during development of the COSs:

1. Which outcomes are reported by studies comparing surgical interventions for HD?
2. Which outcomes are reported by studies comparing surgical interventions for gastroschisis?
3. Which outcomes are most important to key stakeholders in determining the overall success of treatment of infants with HD?
4. Which outcomes are most important to key stakeholders in determining the overall success of treatment of infants born with gastroschisis?
5. How should the identified HD and gastroschisis core outcomes be defined and measured?
6. At what age should the core outcomes be assessed?

3.3. Scope of the core outcome sets

3.3.1. Hirschsprung's disease

The aim of treatment of infants with HD is to allow them to open their bowels in a manner that is acceptable to them and their family during childhood and also as they

develop into adolescence and adulthood. Broadly speaking, this aim is the same regardless of the severity of their HD, the way in which their HD is treated, or whether they have any comorbidities.

Given that the broad aims of all surgical interventions for HD are the same, it is prudent for a developed COS to be useful in studies comparing any treatment options. With the implications of surgical intervention being life-long, it is also essential that the COS should assess outcomes distant to the intervention, not simply in the immediate post-operative period. In order to allow full comparison of surgical interventions, it must also include an assessment of the negative outcomes that are potentially associated with treatment, as well as the positive. The scope of this COS therefore covers all studies comparing interventions for the treatment of children with HD, and is intended to be used for assessing the overall success of treatment.

As treatment of, and outcomes from, HD are likely to vary significantly between high-income, and low- and middle-income countries, participation in the consensus process was limited to experts from high-income countries only. The developed COS is therefore only applicable to research taking place in high-income settings.

3.3.2. Gastroschisis

The only definitive treatments for gastroschisis are surgical, and each of these has the same broad objective, to return the herniated abdominal organs to the abdominal cavity and to close the defect in the anterior abdominal wall. Within high-

income countries, although there are differences in surgical technique, the management of infants born with gastroschisis, and their post-intervention outcomes are broadly similar(5, 69). Within low- and middle-income countries however, less developed neonatal intensive care facilities mean that management and outcomes are very different from those of high-income countries(70). A developed COS is therefore likely to only be applicable in either high-income countries, or low and middle-income countries. As the vast majority of gastroschisis research is currently conducted in high-income countries, the largest benefit to gastroschisis research will be seen by developing a COS that is applicable in these countries.

Currently, antenatal interventions for infants with gastroschisis are being developed and implemented in clinical practice. However, outcomes that are relevant to these interventions are likely to be different to the outcomes that are relevant to postnatal interventions for the treatment of infants with gastroschisis. Again, as the vast majority of gastroschisis research takes place in the postnatal period, the greatest benefit will be seen by developing a COS that is applicable to these studies.

The scope of this COS was therefore limited to studies comparing post-natal surgical interventions for the treatment of infants born with gastroschisis in high-income countries. It was not intended to be applicable to studies investigating antenatal interventions, or factors related to the mode or timing of delivery of babies with a prenatal diagnosis of gastroschisis, and its applicability in low and middle-income countries must be carefully considered before it is used.

3.4. Methods

3.4.1. Summary

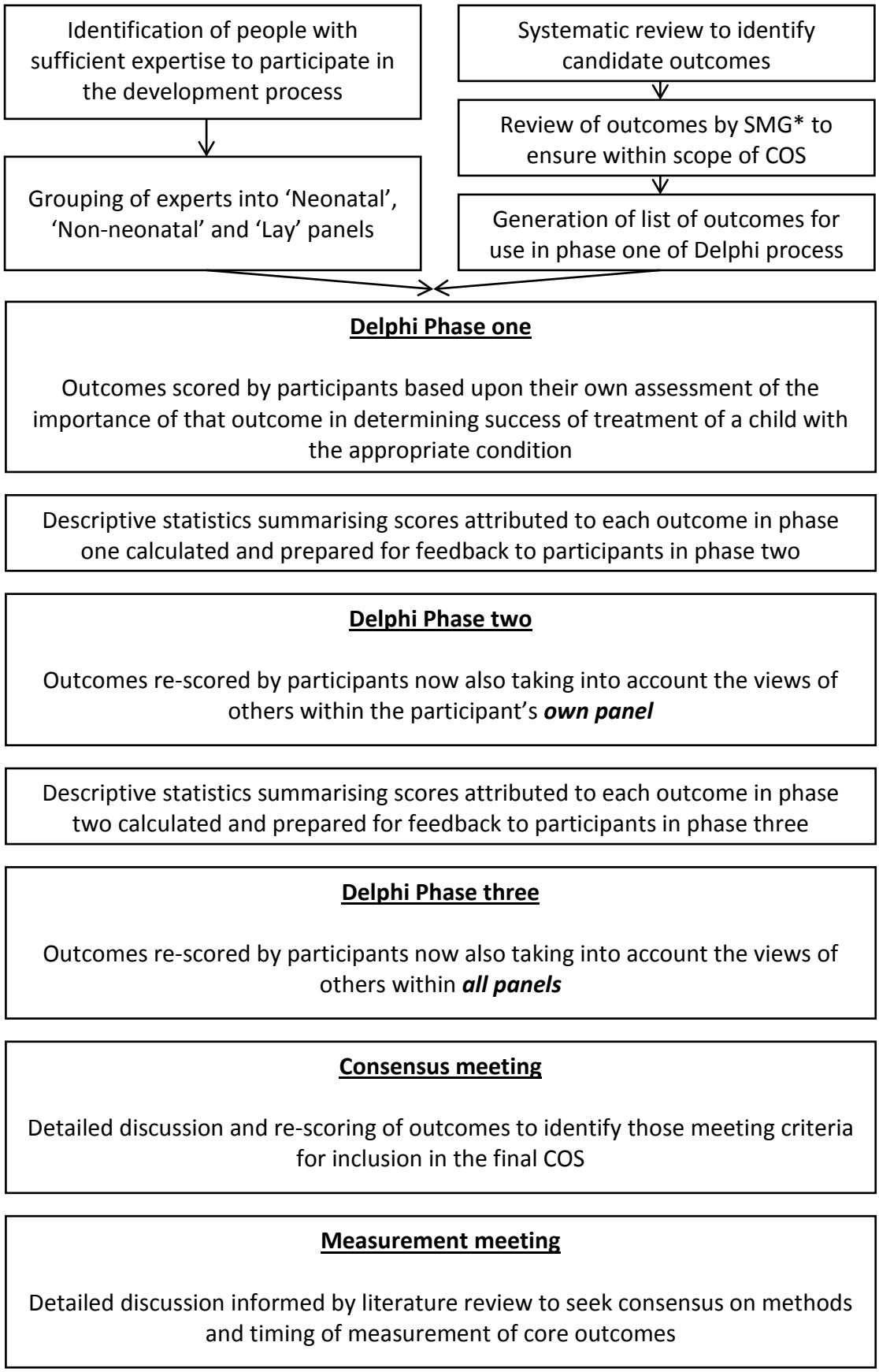
Both studies were prospectively registered on the COMET initiative website (http://www.comet-initiative.org/studies/details/787?result=true and http://www.comet-initiative.org/studies/details/746), and the protocols were published in peer reviewed journals (Appendices 1 and 2)(71, 72).

The structure of both studies was broadly similar and consisted of four parts:

1. A systematic review designed primarily to identify which outcomes were already being reported in studies comparing surgical interventions for HD and gastroschisis.
2. A three-phase, online Delphi process consisting of multiple stakeholder groups for each condition.
3. A face-to-face consensus meeting with a representative sample of participants from the Delphi process for each condition.
4. A face-to-face core outcome measurement meeting with a representative sample of participants from the Delphi process for each condition.

The study design is summarised in Figure 2.

Figure 2: Flow diagram summarising the COS development processes



SMG – Study Management Group
COS – Core Outcome Set

3.4.2. Systematic Review

A systematic review(73) was conducted according to a pre-specified protocol that was prospectively registered on PROSPERO (CRD42015024996). Multiple search strategies were used via the OVID interface to identify relevant articles from Medline and EMBASE. Search terms were identified from database thesauri and free text relating to HD and operative interventions for HD, or gastroschisis and interventions for gastroschisis, and combined using Boolean operators. Searches were limited to papers published in or after 2010 in order to ensure that identified outcomes were contemporaneous (see Appendices 1 and 2 for full search strategies).

3.4.2.1. Study selection and data extraction

Identified titles were assessed for inclusion by three investigators acting independently. Any conflicts were resolved by discussion, with recourse to a fourth investigator where necessary. The same investigators extracted data from included articles independently, with conflicts resolved in the same manner. The following data were extracted from all studies: study design, year of study, interventions investigated, population investigated, size of study population, inclusion and exclusion criteria, outcomes reported, whether outcomes were primary or secondary, time-points at which outcomes were measured, which of Harman et al's criteria for complete reporting(74) the study met, and the ORBIT grade(28) for each investigated outcome. ORBIT grades range from A-I and are used to assess whether it is likely that data are missing from the study report, and if so, whether those missing data are likely to have biased the studies conclusions.

3.4.2.2. Inclusion and exclusion criteria:

All study designs except case studies and expert opinion were considered for inclusion in the review. Studies where only the abstract was available (e.g. conference proceedings) were not included in the assessment of completeness of data reporting, as this could only be analysed from the full study report. The search was limited to papers published after 2010. Only studies including more than 10 infants were eligible for inclusion. Both searches were undertaken in August 2015.

HD studies were eligible for inclusion if:

- They compared two or more interventions for infants with biopsy confirmed HD

And

- They reported outcomes following the primary definitive procedure

HD studies were excluded if:

- They only reported outcomes from one intervention without a comparator
- They only reported outcomes for infants undergoing a re-do procedure

Or

- They only reported outcomes from a non-definitive procedure e.g. stoma formation in infants planned for a staged procedure.

Gastroschisis studies were eligible for inclusion if:

- They compared two or more methods of visceral reduction and defect closure in infants with gastroschisis,

Gastroschisis studies were excluded if:

- They only reported outcomes from one intervention without a comparator

The stated inclusion criteria were utilised in order to achieve two aims. Firstly, to ensure that sufficient numbers of studies were included to identify all relevant outcomes whilst not necessitating review of additional studies long past the point of outcome saturation, and secondly, to try to increase the likelihood that identified outcomes were both relevant to contemporary clinical practice, and also relevant to achieving the aims of the COSs. Including only comparative studies published after 2010 prevented identification of historically investigated outcomes which were no longer relevant to clinical practice, allowed outcomes that were utilised in both historic and contemporary studies to be identified without having to review manuscripts for both the current and the historic study, and ensured that all identified outcomes had been utilised previously to compare interventions for one of the target conditions, therefore increasing the likelihood that they would be useful for achieving the stated aims of the two COSs. Studies were then excluded if they reported data for ten or fewer infants so as to reduce identification of outcomes that were potentially only relevant to selected infants, interventions, or institutions. It was felt likely that all relevant outcomes investigated in the excluded small studies would also be investigated in the included larger comparative studies, and would therefore still be identified for assessment in the COS development process.

3.4.2.3. Outcome description

A list of all outcomes reported by eligible studies was generated. Similar outcomes were merged to one common term prior to analysis, and as per the OMERACT filter 2.0 (37), categorised as relating to life impact, resource use, pathophysiological manifestations, or death. Adverse event outcomes included in the above categories were identified separately. The number of outcomes reported in each eligible study and the number of times each outcome was reported were counted, and medians and interquartile ranges calculated.

3.4.2.4. Identification of additional gastroschisis outcomes

A systematic review conducted by Ross et al, describing outcomes reported in RCTs and systematic reviews comparing interventions for gastroschisis was used as a secondary source for identifying reported gastroschisis outcomes (75).

3.4.3. Delphi Process

A three phase, online Delphi process involving multiple stakeholder groups was conducted for each condition.

3.4.3.1. Stakeholder recruitment

Experts were recruited to each of the development processes from a range of stakeholder groups according to the strategies described in Table 1. Prior to inclusion in the development process, experts were asked to register their interest via a customised website where details were collected documenting their clinical or

personal experience of the target condition. Registrations were reviewed by the study management group (SMG) to ensure that registrants had sufficient expertise to participate in the development process, and those who did were subsequently asked to nominate additional potentially eligible stakeholders. Target recruitment was a minimum of 50 experts with two or more from each stakeholder group.

Data presentation for the Delphi process was simplified by combining stakeholder groups into a neonatal panel, a non-neonatal panel and a personal experience panel as described in Table 1, within which, opinions were anticipated to be broadly similar.

Participants were deemed to have withdrawn from the development process if they did not complete a phase of the Delphi process prior to the pre-specified deadline, and were thus ineligible for participation in later phases or the consensus meeting. A representative sample of participants completing the Delphi process was invited to the subsequent consensus meeting and measurement meeting.

Table 1: Stakeholder recruitment strategies

Hirschsprung's disease		
Stakeholder group	**Panel**	**Recruitment methods**
People with HD Parents of children born with HD	Personal experience panel	• Mailing lists, websites and Facebook groups of British and international HD support groups including the Hirschsprung's and Motility Disorders Support Network, and the CHAMPS Appeal • Mailing lists and meetings for a Parental Advisory Group established by the National Perinatal Epidemiology Unit
Paediatric surgeons	Neonatal panel	• Mailing list of the United Kingdom Paediatric Colorectal Group • Direct approaches to experts known to members of the SMG and those identified on a search of the British Association of Paediatric Surgeons (BAPS) register as having a special interest in management of children with HD. • BAPS mailing lists, newsletters and website. • Direct approach to clinical leads at each paediatric surgical centre in the British Isles for the BAPS-CASS HD study • Direct approach to the editors of the Journal of Pediatric Surgery and Paediatric Surgery International
Neonatologists	Neonatal panel	• Direct approach to experts known to members of the SMG • Mailing lists, bulletin and website of the British Association of Perinatal Medicine • Mailing lists, bulletin and website of the Royal College of Paediatrics and Child Health

Table 1: Stakeholder recruitment strategies - Continued

Hirschsprung's disease		
Stakeholder group	**Panel**	**Recruitment methods**
Paediatric Gastroenterologists	Non-neonatal panel	• Direct approach to experts known to members of the SMG • Mailing list of the British Society of Paediatric Gastroenterology Hepatology and Nutrition
Researchers	Non-neonatal panel	• Direct approaches to experts known to members of the SMG, and prominent HD researchers identified through searches of the literature.
Specialist nurses	Non-neonatal panel	• Direct approaches to experts known to members of the SMG • Mailing list of the paediatric stoma nurses group
Gastroschisis		
Stakeholder group	**Panel**	**Recruitment methods**
Paediatric Surgeons	Neonatal Panel	• Direct approaches to experts known to members of the SMG and those identified on a search of the British Association of Paediatric Surgeons (BAPS) register as having a special interest in management of children with gastroschisis. • BAPS mailing lists, newsletters and website. • Direct approach to clinical leads at each paediatric surgical centre in the British Isles for the BAPS-CASS gastroschisis study
Neonatologists	Neonatal Panel	• Direct approach to experts known to members of the SMG • Mailing lists, bulletin and website of the British Association of Perinatal Medicine
Fetal Medicine Specialists	Neonatal Panel	• Direct approach to experts known to members of the SMG • Mailing list of the fetal medicine clinical study group of the British Maternal and Fetal Medicine Society

Table 1: Stakeholder recruitment strategies - Continued

Gastroschisis		
Stakeholder group	**Panel**	**Recruitment methods**
People born with gastroschisis Parents of children born with gastroschisis	Personal experience panel	• Mailing lists, websites and Facebook groups of British and international gastroschisis support groups • Mailing lists and meetings for a Parental Advisory Group established by the National Perinatal Epidemiology Unit
Specialist Nurses	Neonatal Panel	• Direct approaches to experts known to members of the SMG • Mailing list of the Neonatal Nurses Association, and the National Neonatal Surgical Benchmarking Group
Paediatricians	Non-neonatal panel	• Direct approach to experts known to members of the SMG • Mailing list of the British Society of Paediatric Gastroenterology Hepatology and Nutrition
Researchers	Non-neonatal panel	• Direct approaches to experts known to members of the SMG, and prominent gastroschisis researchers identified through searches of the literature.
Specialist paediatric surgical nurses	Neonatal panel	• Direct approach to experts known to members of the SMG
Dieticians	Non-neonatal panel	• Direct approach to experts known to members of the SMG • Mailing list of the British Society of Paediatric Gastroenterology Hepatology and Nutrition

3.4.3.2. International participation

The HD consensus meeting was held in conjunction with an international congress at which a large proportion of international clinical experts were present. Experts from a range of high-income countries could therefore, within the constraints of funding, be invited to attend the consensus meeting alongside British Isles-based experts. As a result, it was possible to recruit international experts to take part in the consensus process and still ensure that attendees at the consensus meeting were representative of the wider group of participants.

In the gastroschisis study however, it was not possible to ensure participation of international experts in the consensus meeting, and therefore clinical stakeholders were recruited only from the British Isles. It was initially proposed that people born with gastroschisis and parents of children born with gastroschisis would also only be recruited from the British Isles. However, despite extensive work with gastroschisis charities it proved difficult to recruit to these stakeholder groups when participation was limited to the British Isles. It was therefore decided by the SMG that it was more important to ensure a strong personal experience voice throughout the study than it was to ensure that it was feasible for all participants to have the opportunity to attend the consensus meeting, and recruitment was therefore expanded to include people with personal experience of gastroschisis who were treated, or whose children were treated, in other high-income countries.

3.4.3.3. Information sources

In order to ensure that each outcome was unique and fell within the scope of the COS, members of the SMG reviewed all outcomes identified from the literature. Members of the SMG also proposed additional outcomes if they felt they were important and not represented by those identified through the systematic review. The combined list for each condition formed the candidate outcomes for assessment in phase one of the Delphi processes. Lay equivalents were developed for each outcome by the SMG with the involvement of appropriate members of the National Perinatal Epidemiology Unit (NPEU)'s Parent Advisory Group.

3.4.3.4. Delphi process summary

Limesurvey (https://www.limesurvey.org) was used to create a customised data collection system which was hosted on the NPEU's secure servers, and used to facilitate a three-phase online Delphi process run in parallel for the neonatal, non-neonatal and lay panels. In each phase, participants were asked to score outcomes from 1-9 based on their importance in determining the overall success of treatment of a child with the relevant condition. In phases two and three, participants were provided with gradually more information about other participants' scores to help guide the group towards a consensus. Participants were only eligible to contribute to phase two if they completed phase one, and phase three if they completed phase two.

At the start of each phase, eligible participants were sent an electronic invite to access the appropriate questionnaire. Participants were then reminded of the scope of the COS and provided with tailored instructions for that phase (Appendix 3). This information built upon that provided in newsletters sent to participants between phases (Appendices 4 and 5).

In each phase of the Delphi process, participants were presented with the list of outcomes to be scored. In the HD Delphi process the outcomes were presented in groups of ten in alphabetical order. However, feedback from participants suggested that scoring similar outcomes in different sections of the Delphi process made it difficult to compare their relative merits. For the gastroschisis Delphi process, outcomes were therefore presented organised in groups of similar outcomes up to a maximum of ten outcomes per page. For the neonatal and non-neonatal panels, outcomes were primarily presented using medical terminology, whereas for the personal experience panel, lay terminology was used. For all three panels, hovering the mouse over the outcome displayed the alternate outcome description.

3.4.3.5. Delphi process – outcome scoring and data feedback

Based upon recommendations from the COMET initiative, the GRADE scale of measurement was chosen to score outcomes(20). If participants felt unable to allocate a score to an outcome, they were able to select 'Don't Know'. If participants did not complete the questionnaire they were sent reminder emails with two weeks, 1 week, and 48 hours remaining in the phase.

At the end of phase one, descriptive statistics, including the median and distribution of scores were calculated for each outcome for each panel. In phase two, participants were shown graphical and numerical representations of the descriptive statistics for each outcome for their panel from phase one, along with a reminder of the score they allocated to each outcome in phase one (Figure 3). At the end of phase two, the same descriptive statistics were again calculated for each outcome for each panel. In phase three, participants were shown graphical representations of the descriptive statistics for all three panels, along with a reminder of the scores they allocated to each outcome in phase two (Figure 4).

Figure 3: Annotated example of the graphical representations used to feed back descriptive statistics to participants in phase two

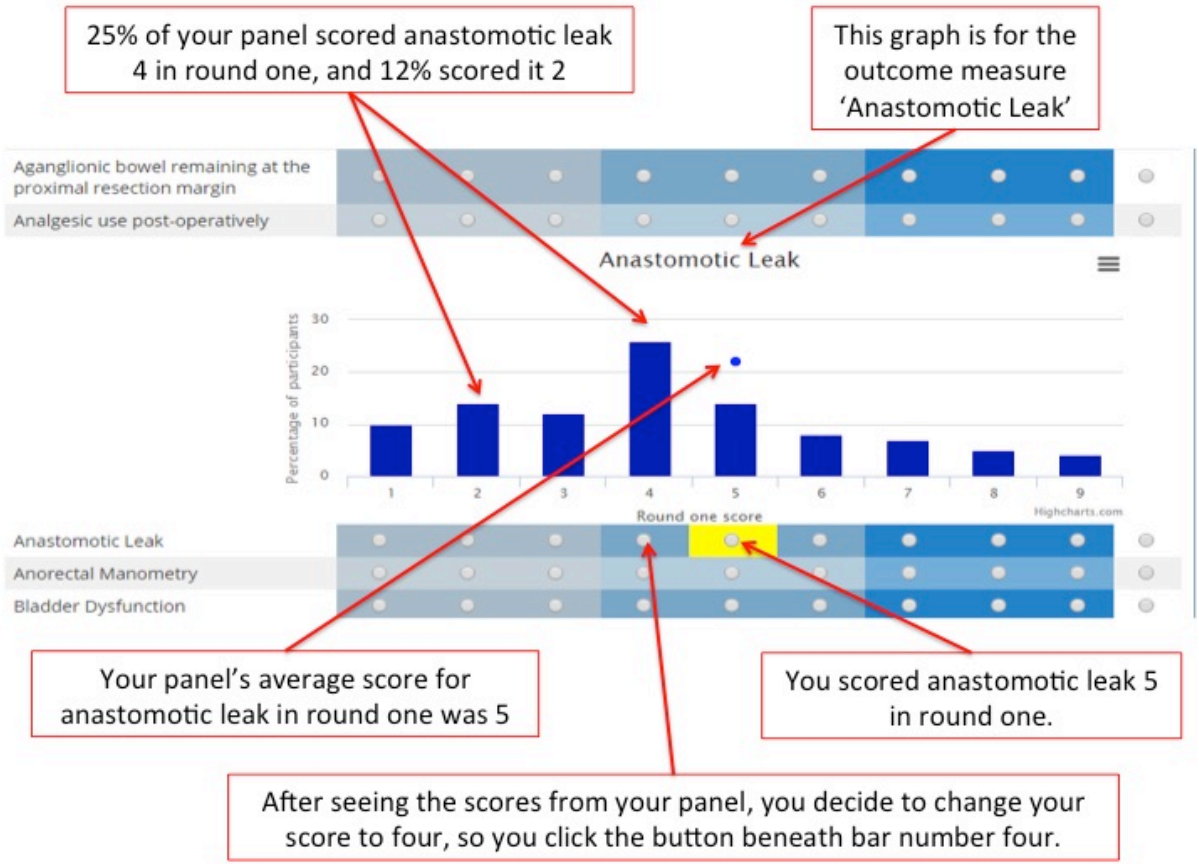
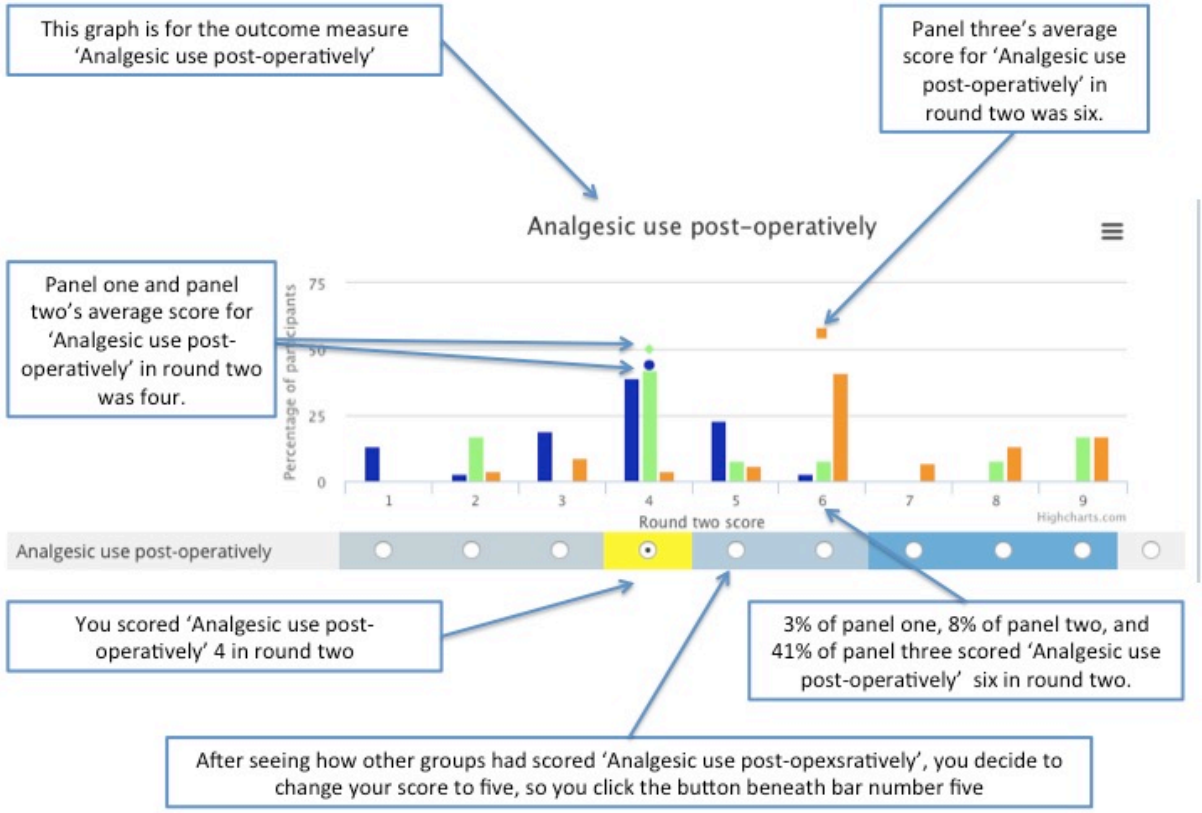


Figure 4: Annotated example of the graphical representations used to feed back descriptive statistics to participants in phase three



3.4.3.6. Delphi process – addition and dropping of outcomes

After completion of outcome scoring in phase one, participants were asked to list any additional outcomes they considered important in determining whether treatment of their/their child's/their patient's condition had been successful, but which they had not already been asked to score. They were able to list as many outcomes as they considered necessary. Additional outcomes proposed by participants, along with comments left in relation to individual outcomes were reviewed by the SMG. Outcomes that required clarification based upon feedback from participants were revised by the SMG. De novo outcomes proposed by phase one participants that were deemed to be within the scope of the COS were added to the list of outcomes to be scored in phase two. These outcomes were added into the phase two questionnaire alongside similar outcomes. No outcomes were dropped between phase one and phase two.

It was initially proposed that no outcomes would be dropped between phase two and phase three of the Delphi process. However, after publication of the protocols(72, 76), but prior to phase one of the Delphi processes, it was decided by the SMGs that in order to allow participants to focus on outcomes likely to be of greater importance, outcomes would be dropped after phase two of the Delphi process if more than 50% of participants in ***at least one panel*** scored the outcome 1-3, and less than 50% of participants in ***all panels*** scored it 7-9. Outcomes that were dropped between phase two and phase three were listed at the end of phase three, and participants were invited to leave comments if they felt it necessary.

3.4.3.7. Delphi process – attrition of participants

The numbers of experts invited to participate; registering to participate, and completing each phase of the Delphi process from each stakeholder group were calculated.

3.4.4. Consensus meeting summary

It was pre-determined that the COS would be formed from a maximum of ten outcomes based upon the scores allocated at a face-to-face consensus meeting. The purpose of the consensus meeting was to facilitate open group discussion of the highest scoring outcomes from phase three in order to understand in detail the rationale behind scores allocated to them by each stakeholder group. Following discussion of each outcome, meeting attendees were asked to re-score the outcome using the same nine-point Likert scale, in light of the group discussion that had been held. These final scores were used to determine which outcomes formed the COS.

3.4.4.1. Consensus meeting attendees

Participants who had completed all three phases of the Delphi process and who had indicated their availability for the date of the consensus meeting were invited in a purposive manner to achieve a spread of attendees across all three panels, all stakeholder groups, and geographical location. Prior to the date of the meeting, participants who confirmed their attendance were sent electronically a meeting handbook containing instructions for the day, a list of all outcomes to be discussed, graphical representations of the descriptive statistics for each outcome for each

panel following phase three scoring, the percentage of each panel that scored each outcome 7-9 in phase three, and a reminder of the scores that they personally allocated to each outcome in phase three.

3.4.4.2. Consensus meeting structure

Outcomes were automatically discussed at the consensus meeting if in phase three of the Delphi process two or more panels deemed them to meet the threshold for inclusion in the COS. As per guidance from the COMET initiative, the threshold for inclusion in the COS was defined as ≥70% participants scoring an outcome 7-9, and <15% scoring 1-3 (77). Other outcomes were only discussed and re-scored at the consensus meeting if there was unanimous agreement amongst the meeting attendees that they warranted further discussion.

At the consensus meeting, all outcomes reaching 'consensus in' status in two or three panels were discussed first, grouped according to the outcome's OMERACT filter 2.0 core area. Adverse event outcomes were discussed as a group as opposed to within their core areas. Outcomes not meeting the criteria for automatic discussion, but which were unanimously agreed by meeting attendees to require further review were discussed after all other outcomes had been scored.

A non-voting chair facilitated discussion and scoring at the consensus meeting, and each attendee had access to a hard copy of the meeting handbook. Whilst outcomes were being discussed and scored, graphical representations of the descriptive

statistics for that outcome from phase three, and the percentage of participants in each panel scoring the outcome 7-9 in phase three were displayed. All scoring of outcomes was electronic and anonymous, with group scores fed back to attendees immediately following scoring.

3.4.4.3. Formation of the core outcome set

Outcomes where ≥70% of meeting attendees allocated scores of 7-9, and <15% allocated scores of 1-3, were determined to have met consensus for inclusion in the COS. It was pre-specified that if less than ten outcomes met consensus for inclusion, that all would be included, but that if more than ten met consensus for inclusion, then in order to ensure practicality of use of the COS, only the following ten would be included:

- The highest scoring outcome meeting consensus for inclusion in the COS from each of the OMERACT filter 2.0 core areas
- The highest scoring adverse event outcome meeting consensus for inclusion in the COS (if not already included as the highest scoring outcome in one of the four core areas)
- The remaining outcomes meeting consensus for inclusion in the COS, added in order of highest score regardless of OMERACT filter 2.0 core area, up until a maximum of ten outcomes were included.

Highest scoring was defined as greatest percentage of participants allocating scores of 7-9 in the consensus meeting. If there was a tie based on this score, then the highest scoring outcome was the one with the greatest percentage of participants allocating a score of 9, then 8, then 7, continued through to 1 if necessary.

3.4.5. Core Outcome Measurement Meeting

Following the consensus meeting, a review was undertaken of all papers identified in the systematic review as having reported one of the identified core outcomes. The methods of measurement of the outcome, along with timing of the outcome measurement were recorded. An expanded literature search was then conducted to identify methods of measurement of the core outcomes that were used in other specialties or conditions, but which had not previously been used by one of the studies included in the systematic review. The results of the literature reviews were discussed by the SMG and summarised in core outcome measurement documents. Proposals for the definition, method of measurement and timing of measurement were also summarised in the core outcome measurement documents.

Participants who attended the consensus meeting and indicated they were available on the date of the core outcome measurement meeting were invited to attend. Each registered attendee was sent an electronic copy of the core outcome measurement document in advance of the meeting. A round table, face-to-face meeting was then held, chaired by the same independent chair as the consensus meeting. Each core outcome was discussed in detail, along with the pros and cons of each proposed

method of measurement, including how well the measurement tool performed against the criteria of truthfulness, discrimination and feasibility of use described by Boers et al(37). Facilitated group discussion was used to attain consensus on definitions, methods of measurement, and timings of measurement for each core outcome.

3.4.6. Assessment of attrition bias

In order to assess whether drop out of participants throughout the gastroschisis Delphi process was likely to have affected outcomes, median phase one scores for the outcomes included in the COS (or their nearest approximation where the outcome was added after phase one) were compared between participants within each panel who completed all three phases of the Delphi process and those who only completed phase one. The Wilcoxon Rank Sum test was used to compare scores, and in order to reduce the risk of a type I error, the Bonferroni correction was used to set the level of significance at a p-value of <0.002. All statistical analyses were conducted using Stata Version 14 (StatCorp, 4905 Lakeway Drive, College Station, TX 77845, United States of America).

3.4.7. Ethics approval

The HRA deemed the studies to be service evaluation/service development, which did not require review by a research ethics committee.

3.5. Results

3.5.1. Systematic review

3.5.1.1. Hirschsprung's Disease included studies

The search retrieved 696 unique titles related to HD, 640 of which were excluded following title and abstract review. Following full paper review, a further 21 papers were excluded (Appendix 6), leaving 35 studies as eligible for inclusion in the review (Figure 5).

3.5.1.2. Hirschsprung's Disease reported outcomes

In the 35 included studies, 95 outcomes were investigated a total of 337 times. Thirty-five outcomes were considered to be too similar to at least one other outcome to be meaningfully differentiated, and these were therefore mapped to one common term (e.g. continence/incontinence, or frequency of stool/bowel movement frequency). Following this exercise, 74 unique outcomes were identified as having been reported (Table 2). Outcomes were mapped to the OMERACT filter 2.0. Overall, 33 'adverse event' outcomes (45%); 28 'life impact' outcomes (38%); seven 'resource use' outcomes (9%); five 'pathophysiological manifestation' outcomes (7%); and one 'death' outcome (1%) were reported. Adverse event outcomes accounted for 171 of the 338 outcomes that studies investigated (51%), whilst life impact outcomes accounted for 109 (32%). Thirty-three (45%) of the 74 unique outcomes were only investigated in one study. The median number of outcomes investigated per study was 11 (IQR6-13).

For further details of the completeness and transparency with which outcomes were reported, see the published systematic review manuscript in Appendix 7.

Figure 5: Hirschsprung's Disease PRISMA flow chart

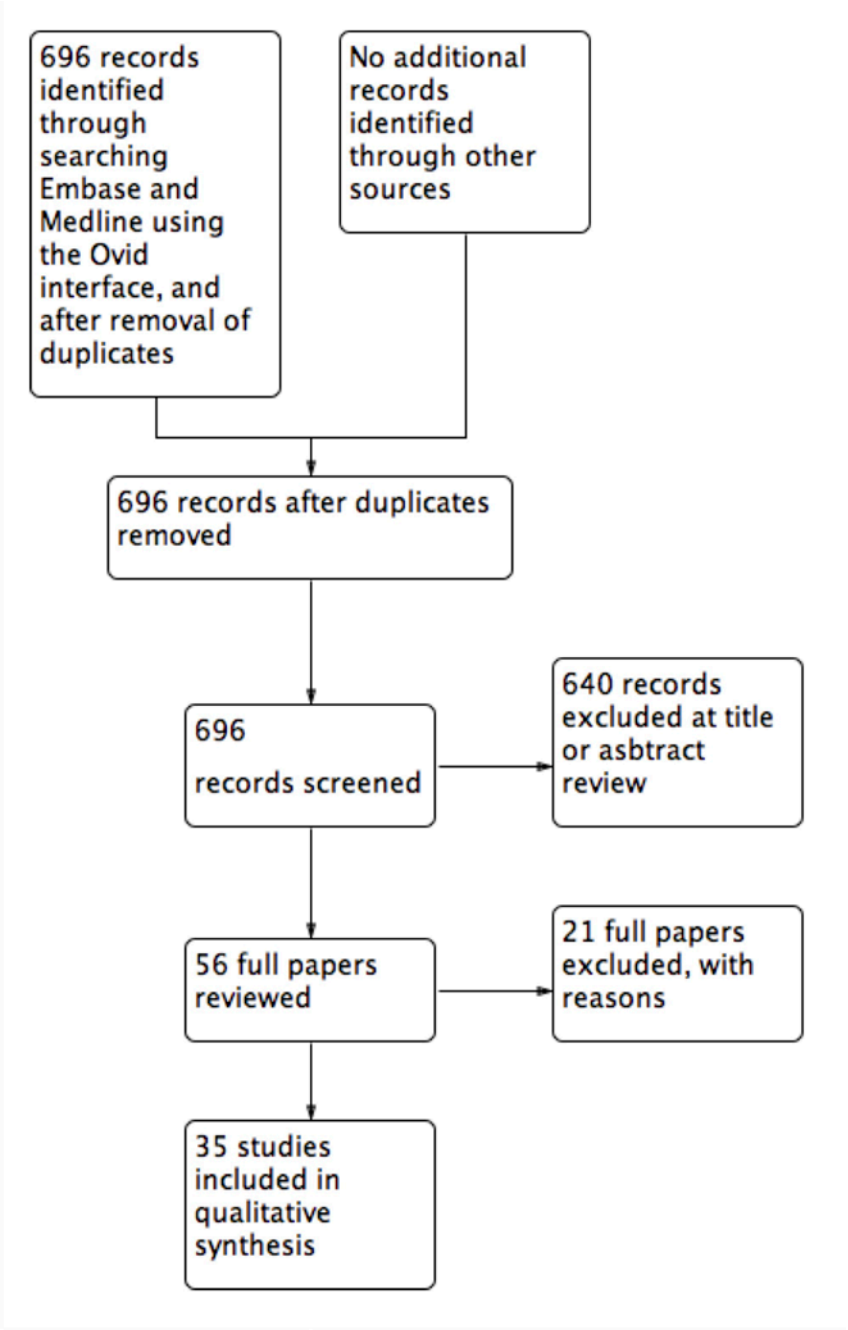


Table 2: Hirschsprung's Disease outcomes and number of times reported

Life Impact Outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Development - Social	1 (3%)	Medication – laxative	2 (6%)	Voluntary bowel movements	2 (6%)
Sleep disturbance	1 (3%)	Dilations	1 (3%)	Frequency of bowel movements	13 (37%)
Depression	1 (3%)	Continence – urinary	1 (3%)	Time to normal bowel habits	1 (3%)
Psychological stress	1 (3%)	Assessment of bowel function	1 (3%)	Requiring nappy	1 (3%)
Cosmetic results	2 (6%)	Bowel Function Score (BFS) questionnaire	2 (6%)	Faecal incontinence	32 (91%)
Parenteral nutrition use	1 (3%)	Gastrointestinal Quality of Life Index (GIQLI) questionnaire	2 (6%)	Encopresis	1 (3%)
Time until first feed (post-operatively)	7 (20%)	Krickenbeck score	2 (6%)	Consistency of stool	3 (9%)
Diet tolerated	1 (3%)	Sensation of need to defecate	2 (6%)	Urgency period	3 (9%)
Long-term bowel dysfunction	1 (3%)	Diarrhoea	3 (9%)	Constipation	20 (57%)
Faecal Impaction	1 (3%)				

Table 2: Hirschsprung's Disease outcomes and number of times reported – Continued

Pathophysiological manifestation outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Bowel Movement – first post-op	3 (9%)	Manometry	1 (3%)	Aganglionic bowel remaining	1 (3%)
Bladder Dysfunction	1 (3%)	Early pelvic inflammation	1 (3%)		
Adverse event outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Post-operative infection	9 (26%)	Intra-operative complication	4 (11%)	Colostomy morbidity	1 (3%)
Fever	1 (3%)	Intra-operative visceral injury	2 (6%)	Narrowing of anastomosis or cuff	22 (63%)
Abscesses	5 (14%)	Colonic torsion	2 (6%)	Impotence	1 (3%)
Anastomotic Leak	13 (37%)	Ischaemia	1 (3%)	Abdominal distension	3 (9%)
Pneumonia	2 (6%)	Enterocolitis	23 (66%)	Sphincter achalasia	1 (3%)
Dehiscence	7 (20%)	Granuloma	1 (3%)	Feeding intolerance	1 (3%)
Conversion	6 (17%)	Fistula	1 (3%)	Prolapse	2 (6%)
Intra-operative blood loss	13 (37%)	Necrosis of and retraction of colon	1 (3%)	Rectal muscularis infection	1 (3%)
Reoperations	11 (31%)	Adhesions	1 (3%)	Herniation	6 (17%)
Excoriation	10 (29%)	Post-operative 'complications'	3 (9%)	Colostomy retractions	1 (3%)
Anal lacerations	1 (3%)	Early or persistent obstruction	8 (23%)	Late or adhesional obstruction	7 (20%)

Table 2: Hirschsprung's Disease outcomes and number of times reported – Continued

Mortality outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Death	7 (20%)				
Resource use outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Operation length	17 (49%)	ICU admission	1 (3%)	Readmission	2 (6%)
Time of antibiotic administration	1 (3%)	Hospital stay (length)	18 (51%)	Cost	2 (6%)
Analgesic use post-operatively	2 (6%)				

3.5.1.3. Gastroschisis included Studies

The search strategy returned 234 titles related to gastroschisis, reduced to 211 after exclusion of duplicates. Following review of titles and abstracts, 167 records were excluded. A further fourteen records were then excluded following full paper analysis (Appendix 8), resulting in 30 studies that were deemed eligible for inclusion in the review (Figure 6).

3.5.1.4. Gastroschisis reported outcomes

Within the included studies, 102 outcomes were investigated a total of 247 times. Within these 102 outcomes there were 63 that were felt to be too similar to at least one other outcome to be meaningfully differentiated, and these were therefore mapped to one common term. Following this mapping process, 62 unique outcomes remained and were mapped to the OMERACT filter 2.0 core areas (Table 3). Overall, 22 'adverse event' outcomes (35%), 18 'pathophysiological manifestation' outcomes (29%), 12 'life impact' outcomes (20%), nine 'resource use' outcomes (15%), and one 'death' outcome (1%) were reported. 'Adverse event' outcomes were reported 97 times (39% of all reported outcomes), whilst 'life impact' outcomes were reported 58 times (23% of all reported outcomes). The median number of times an outcome was reported was once (IQR1-2). The median number of outcomes reported per study was 9 (IQR5-11).

Figure 6: Gastroschisis PRISMA flow chart

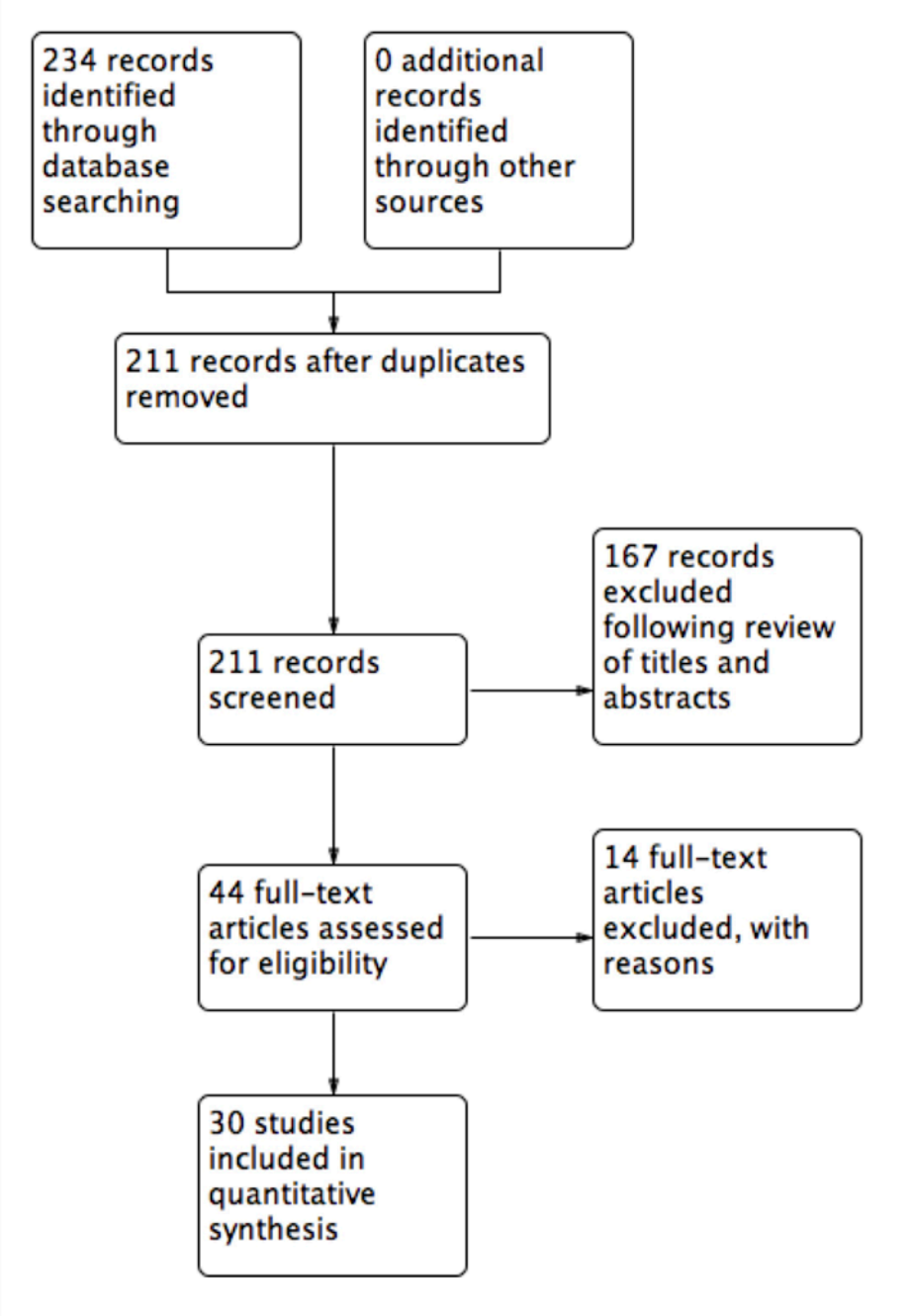


Table 3: Gastroschisis outcomes and number of times reported

Life impact outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Time on ***total*** parenteral nutrition	9(30%)	Feeding, initiation of feed in the Neonatal Intensive Care Unit (NICU)	1(3%)	Short Bowel Syndrome	4(13%)
Time on parenteral nutrition	12(40%)	Feeding, full feeds at discharge from NICU	1(3%)	bowel lengthening procedure required	1(3%)
Parenteral nutrition ever required	1(3%)	Time to first oral feed	13(43%)	liver transplantation	1(3%)
Parenteral nutrition required post-discharge	1(3%)	Time to full oral feeds	13(43%)	Neurodevelopmental delay	1(3%)
Pathophysiological manifestation outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Weight gain	1(3%)	Total time on mechanical ventilation	13(43%)	Post-operative ventilation required	1(3%)
Hypothyroidism	1(3%)	Post closure time on mechanical ventilation	3(10%)	Respiratory compromise	1(3%)

Table 3: Gastroschisis outcomes and number of times reported - Continued

Pathophysiological manifestation outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Bacteraemia	2(7%)	Ventilation, peak inspiratory pressure	1(3%)	Neonatal Respiratory Distress Syndrome	1(3%)
pH, time acidotic	1(3%)	Ventilation, peak concentration inspired oxygen	1(3%)	Cholestasis	2(7%)
Kidney dysfunction	1(3%)	Need for mesh at closure	1(3%)	Volume of IV fluid required	1(3%)
Urine output	3(10%)	Weight<10th centile	1(3%)	Blood pressure, mean arterial	1(3%)
Adverse event outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Infection free survival	1(3%)	Anastomotic stricture	2(7%)	Infection, unspecified or other	7(23%)
Infection, urinary or respiratory	3(10%)	Intestinal perforation	3(10%)	Infection, central line related	6(20%)
Number of transfusions	1(3%)	Abdominal compartment syndrome	7(23%)	Wound infection or breakdown	12(40%)
Silo Complication	2(7%)	NEC	16(53%)	Infection with systemic sequelae	8(27%)

Table 3: Gastroschisis outcomes and number of times reported - Continued

Adverse event outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Ischaemic bowel	2(7%)	Stoma complication	2(7%)	Adhesional small bowel obstruction	3(10%)
Reoperation, need for enlargement of gastroschisis defect	1(3%)	GI complication	1(3%)	Intestinal Failure Associated Liver Disease	6(20%)
Reoperation, need for silo replacement	1(3%)	Non-GI complication	1(3%)	Unplanned reoperation	9(30%)
Umbilical hernia	3(10%)				
Pathophysiological manifestation outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Length of stay	24(80%)	General anaesthesia, number of days, indication	3(10%)	Hospital charge	1(3%)
NICU length of stay	4(13%)	Central-line usage ratio (days with central line/hospital days)	24(80%)	Days to abdominal wall closure	1(3%)
Discharge, NICU to home	1(3%)	Duration of antibiotics	4(13%)	Rehospitalisation	3(10%)

Table 3: Gastroschisis outcomes and number of times reported - Continued

Mortality outcomes					
Outcome	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**	**Outcome**	**Number of studies reported in n(%)**
Mortality	19(63%)				

3.5.2. Hirschsprung's disease Delphi process

3.5.2.1. Participants

One hundred and forty-five experts registered to participate in the study, 108 (74%) of whom completed phase one of the Delphi process. Ninety-six eligible participants (89%) completed phase two, and 89 eligible participants (93%) completed phase three. Seventeen participants were selected to attend the consensus meeting, and 14 the measurement definition meeting (Tables 4 and 5).

Table 4: Summary of Hirschsprung's disease delphi process participants

	Registering for phase one	Completing phase one	Completing phase two	Completing phase three	Consensus Meeting	Measurement Meeting
		n(%)*	n (%)*	n (%)*	n	n
Neonatal Panel	41	34 (83%)	33 (97%)	31 (94%)	9	7
Non-neonatal panel	15	13 (87%)	12 (92%)	12 (100%)	2	3[#]
Personal experience panel	89	61 (69%)	51 (84%)	46 (87%)	6	4
Total	145	108 (74%)	96 (89%)	89 (93%)	17	14

*Percentage of those eligible to participate in the phase

The Hirschsprung's disease researcher who acted as non-voting chair for the consensus meeting actively participated in the measurement meeting, and is therefore included in the participant numbers for the measurement meeting, but not the consensus meeting.

Table 5: Characteristics of participants in the Hirschsprung's disease Delphi process

	Parents of children with HD											
	Location*		**Age of Child (years)**				**Parent-reported severity of child's HD^**				**Gender**	
	British Isles	**Other**	**≤ 5**	**6-10**	**11-15**	**≥16**	**Median on 1-9 scale (IQR)**	**Ultra-short segment**	**Short segment**	**Long segment**	**Male**	**Female**
Completed Delphi process	29 (76%)	9 (24%)	19 (49%)	13 (33%)	1(3%)	6 (15%)	7 (6-8)	1 (3%)	22 (59%)	14 (38%)	1 (3%)	38 (97%)
Only completed phase one	12 (86%)	2 (14%)	6 (43%)	5 (36%)	1 (7%)	2 (14%)	Not collected until phase two				14	0
	People with HD											
	Location		**Age**				**Self-reported severity HD$**				**Gender**	
	British Isles	**Other**	**11-15 years old**		**≥ 21 years old**		**Median on 1-9 scale (IQR)**	**Ultra-short segment**	**Short segment**	**Long segment**	**Male**	**Female**
Completed Delphi process	4 (57%)	3 (43%)	1 (14%)		6 (86%)		7 (5-8)	0 (0%)	0 (0%)	6 (100%)	4 (57%)	3 (43%)
Only completed phase one	1 (100%)	0 (0%)	0 (0%)		1 (100%)		Not collected until phase two				0 (0%)	1 (100%)

*One person preferred not to say, ^ One person preferred not to score, and two did not know the length of affected bowel, $ One person did not know the length of affected bowel

Table 5: Characteristics of participants in the Hirschsprung's disease Delphi process - Continued

Neonatal Panel										
	Location		**Prior involvement in HD Research**		**Number of HD patients treated per year**		**Stakeholder group**		**Gender**	
	British Isles	**Other**	**No**	**Yes**	**≤ 10**	**>10**	**Paediatric surgeons**	**Neonatologists**	**Male**	**Female**
Completed Delphi process	29 (94%)	2 (6%)	11 (35%)	20 (65%)	21 (68%)	10 (32%)	27 (87%)	4 (13%)	23 (74%)	8 (26%)
Only completed phase one	2 (66%)	1 (33%)	0(0%)	3 (100%)	0 (0%)	3 (100%)	3 (100%)	0 (0%)	3	0

Non-neonatal panel											
	Location		**Prior involvement in HD Research**		**Number of HD patients treated per year#**		**Stakeholder group**			**Gender**	
	British Isles	**Other**	**No**	**Yes**	**≤ 10**	**>10**	**Specialist Nurses**	**Paediatric gastroenterologists**	**HD Researchers**	**Male**	**Female**
Completed Delphi process	12 (100%)	0 (0%)	9 (75%)	3 (25%)	7 (58%)	3 (42%)	7 (58%)	4 (33%)	1 (8%)	4 (33%)	8 (66%)
Only completed phase one	1 (100%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)

[#]One preferred not to say, and one participant was not a clinician and therefore this question was not applicable.

3.5.2.2. Outcome modification prior to phase one

Following SMG review of the 74 outcomes identified by the systematic review, a total of 10 outcomes (14%) were removed and 10 were added, meaning the number of outcomes taken forward to phase one of the Delphi process remained at 74 (Table 6). Three outcomes (4%) relating to the areas of re-admission, anastomotic narrowing and perianal excoriation which were each felt to represent multiple outcomes, and were therefore split into eight unique outcomes. Nine outcomes (12%) relating to the areas of bowel function, bowel obstruction and feeding overlapped significantly and were merged to four outcomes. Five outcomes, “time to full feeds”, “painful defecation”, “post-operative experience of pain”, “incisional hernia”, and “stomal stenosis”, not identified by the systematic review were deemed important by the SMG and within the scope of the COS and were added to the long-list of candidate outcomes. Definitions of a further three outcomes (4%) required clarification. Five outcomes (constipation, diarrhoea, encopresis, anal lacerations, necrosis and retraction of the colon) were deemed out of the scope of the COS and were therefore removed by the SMG.

Table 6: Outcomes taken forward to phase one of the NETS[1HD] Hirschsprung's disease Delphi process

Professional Term	Lay Term
Abdominal distension	Whether the tummy remains swollen/distended
Abscesses	Whether an abscess (a collection of pus) develops after the operation
Adhesions	Whether adhesions (scar tissue) form inside the abdomen
Aganglionic bowel remaining at the proximal resection margin	Whether there is any abnormal bowel remaining after the operation.
Analgesic use post-operatively	How much pain relief was needed after the operation
Anastomotic Leak	Whether the point where two bits of bowel have been joined together (anastomosis) develops a leak
Anorectal Manometry	What pressure is produced by the muscles that control when the bowels open (as measured by a test called anal manometry)
Bladder Dysfunction	Whether the bladder works normally
Colonic torsion	Whether the bowel was accidentally left twisted at the end of the operation
Consistency of stool	How hard or soft the poo is
Conversion to open	Whether an operation that started as a keyhole operation has to instead be performed through a bigger wound
Cosmetic results	What the tummy looks like after the operation, for example the appearance of the scars
Cost	How much the operation cost
Cuff infection	Whether there is an infection of the layer of muscle around the bowel where it has been joined onto the bottom.
Death	Death
Dehiscence	Whether the cuts that were made to do the operation open up again
Depression	Depression
Dilations	Whether regular stretching of the anus is required
Duration of post-operative antibiotic use	How long antibiotics were given for after the operation
Early pelvic inflammation	Whether there is internal inflammation (swelling) after the operation
Enterocolitis	Development of Hirschsprung's Enterocolitis (a serious infection of the bowel)

Table 6: Outcomes taken forward to phase one of the NETS[1HD] Hirschsprung's disease Delphi process - Continued

Professional Term	Lay Term
Faecal Impaction	When hard poo gets stuck in the bowel, needing to be cleared by medicines, enemas (liquid medicine given via the bottom), or manually removed
Faecal incontinence	Unable to control the bowels so poo leaks out without control
Fever	Whether there is an abnormally high temperature after the operation
First post-operative bowel movement	How long it was between the operation and bowels first opening
Fistula	Whether an abnormal connection called a fistula is formed between the skin and part of the bowel
Frequency of bowel movements	How often the bowels open
Granuloma	Abnormal excessive healing tissue around a wound
Hospital stay (length)	How long the total hospital stay was after the operation
ICU or HDU admission	Whether admission to the intensive care unit or high dependency unit was needed after the operation
Impotence	Inability to achieve or maintain an erection
Incisional hernia	Whether an incisional hernia develops. An incisional hernia is where there is a weakness in the muscle under the cuts that were used to perform the operation, so that that bowel pokes through the muscle causing a lump under the skin.
Intra-operative blood loss	Whether there is bleeding during the operation
Intra-operative complication	Whether there is a complication during the operation
Intra-operative visceral injury	Whether there is injury to another organ during the operation
Ischaemic bowel	Whether the blood supply to the bowel is affected during the operation
Laxative medications	Whether laxatives (medicines that make the poo softer, or increase how often the bowels open) are required
Long-term difficulty in feeding, or intolerance of food	Whether there is difficulty in feeding
Narrowing of anastomosis	Whether there is a narrowing of the point where healthy bowel has been joined to the bottom
Narrowing of cuff	Whether the layer of muscle around the bowel where it has been joined to the bottom becomes too tight

Table 6: Outcomes taken forward to phase one of the NETS[1HD] Hirschsprung's disease Delphi process - Continued

Professional Term	Lay Term
Objective score of bowel function	A scoring system that gives an overall numerical representation of how well the bowels are working
Objective score of quality of life	A scoring system that gives an overall numerical representation of how good quality of life is
Operation length	How long the operation took
Painful defecation	Whether it is painful to go for a poo
Parastomal Hernia	Development of a hernia around the stoma. A stoma is where the bowel is joined to the skin on the tummy wall so that poo goes into a bag on the tummy as opposed to through the bottom. A hernia is where there is a weakness in the muscle so that that bowel pokes through the muscle causing a lump under the skin.
Parenteral nutrition use	Whether nutrition given through a drip into a vein is required (intravenous nutrition, or TPN)
Peri-anal Excoriation with significant impact on daily life	Whether there is nappy rash (irritation and breakdown of the skin around the bottom), that is having a significant impact on daily life, e.g. requiring extensive skin care regimes
Peri-anal Excoriation without significant impact on daily life	Whether there is nappy rash (irritation and breakdown of the skin around the bottom), without significant impact on daily life
Peri-stomal Excoriation with significant impact on daily life	Irritation and breakdown of skin around the stoma that has a significant impact on daily life e.g. requiring excessive stoma bag changes, or extensive skin care regimes. A stoma is where the bowel is joined to the skin on the tummy wall so that poo goes into a bag on the tummy as opposed to through the bottom.
Peri-stomal Excoriation without significant impact on daily life	Irritation and breakdown of skin around the stoma that has a minimal impact on daily life. A stoma is where the bowel is joined to the skin on the tummy wall so that poo goes into a bag on the tummy as opposed to through the bottom.
Planned readmission (e.g. for anal dilatations)	Whether another planned admission was needed after being discharged from the initial operation e.g. for regular stretching of the anus
Pneumonia	Whether a chest infection develops after the operation
Post-operative 'complications'	Whether there are complications after the operation
Post-operative Bowel obstruction	Whether the bowel becomes blocked after the operation

Table 6: Outcomes taken forward to phase one of the NETS[1HD] Hirschsprung's disease Delphi process - Continued

Professional Term	Lay Term
Post-operative experience of pain	How much pain was experienced after the operation
Post-operative infection	Whether there is an infection after the operation
Psychological stress	Stress and Anxiety
Reoperations	Whether more than one operation is required
Requiring nappy or pad	Whether a nappy or pad is required
Sensation of need to defecate	Whether there is the normal feeling of needing to open the bowels
Sleep disturbance	Sleep disturbance
Social development	Development of normal social interactions
Sphincter achalasia	High pressure of the muscles around the bottom that control when the bowels open (as measured by a test called anal manometry)
Stoma morbidity	Whether there are problems with the stoma (if one was made). A stoma is where the bowel is joined to the skin on the tummy wall so that poo goes into a bag on the tummy as opposed to through the bottom
Stomal Prolapse	Whether the stoma comes out further than it should. A stoma is where the bowel is joined to the skin on the tummy wall so that poo goes into a bag on the tummy as opposed to through the bottom
Stomal retraction	Whether the stoma shrinks back inside the abdomen. A stoma is where the bowel is joined to the skin on the tummy wall so that poo goes into a bag on the tummy as opposed to through the bottom
Stomal stenosis	Whether the stoma becomes narrowed. A stoma is where the bowel is joined to the skin on the tummy wall so that poo goes into a bag on the tummy as opposed to through the bottom
Time to full feeds (post-operatively)	Time between the operation and taking full feeds by mouth without any need for fluid or feed through a drip
Time to normal bowel habits	How long there is between the operation and bowels working normally
Time until first feed (post-operatively)	Time between the operation and first being able to have milk/food by mouth
Unplanned Readmission	Whether another unplanned admission was needed after being discharged from the initial operation
Urgency of stool	Whether it is difficult to get to the toilet for a poo in time without an accident
Urinary incontinence	Unable to control the bladder so urine leaks out without control

Table 6: Outcomes taken forward to phase one of the NETS[1HD] Hirschsprung's disease Delphi process - Continued

Professional Term	Lay Term
Voluntary bowel movements	Whether the bowels work without needing enemas (liquid medicine given via the bottom), washouts (water or saline given via the bottom to washout poo) or a stoma (A stoma is where the bowel is joined to the skin on the tummy wall so that poo goes into a bag on the tummy as opposed to through the bottom).

3.5.2.3. Outcome handling after phase one

Overall, 140 individual comments were made by participants during phase one, 62 of which (44%) were made by 15 members (44%) of the neonatal panel, 73 (52%) by 35 members (57%) of the personal experience panel, and five (4%) by two members (15%) of the non-neonatal panel. Based on these comments, the SMG clarified 19 outcomes (26%), and added 28 new outcomes for assessment in phase two. Six of these outcomes (21%) were proposed by the personal experience panel, six (21%) by other panels, and the remaining 16 (57%) by multiple panels. Overall, 102 outcomes were taken forward to phase two. Following completion of phase two, 13 outcomes (13%) were dropped, and following phase three, 44 outcomes (49%) did not meet criteria for automatic progression to the consensus meeting (Figure 7 and Table 7). Following discussions, modifications and additions (Figure 7 and Appendix 9) a total of 45 outcomes were scored at the consensus meeting. Of these 45 outcomes, fifteen met the criteria for inclusion in the COS, and ten were retained (Table 8 and Table 9). The final NETS^{1HD} Hirschsprung's disease COS is described in Box 1.

Figure 7: Flow of outcomes through the NETS[1HD] Delphi process

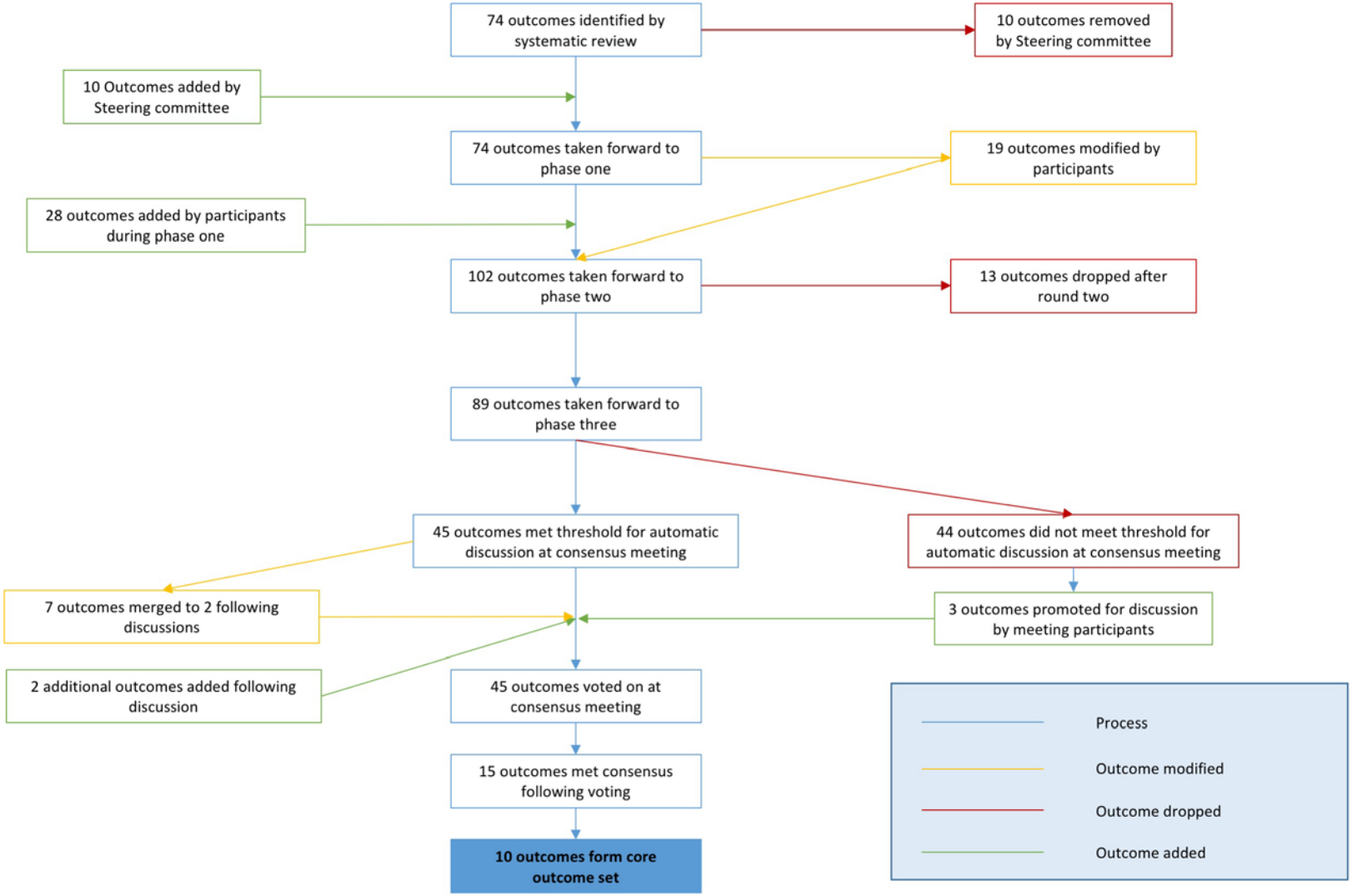


Table 7: Outcome handling in the NETS[1HD] Delphi process

Outcomes modified between phase one and two	
Description in phase one	**Description in phase two**
Bladder Dysfunction	Long-term bladder dysfunction
Cost	Operative cost
Dehiscence	Wound dehiscence
Depression	One or more periods of depression requiring treatment, at any age, as a result of the physical or psychological impact of the HD or its treatment
Dilations	Need for anal dilations (other than a single post-operative calibration)
Duration of post-operative antibiotic use	Duration of therapeutic, not prophylactic antibiotic use post-operatively
Faecal incontinence	Long-term faecal incontinence
Granuloma	Granuloma/excessive granulation tissue formation
Intra-operative complication	*Any* intra-operative complication
Intra-operative visceral injury	*Any* intra-operative visceral injury
Long-term difficulty in feeding, or intolerance of food	Long-term difficulty in feeding
Objective score of quality of life	Objective score of quality of life, using appropriate age specific measures
Parenteral nutrition use	Duration of parenteral nutrition use
Post-operative complications	*Any* post-operative complication
Psychological stress	Long-term psychological stress
Stoma morbidity	Any stoma morbidity that results in the child requiring additional pharmacological interventions
Time to normal bowel habits	Time from operation to development of bowel habits that would be considered normal for someone without HD
Urinary incontinence	Long-term urinary incontinence
Voluntary bowel movements	Long-term voluntary bowel movements without need for enemas, Peristeen, washouts or an ACE.

Table 7: Outcome handling in the NETS[1HD] Delphi process - Continued

Outcomes added between phase one and phase two
Lifetime healthcare costs
Ability to control flatus
Long-term offensive odour secondary to lack of control of faeces, or flatus, or inability to maintain hygiene
Intra-operative complication - minor impact on recovery (Clavien-Dindo grade one)
Intra-operative complication - requires additional medication (Clavien-Dindo grade two)
Intra-operative complication - requires additional surgery (Clavien-Dindo grade three)
Intra-operative complication - life threatening (Clavien-Dindo grade four)
Intra-operative complication resulting in death (Clavien-Dindo grade five
Intra-operative visceral injury - minor impact on recovery (Clavien-Dindo grade one)
Intra-operative visceral injury - requires additional medication (Clavien-Dindo grade two)
Intra-operative visceral injury - requires additional surgery (Clavien-Dindo grade three)
Intra-operative visceral injury - life threatening (Clavien-Dindo grade four)
Intra-operative visceral injury resulting in death (Clavien-Dindo grade five)
Long-term need for dietary supplementation, or specialist exclusion diet
Whether home parenteral nutrition is required
Post-operative complication - minor impact on recovery (Clavien-Dindo grade one)
Post-operative complication - requires additional medication (Clavien-Dindo grade two)
Post-operative complication - requires additional surgery (Clavien-Dindo grade three)
Post-operative complication - life threatening (Clavien-Dindo grade four)
Post-operative complication resulting in death
Any stoma morbidity requiring surgical intervention
Need for a long-term or permanent stoma
Need for a new stoma at any point after the pull-through procedure
Difficulty in conceiving a child
Difficulty with sexual relations or sexual intercourse, because of the psychological or physical impact of HD or its treatment.
Regular post-operative anal sphincter Botox injections
Outcomes dropped after phase two
Whether an operation that started as a keyhole operation has to instead be performed through a bigger wound
How much the operation cost (regardless of who pays these costs)
How long antibiotics were given for to treat an infection after the operation
Whether there is an abnormally high temperature after the operation
How long it was between the operation and bowels first opening
Abnormal excessive healing tissue around a wound
How long the total hospital stay was after the operation
Complication during the operation that has a minor impact on recovery
Complication during the operation which requires additional medicine to be given to treat it
How long the operation took
A complication after the operation which has minimal impact on recovery
Time between the operation and first being able to have milk/food by mouth

Table 7: Outcome handling in the NETS[1HD] Delphi process - Continued

Outcomes dropped after phase two
Time between the operation and taking full feeds by mouth without any need for fluid or feed through a drip
Outcomes dropped after phase three
Regular post-operative anal sphincter Botox injections
Need for anal dilations (other than a single post-operative calibration)
Unplanned Readmission
Analgesic use post-operatively
ICU or HDU admission
Abdominal distension
Ability to control flatus
One or more periods of depression requiring treatment, at any age, as a result of the physical or psychological impact of the HD or its treatment
Post-operative experience of pain
Sleep disturbance
Lifetime healthcare costs
Intra-operative visceral injury –minor impact on recovery (Clavien-Dindo grade one)
Planned readmission (e.g. for anal dilatations)
Long-term need for dietary supplementation, or specialist exclusion diet
Consistency of stool
Duration of parenteral nutrition use
Frequency of bowel movements
Sphincter achalasia
Post-operative complication - requires additional surgery (Clavien-Dindo grade three)
Intra-operative visceral injury - requires additional surgery (Clavien-Dindo grade three)
Any intra-operative complication
Laxative medications
Cosmetic results
Peri-anal Excoriation without significant impact on daily life
Peri-stomal Excoriation without significant impact on daily life
Early pelvic inflammation
Time from operation to development of bowel habits that would be considered normal for someone without HD
Any stoma morbidity requiring surgical intervention
Any post-operative complication
Post-operative infection
Adhesions
Any stoma morbidity that results in the child requiring additional pharmacological interventions
Anorectal Manometry
Objective score of bowel function
Abscesses
Stomal stenosis
Intra-operative blood loss

Outcome handling in the NETS[1HD] Delphi process - Continued

Outcomes dropped after phase three
Intra-operative visceral injury - requires additional medication (Clavien-Dindo grade two)
Stomal retraction
Incisional hernia
Stomal Prolapse
Parastomal Hernia
Post-operative complication - requires additional medication (Clavien-Dindo grade two)
Pneumonia

Table 8: Outcomes scored at the NETS[1HD] consensus meeting

Mortality outcomes
Death with cause specified*
Resource use outcomes
Whether home parenteral nutrition is required
Unplanned reoperation with indication specified*
Unplanned readmission
Associated healthcare costs
Societal costs*
Life Impact outcomes
Long-term faecal incontinence*
Long-term voluntary bowel movements without need for enemas, or rectal or colonic irrigation*
Long-term urinary incontinence*
Long-term offensive odour secondary to lack of control of faeces or flatus, or inability to maintain hygiene.
Requiring nappy or pad
Impotence
Difficulty in conceiving a child
Attendance at school, or time spent missing lessons
Long-term psychological stress-family*
Long-term bladder dysfunction
Sensation of need to defecate*
Peri-anal excoriation with significant impact on daily life*
Peri-stomal excoriation with significant impact on daily life
Need for a permanent stoma, with indication specified*
Need for a new stoma at any point after the pull-through procedure
Long-term psychological stress for the individual with HD*
Painful defecation
Difficulty with sexual relations or sexual intercourse, because of the psychological or physical impact of HD or its treatment*
Long-term difficulty in feeding
Social Development
Objective score of quality of life, using appropriate age specific measures*
Urgency of stool
Pathophysiological manifestation outcomes
Aganglionic bowel remaining at the proximal resection margin
Hirschsprung's Associated Enterocolitis*
Normal growth
Objective score of bowel function*
Adverse event outcomes
Intra-operative complication - life threatening (Clavien-Dindo grade four)

*Outcomes meeting consensus for inclusion in the COS

Table 8: Outcomes scored at the NETS[1HD] consensus meeting - Continued

Adverse event outcomes
Post-operative complication - life threatening (Clavien-Dindo grade four)
Intra-operative visceral injury - life threatening (Clavien-Dindo grade four)
Anastomotic leak
Colonic torsion
Post-operative bowel obstruction
Narrowing of anastomosis
Fistula
Any intra-operative visceral injury
Cuff infection
Ischaemic bowel
Faecal impaction
Wound dehiscence

*Outcomes meeting consensus for inclusion in the COS

Table 9: Consensus meeting scores for the NETS[1HD] core outcome set

Highest scoring outcomes in each OMERACT Filter 2.0 core area			
Core Outcome	**Percentage score 7-9 at consensus meeting**	**Minimum reporting age**	**OMERACT filter 2.0 Core area**
Death with cause specified	100%	No minimum	Death
Long-term faecal incontinence	100%	Five years of age	Life Impact
Objective score of bowel function	94%	No minimum	Pathophysiological Manifestations
Unplanned re-operation, with indication specified	89%	No minimum	Resource use and adverse event
Outcomes included regardless of OMERACT core area			
Core Outcome	**Percentage score 7-9 at consensus meeting**	**Minimum reporting age**	
Long-term voluntary bowel movements without need for enemas, or rectal or colonic irrigation.	100%	Five years of age	
Long-term psychological stress for the individual with HD	100%	Five years of age	
Long-term urinary incontinence	94%	Five years of age	
Objective score of quality of life using appropriate age-specific measures	94%	Five years of age	
Need for a permanent stoma, with indication specified	88%	Five years of age	
Hirschsprung's Associated Enterocolitis	88%	No minimum	

Box 1: The NETS[1HD] Hirschsprung's disease Core Outcome Set

Death with cause classified as due to:

- A complication of treatment (excluding Hirschsprung's Associated Enterocolitis)
- Hirschsprung's Associated Enterocolitis
- An associated anomaly
- Other

Long-term faecal incontinence:

- Defined as involuntary passage of faecal matter in an inappropriate place by a child aged five or over.
- Graded as:
  - Occasionally (e.g. once or twice per week), with or without social problems
  - Every day, but without social problems
  - Constant, with social problems

Objective score of bowel function:

- Measured using the Paediatric Incontinence and Constipation Score in children under 18 years of age, and the Gastrointestinal Quality of Life Index in adults over 18 years of age.

Unplanned reoperation:

- Unplanned is defined as any procedure not considered part of routine post-intervention practice
- Includes any procedure that is performed as a direct result of the diagnosis or treatment of the participants HD, and any episodes of general anaesthesia that are required as a direct result of the diagnosis or treatment of the participant's HD, regardless of whether an operative intervention is undertaken (e.g. an examination under anaesthesia, or manual evacuation).
- Indication classified according to NICE criteria as minor, intermediate, or major/complex.

Long-term psychological stress for the individual with HD:

- Measured by the PedsQL in children under 18
- Measured by the Gastrointestinal Quality of Life index in adults over the age of 18

Quality of life:

- Measured by the age-appropriate PedsQL questionnaire.

Need for a permanent stoma:

- As a direct result of the diagnosis, or treatment of the participant's HD, including where the decision for a stoma has been made out of patient, or parental preference, or for continence management.
- A permanent stoma is defined as one that was created without the intention of later reversal.
- The indication for stoma formation should be reported.

Hirschsprung's Associated Enterocolitis:

- Defined as a score of ten or more on the Hirschsprung's Associated Enterocolitis Delphi score developed by Pastor et al.
- Where it is not possible to use the Hirschsprung's Associated Enterocolitis Delphi score, for example, in hospitals where left shift of white cells is not reported, Hirschsprung's Associated Enterocolitis should instead be defined as "Clinician decision to admit and instigate treatment for Hirschsprung's Associated Enterocolitis".
- Information should be reported on whether a participant has had any episodes of Hirschsprung's Associated Enterocolitis up to a standard time-point, but also whether they have had zero, one or two episodes of Hirschsprung's Associated Enterocolitis in the previous 12 months, or up to the time-point of measurement, whichever is shorter.

Long-term voluntary bowel movements:

- Defined as voluntary bowel movement without need for enemas, or rectal or colonic irrigation

Long-term urinary incontinence:

- Defined as involuntary voiding of urine that is constant, associated with social problems, or requiring catheterisation:

3.5.2.4. Defining and measuring the core outcomes

Fourteen experts participated in the core outcome measurement meeting. This included six surgeons (42%), one neonatologist (7%) who commented on the outcomes but did not attend the meeting in person, one specialist paediatric surgical colorectal nurse (7%), one paediatric gastroenterologist (7%), one HD researcher (7%), three people with HD (21%), and one parent of a child with HD (7%).

The group defined two sets of standard measurement time-points, the 'Intervention cohort' time-points, which were for use in studies where the entry time-point was the point of surgical intervention, and the 'Birth cohort' time-points, which were for use in studies where the entry time-point was the infant's date of birth (Box 2). Where the group determined that specific outcomes should not be measured prior to a specific age, this was defined within the individual outcome.

Box 2: Time points for measurement of the NETS[1HD] core outcomes

The following time-points reflect standard points of outcome measurement common to many paediatric or surgical studies. Outcomes should be reported at the appropriate time-points dependent upon whether an infant enters the study at birth, or following an intervention.

Birth cohort time-points	Intervention cohort time-points
28 days of age	30 days post intervention
One year of age	90 days post intervention
Five years of age	One year post intervention
Ten years of age	Five years post intervention
Every subsequent ten years	Ten years post intervention
	Every subsequent ten years

For all outcomes where previously developed tools were considered as part of the measurement instrument, the meeting participants were very careful to balance the truthfulness and discriminatory ability of the instrument against the feasibility of the instrument's use, particularly in situations where financial costs were levied. Where possible, instruments that were free for use in unfunded research were preferred. A summary of the discussions held at the measurement meeting can be found in Appendix 9, and definitions for each core outcome can be found in Box 1. Further details of the NETS[1HD] COS can be found in the published manuscript (Appendix 10)(78).

3.5.3. Gastroschisis Delphi process

3.5.3.1. Participants

One hundred and sixty-four people registered to participate in the Delphi process, 102 (62%) of whom completed phase one. Eighty-five (83%) of 102 eligible participants then completed phase two, and 71 (84%) of 85 eligible participants completed phase three (Table 10).

Of the 71 participants that completed all three phases of the Delphi process, 19 (27%) were paediatric surgeons, 13 (18%) were neonatologists, 11 (16%) were specialist nurses, two (3%) were paediatric gastroenterologists, two (3%) were paediatric dieticians, and 22 (31%) were parents of children born with gastroschisis. Fourteen (64%) of the parents who completed all three phases of the Delphi process had children born with gastroschisis who were less than five years of age at the time of the study, four (18%) had children between five and ten years, two (1%) had children over ten years, and two (1%) preferred not to say how old their child was.

Table 10: Summary of gastroschisis Delphi process participants

Panel	Registering for phase one	Completing phase one	Completing phase two	Completing phase three	Consensus Meeting	Measurement Meeting
	n*	n (%)*	n (%)*	n (%)*	n	n
Neonatal Panel	58	52 (90%)	47 (90%)	43 (91%)	15	10
Non-neonatal panel	8	8 (100%)	7 (88%)	6 (86%)	4	3
Personal experience panel	98	42 (43%)	31 (74%)	22 (71%)	5	1
Total	164	102 (62%)	85 (83%)	71 (84%)	24	14

*Percentage of those eligible to participate in the phase

3.5.3.2. Outcome modification prior to phase one

Between the two systematic reviews, 86 unique outcomes were identified(73, 75). Ten outcomes (12%) were dropped, as they were only considered relevant for assessing antenatal interventions, and were therefore outside of the scope of the COS. No new outcomes were proposed by the SMG, and there were therefore 76 outcomes carried forward to phase one of the Delphi process (Table 11). The outcome mortality was inadvertently omitted from phase one of the Delphi process, meaning only 75 outcomes were scored. Mortality was therefore added to phase two in the same manner as other newly proposed outcomes.

Table 11: Outcomes taken forward to phase one of the NETS[1G] gastroschisis Delphi process

Outcomes identified by systematic reviews	Merged term	Lay term
Mortality Mortality	Mortality	Death
Time to first enteral feed Time to first oral feed	Time to first enteral feed	How long there is between birth and being able to take some food by mouth
Time to full enteral feed Time to full oral feeds	Time to full enteral feeds	How long there is between birth and being able to take all food by mouth, without requiring any artificial feed into the veins
Incidence of Parenteral Nutrition Parenteral nutrition ever required	Parenteral nutrition ever required	Whether artificial feed given into the veins is ever required
Duration of PN Time on parenteral nutrition	Time on parenteral nutrition	The amount of time that artificial feed given into the veins is required to supplement feeds given by mouth
Time on ***total*** parenteral nutrition	Time on ***total*** parenteral nutrition	The amount of time that artificial feed given into the veins is required to supplement feeds given by mouth
Need for Parenteral Nutrition after discharge Parenteral nutrition required post-discharge	Need for Parenteral Nutrition post discharge	Whether artificial feed into the veins is required after discharge home
Feeding, initiation of feed in NICU	Feeding, initiation of feed in NICU	Whether feeding by mouth is started whilst still in the neonatal intensive care unit

Table 11: Outcomes taken forward to phase one of the NETS[1G] gastroschisis Delphi process - Continued

Outcomes identified by systematic reviews	Merged term	Lay term
Feeding, full feeds at discharge from NICU	Feeding, full feeds at discharge from NICU	Whether all feeds are being given by mouth, without any need for artificial feed into the veins, prior to being discharged from the neonatal intensive care unit
Short gut syndrome Short Bowel Syndrome	Short bowel syndrome	Whether problems occur with absorbing nutrition from the bowel because there is not enough bowel left (either because it was damaged by gastroschisis, or need to be removed at an operation).
Bowel lengthening procedure required	Bowel lengthening procedure required	Whether an operation is required to make the bowel longer
Liver transplantation	Liver transplantation	Whether a liver transplant is required
Neurodevelopmental outcome Neurodevelopmental delay	Neurodevelopmental outcomes	Whether key markers of development (such as smiling, walking, talking etc.) are met at the correct time
Developmental milestones >6m	Developmental milestones >6m	Whether appropriate markers of development for children aged greater than 6 months (such as walking, talking etc.) are met at the appropriate age.
Ever ventilated? Incidence of ventilation	Ventilation ever required	Whether artificial ventilation (support from a machine to help with breathing) is required at any point because the lungs aren't working well enough
Post-operative ventilation required	Post-operative ventilation required	Whether artificial ventilation is required after the operation because the lungs aren't working well enough

Table 11: Outcomes taken forward to phase one of the NETS[1G] gastroschisis Delphi process - Continued

Outcomes identified by systematic reviews	Merged term	Lay term
Duration of respiratory support	Duration of respiratory support	How long support with breathing (either from a machine, or just from additional oxygen) is required for in total
Total time on mechanical ventilation Duration of ventilation	Duration of ventilation	How long artificial ventilation is required for in total
Ventilated beyond 24hr	Ventilated beyond 24hr	Whether artificial ventilation is required for more than 24 hours because the lungs aren't working well enough
Post closure time on mechanical ventilation	Post closure time on mechanical ventilation	How long artificial ventilation is required for after the gastroschisis is repaired
Ventilation, peak inspiratory pressure	Ventilation, peak inspiratory pressure	The highest pressure that is required on a ventilator to make sure that the lungs are working ok
Ventilation, peak concentration inspired oxygen	Ventilation, peak concentration inspired oxygen	The largest amount of oxygen that is required on a ventilator to make sure that the lungs are working ok
Need for oxygen after Discharge	Need for oxygen after Discharge	Whether additional oxygen is required after discharge from hospital
Duration of oxygen therapy	Duration of oxygen therapy	How long additional oxygen is required for
Respiratory compromise	Respiratory compromise	Whether there are problems with breathing
Diagnosis of Respiratory Distress Syndrome Neonatal Respiratory Distress Syndrome	Respiratory distress syndrome	Whether breathing problems occur as a result of being born too early
Cholestasis	Cholestasis	Whether there is too much of a substance called bile in the blood. This suggests that the liver may not be working properly

Table 11: Outcomes taken forward to phase one of the NETS[1G] gastroschisis Delphi process - Continued

Outcomes identified by systematic reviews	Merged term	Lay term
Hypothyroidism	Hypothyroidism	Whether the thyroid (a gland in the neck that produces hormones) isn't producing enough thyroxine (a hormone that affects many things including heartbeat, ability to gain weight, and ability to develop normally).
Bacteraemia	Bacteraemia	Whether bacteria are found in the blood stream
pH, time acidotic	pH, time acidotic	Whether the blood is too acidic, and how long it is too acidic for. Acidic blood is a marker of the fact that someone is unwell.
Kidney dysfunction	Kidney dysfunction	Whether the kidneys stop working properly
Urine output	Urine output	How much urine is produced. This is a marker of how well the kidneys are working
Volume of IV fluid required	Volume of IV fluid required	How much fluid into the veins is required
Blood pressure, mean arterial	Blood pressure, mean arterial	What the average blood pressure is
Need for stoma	Need for stoma	Whether a stoma is needed (a stoma is where the bowel is joined to the skin on the tummy wall so that poo goes into a bag on the tummy as opposed to through the bottom).
Bowel Resection	Bowel Resection	Whether part of the bowel needs to be removed
Need for mesh at closure	Need for mesh at closure	Whether an artificial mesh is needed to close the gastroschisis hole
Growth outcome Weight gain	Unspecified measures of growth	Whether normal growth occurs

Table 11: Outcomes taken forward to phase one of the NETS[1G] gastroschisis Delphi process - Continued

Outcomes identified by systematic reviews	Merged term	Lay term
Weight<10th centile	Weight<10th centile	Whether weight is in the lowest ten percent of the population
Length of Hospital Stay Length of stay	Length of hospital stay	How many days are spent in hospital
NICU length of stay	NICU length of stay	How many days are spent in the neonatal intensive care unit (NICU)
Discharge, NICU to home	Discharge, NICU to home	Whether discharge home occurs directly from the neonatal intensive care unit, without first going to another ward
Total number of GA	Total number of General Anaesthetics	The total number of general anaesthetics required
General anaesthesia, number of days, indication	General anaesthesia, number of days, indication	The number of days that the child is kept asleep for, and the reasons why
Central-line usage ratio (days with central line/hospital days)	Central-line usage ratio (days with central line/hospital days)	The number of days that a central line is required for. A central line is a long tube into a big vein, and is often used to give artificial feed.
Duration of antibiotics	Duration of antibiotics	How long antibiotics are required for to treat an infection
Hospital charge	Hospital charge	How much the overall cost of treatment is, regardless of whether this is paid privately, or by the NHS.
Days to abdominal wall closure	Days to abdominal wall closure	How many days it is between birth and closing the hole in the tummy wall through which the bowel is protruding

Table 11: Outcomes taken forward to phase one of the NETS[1G] gastroschisis Delphi process - Continued

Outcomes identified by systematic reviews	Merged term	Lay term
Rehospitalisation	Rehospitalisation	Whether readmission to hospital is required for any reason
Infectious complications Infection, unspecified or other	Unspecified infection	Whether any infection develops
CVC sepsis Infection, central line related	Central line related infections	Whether an infection develops on the central line (the line that is usually used for given artificial feed into the veins).
Wound infection or breakdown	Wound infection or breakdown	Whether an infection develops in the wound
Infection with systemic sequelae	Infection with systemic sequelae	Whether a serious infection develops that causes the child to be unwell.
Infection free survival	Infection free survival	Survival without experiencing an infection related to the gastroschisis
Infection, urinary or respiratory	Infection, urinary or respiratory	Whether a chest infection or a urinary infection develops
Blood transfusion Number of transfusions	Transfusions	Whether a blood transfusion is needed
Silo Complication	Silo Complication	Whether a complication occurs with the silo
Bowel ischaemia Ischaemic bowel	Bowel ischaemia	Whether the blood supply to the bowel is affected
Anastomotic stricture Anastomotic stricture	Anastomotic Stricture	Whether the blood supply to the bowel is affected
Perforation Intestinal perforation	Intestinal perforation	Whether a hole develops in the bowel

Table 11: Outcomes taken forward to phase one of the NETS[1G] gastroschisis Delphi process - Continued

Outcomes identified by systematic reviews	Merged term	Lay term
Intra-abdominal pressure	Intra-abdominal pressure	How high the pressure inside the tummy is. This can be a marker of abdominal compartment syndrome
Abdominal compartment syndrome	Abdominal compartment syndrome	Whether after the gastroschisis has been repaired the pressure in the tummy is so high that it causes problems with organs (such as the kidneys) inside the tummy. This will require another operation.
NEC NEC	NEC	Whether necrotising enterocolitis (NEC) develops. NEC is a severe infection of the bowel that can cause sections of the bowel to develop holes, or to lose their blood supply.
Stoma complication	Stoma complication	Whether a complication occurs with the stoma (if one was made)
Obstruction Adhesional small bowel obstruction	Bowel obstruction	Whether bowel becomes blocked
TPN liver disease Intestinal Failure Associated Liver Disease	Intestinal failure associated liver disease	Whether liver damage occurs because the bowel isn't working properly
Re-operation Unplanned surgery Unplanned reoperation	Re-operation	Whether a second operation is required for any reason

Table 11: Outcomes taken forward to phase one of the NETS[1G] gastroschisis Delphi process - Continued

Outcomes identified by systematic reviews	Merged term	Lay term
Reoperation, need for enlargement of gastroschisis defect	Reoperation, need for enlargement of gastroschisis defect	Whether a second operation is required to make the gastroschisis hole bigger, so that the bowel can be more easily put back into the tummy using a silo. A silo is a plastic tube that is used to gradually return the bowel to the tummy.
Reoperation, need for silo replacement	Reoperation, need for silo replacement	Whether a second operation is required in order to replace the silo with a new one
Ventral hernia Umbilical hernia	Ventral hernia	Whether a hernia develops at the point where the gastroschisis hole was closed (A hernia is where there is a weakness in the muscle so that that bowel pokes through the muscle causing a lump under the skin).
GI complication	Gastrointestinal complication	A complication affecting the gut
Non-GI complication	Non-gastrointestinal complication	Whether a complication affecting a part of the body other than the gut occurs.
Retinopathy of prematurity	Retinopathy of prematurity	Whether there is damage to the retina at the back of the eyes, as a result of being born too early
Neonatal convulsions	Neonatal convulsions	Whether seizures (fits) occur in the first few weeks of life.
QT interval	QT interval	The time between two different parts of the heart beat, as measured by looking at an electrical tracing of the heart (ECG)
Cosmesis	Cosmesis	What the tummy looks like after the operation

Table 11: Outcomes taken forward to phase one of the NETS[1G] gastroschisis Delphi process - Continued

Outcomes identified by systematic reviews	Merged term	Lay term
Presence of peel	Dropped as out of scope	Dropped as out of scope
Gestational Age	Dropped as out of scope	Dropped as out of scope
C-section	Dropped as out of scope	Dropped as out of scope
Birthweight	Dropped as out of scope	Dropped as out of scope
Birthweight below 2500g	Dropped as out of scope	Dropped as out of scope
APGAR at 5M	Dropped as out of scope	Dropped as out of scope
APGAR at 10M	Dropped as out of scope	Dropped as out of scope
Simple vs. complex	Dropped as out of scope	Dropped as out of scope
Birth Related Injury	Dropped as out of scope	Dropped as out of scope
Cord pH<7.1 at birth	Dropped as out of scope	Dropped as out of scope

3.5.3.3. Outcome handling after phase one

Eleven outcomes including mortality were added for phase two, and the existing outcome "need for stoma" was split into two new outcomes "need for a permanent stoma" and "need for a temporary stoma". A total of 87 outcomes were therefore assessed in phase two of the Delphi process. Between phase two and phase three, one outcome (1%) was dropped, and six outcomes (7%) were modified. Following phase three, 58 outcomes (67%) were dropped, and 28 (33%) were carried forward for automatic discussion at the consensus meeting (Table 12 and figure 8).

During discussions at the consensus meeting, it was determined that the outcome gastrointestinal complication should be renamed as severe gastrointestinal complication, and that seven outcomes in the adverse event category should be scored for inclusion as one of the conditions included in the definition of this new composite outcome, as opposed to for inclusion as standalone outcomes. Four further outcomes were modified during the consensus meeting; "need for parenteral nutrition post-discharge" was modified to "need for parenteral nutrition at a set time-point", "infection with systemic sequelae" was renamed to "sepsis", "anastomotic stricture" was renamed to "any stricture" and "intestinal failure associate liver disease" was renamed to "a marker of liver disease". Two outcomes, "growth" and "length of stay", which did not meet criteria for automatic discussion at the consensus meeting were unanimously promoted for discussion by the group. In total, 33 outcomes were scored at the consensus meeting, eight of which met consensus for inclusion in the COS. All eight of these outcomes were therefore retained in the COS (Table 13 and Box 3).

Table 12: Outcome handling in the NETS[1G] Delphi process

Outcomes modified between phase one and two	
Description in phase one	**Description in phase two**
Need for a stoma	Need for a permanent stoma *and* Need for a temporary stoma
Outcomes added between phase one and phase two	
Quality of life for the child	
Chronic gastrointestinal symptoms	
Gastrointestinal dysfunction, including but not limited to constipation	
Small bowel transplant	
Meningitis	
Mortality	
Full oral feed achieved without any mechanical assistance	
Total number of days with a central line	
Discharge home with mechanical feeding assistance	
Societal costs, including financial cost for the family	
Home ***total*** parenteral nutrition	
Outcomes dropped after phase two	
Retinopathy of prematurity	
Outcomes modified between phase two and phase three	
Description in phase two	**Description in phase three**
Infection free survival	Alive without having developed a gastroschisis related infection
Silo complication	Any complication caused by use of a silo, regardless of severity
Non-GI complication	Any complication affecting a part of the body other than the GI tract, regardless of its severity
Unspecified infection	Any form of infection, regardless of cause or severity
General anaesthesia, number of days, indication	Number of days that sedation, with or without paralysis are required on the neonatal unit, along with the reasons why
Reoperation, need for silo replacement	Requirement for a second operation to place a silo, regardless of the reason the silo is needed
Outcomes dropped after phase three	
Any complication affecting a part of the body other than the GI tract, regardless of its severity	
Blood pressure, mean arterial	
Cosmesis	
Days to abdominal wall closure	
Discharge home with mechanical feeding assistance (e.g. NG tube of gastrostomy)	
Ventilated beyond 24hr	
Ventilation ever required	
Ventilation, peak concentration inspired oxygen	

Table 12: Outcome handling in the NETS[1G] Delphi process - Continued

Outcomes dropped after phase three
Ventilation, peak inspiratory pressure
Ventral hernia
Discharge, NICU to home
Duration of antibiotics
Duration of oxygen therapy
Duration of respiratory support
Duration of ventilation
Feeding, initiation of feed in NICU
Hospital charge
Hypothyroidism
Volume of IV fluid required
Weight<10th centile
Alive without having developed a gastroschisis related infection
Any complication caused by use of a silo, regardless of severity
Any form of infection, regardless of cause or severity
Bacteraemia
Central line related infections
Central-line usage ratio (days with central line/hospital days)
Infection, urinary or respiratory
Intra-abdominal pressure
Need for a temporary stoma
Need for mesh at closure
Need for oxygen after Discharge
Number of days that sedation, with or without paralysis are required on the neonatal unit, along with the reasons why
pH, time acidotic
QT interval
Reoperation, need for enlargement of gastroschisis defect
Developmental milestones at six months of age or older
Feeding, full feeds at discharge from a level three NICU
Full oral feed achieved without any mechanical assistance e.g. NG tube or gastrostomy
Kidney dysfunction
Length of hospital stay
Meningitis
Neonatal convulsions
NICU length of stay
Parenteral nutrition ever required
Requirement for a second operation to place a silo, regardless of the reason the silo is needed
Respiratory distress syndrome
Stoma complication
Time to first enteral feed
Total number of general anaesthetics

Table 12: Outcome handling in the NETS[1G] Delphi process - Continued

Outcomes dropped after phase three
Transfusions
Urine output
Post closure time on mechanical ventilation
Post-operative ventilation required
Respiratory compromise
Time to full enteral feeds
Total number of days with a central line
Unspecified measures of growth
Wound infection of breakdown

Figure 8: Flow of outcomes through the NETS[1G] Delphi process

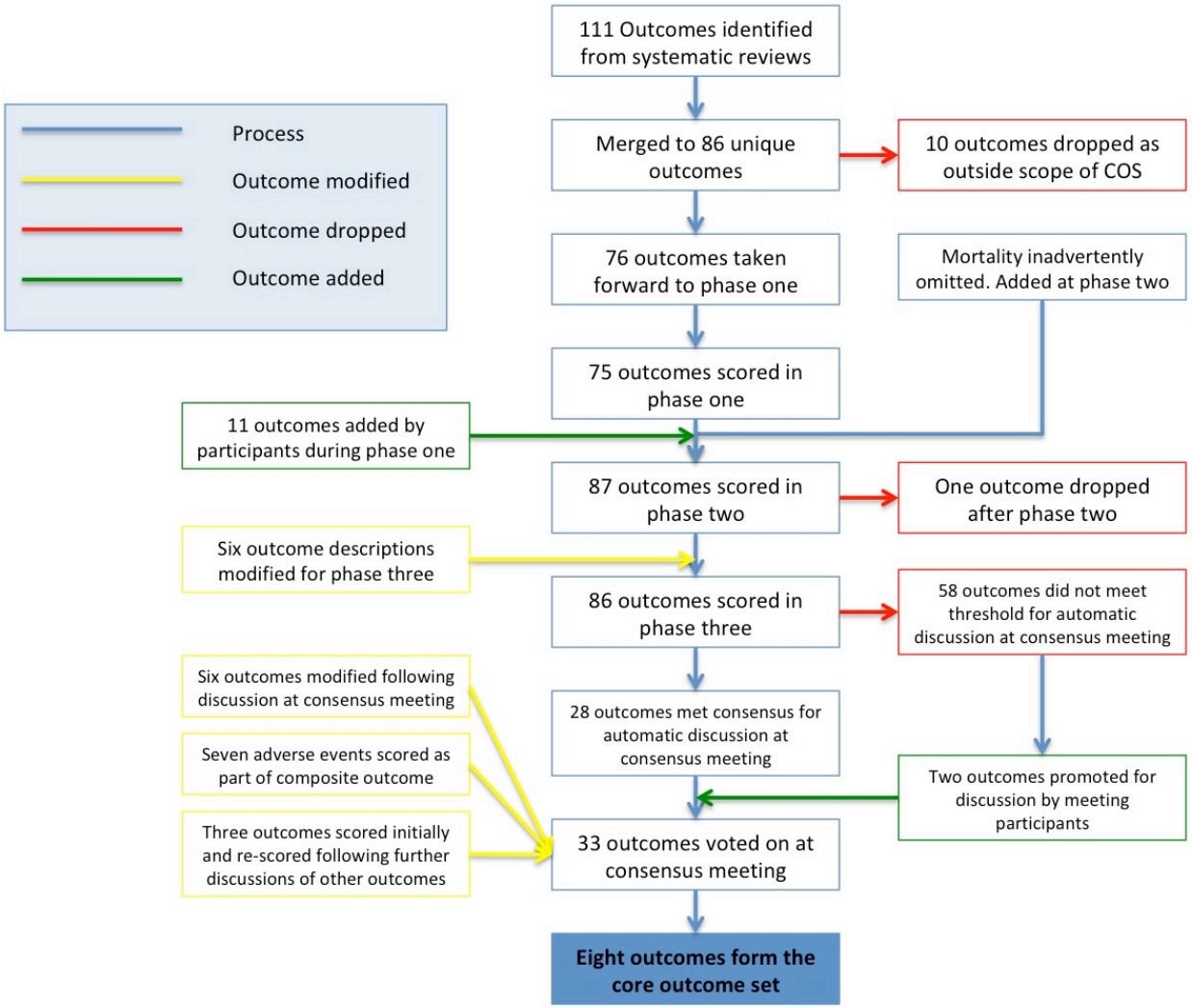


Table 13: Consensus meeting scores for gastroschisis core outcomes

Core Outcome	Percentage score 7-9 at consensus meeting	Reporting time points
Death	100	Cohort or intervention study time-points
Sepsis	100	Cohort or intervention study time-points
Growth	100	Cohort or intervention study time-points
Number of operations	100	Cohort or intervention study time-points
Severe gastrointestinal complication	96	Cohort or intervention study time-points
Time on parenteral nutrition	87	Cohort study time-points only
Liver disease	74	Cohort or intervention study time-points
Quality of life for the child	73	Cohort or intervention study time-points

Box 3: The NETS[1G] Gastroschisis Core Outcome Set

Death

- Number (%) of infants who have died

Sepsis

- Median (IQR and range) number of times treatment was given for proven or presumed sepsis
- Number of episodes where sepsis was proven by a positive blood or CSF culture should be reported separately from the number of episodes where treatment was given for sepsis, but the blood or CSF culture was negative.

Growth

- Mean (95% CI) z-score for weight, length and head circumference in studies reporting outcomes at or prior to one year of age.
- Mean (95% CI) z-score for weight and height in studies reporting outcomes after one year of age.

Number of operations

- Median (IQR and range) number of operations per infant
- The type of operations undertaken should be categorised according to whether they were performed under general or local anaesthetic, and whether they were an abdominal operation, central venous catheter insertion, or 'other' operation. 'Other' operations should only be reported when performed under general, not local anaesthetic.
- ***Each episode of silo placement, replacement, and re-application should be reported as a separate abdominal operation, with abdominal closure reported separately to silo placement.***

Severe gastrointestinal complication

- Median (IQR and range) number of severe gastrointestinal complications per infant
- Severe gastrointestinal complication ***only includes:***
    - Intestinal perforation
    - Any intestinal resection, regardless of amount of bowel removed or the indication for the resection
    - Mechanical intestinal obstruction resulting in a repeat laparotomy
    - Abdominal compartment syndrome*
    - Enterocolitis**

Time on parenteral nutrition

- Median (IQR and range) number of days ***any*** parenteral nutrition was received per infant in studies reporting outcomes at or prior to one year of age.
- Number (%) of infants receiving ***any*** parenteral nutrition in studies reporting outcomes after one year of age.

Liver disease

- Number (%) of infants with persistent conjugated hyperbilirubinaemia (>50 µmol/l) for ≥ two weeks with no known other underlying liver disease.

Quality of life for the child

- Median (IQR and range) PedsQL score in each study group
- If appropriate, the median (IQR and range) score from the PedsQL gastrointestinal symptoms and family impact modules in each study group should also be reported.

*Defined as 'suspected raised intra-abdominal pressure with at least two of oliguria or anuria, respiratory de-compensation, hypotension/shock, or metabolic acidosis, that leads to intervention'.

**Defined as 'suspected enterocolitis with at least one of bilious aspirates or emesis, abdominal distension or occult or gross blood in stool (no fissure), and at least one of pneumatosis intestinalis, hepatobiliary gas, pneumoperitoneum'.

3.5.3.4. Defining and measuring the core outcomes

Fourteen experts attended the measurement meeting, 10 from the neonatal panel, three from the non-neonatal panel, and one from the personal experience panel. Following discussion, unanimous agreement was reached on definitions and methods of measurement for each core outcome (Box 3). Appropriate time-points for reporting these core outcomes were unanimously agreed to be the same as for the previously developed HD COS(79). Details of discussions held at the measurement meeting can be found in Appendix 11, and further details of the NETS[1G] gastroschisis COS can be found in the published manuscript (Appendix 12) (80).

3.5.3.5. Attrition bias

Median phase one scores for the eight outcomes included in the COS, or their nearest approximations, were compared between participants who completed all three phases of the Delphi process, and those who completed phase one only. No statistically significant differences were seen between any of these groups (Table 14).

Table 14: Assesment of attrition bias

Outcome	Panel	p-value* comparing median phase one scores of phase three completers with non-completers
Death	Neonatal	0.3
	Non-neonatal	1
	Personal experience	0.9
Sepsis	Neonatal	0.4
	Non-neonatal	0.7
	Personal experience	0.7
Growth	Neonatal	0.4
	Non-neonatal	0.6
	Personal experience	0.2
Number of operations	Neonatal	0.9
	Non-neonatal	1
	Personal experience	0.2
Severe gastrointestinal complication	Neonatal	0.6
	Non-neonatal	0.6
	Personal experience	0.5
Time on parenteral nutrition	Neonatal	0.8
	Non-neonatal	0.7
	Personal experience	0.6
Liver disease	Neonatal	0.5
	Non-neonatal	0.9
	Personal experience	0.1
Quality of life	Neonatal	0.8
	Non-neonatal	0.4
	Personal experience	0.4

*p-value for Wilcoxon Rank-Sum test

3.6. Discussion

3.6.1. Summarising the core outcome sets

These development processes have identified a COS consisting of ten outcomes for use in studies comparing interventions for the treatment of infants with HD, and a COS consisting of eight outcomes for use in studies comparing surgical interventions for the treatment of infants born with gastroschisis. The outcomes included in each COS represent factors important to key stakeholders and span the breadth of the OMERACT filter 2.0. When used in appropriate studies they will provide a rounded assessment of different interventions for each condition, and going forward, all studies conducted within the scope of these COSs should report data at the specified time-points for the appropriate outcomes. The number of outcomes to report for each condition is relatively small and each has been robustly defined, with an appropriate measure and time-point for reporting identified. This level of detail should enable the immediate practical implementation of the COSs in studies using many different methodologies.

3.6.2. Commonality between core outcome sets

There is overlap between the outcomes identified in the HD COS and the gastroschisis COS. Both sets included death and quality of life, as well as a measure of the need for repeated medical intervention, namely unplanned reoperation with indication specified, and number of operations. No other paediatric surgical COSs have been developed, however, there also appears to be overlap between the developed COSs and a recently developed paediatric asthma COS(33), which also included death, quality of life and a measure of the need for

further medical intervention (exacerbations of asthma). Commonality between these COSs may suggest a role for developing a general paediatric COS that is applicable to all conditions with significant childhood morbidity, and which can then be augmented with smaller disease specific COSs. Results of two further paediatric surgical COSs that are currently in development for appendicitis(81) and burns(82) will help to inform this discussion, as will the results of the COIN study(83) which is developing a neonatal care COS.

3.6.3. Representativeness of participants

Both the HD and gastroschisis COSs have been developed using robust methodology in accordance with recommendations from the COMET initiative. Participation rates for each were significantly above the target recruitment of 50 experts, with a good spread across stakeholder groups. For the HD COS there was good retention across all stakeholder groups throughout the process and it is therefore likely that the COS will be representative of the views of the community as a whole. There are however three areas that may affect its representativeness. Firstly, from the personal experience panel, there were a larger proportion of women taking part than men, meaning that the views of fathers, and men with HD, are potentially under-represented. Secondly, there were slightly greater proportions of participants with long-segment and ultra-short segment HD within the study population than would be expected within the general population. This may skew the priorities of the personal experience panel more towards the extremes of the disease population. Thirdly, the non-neonatal panel consisted of fewer participants than either the neonatal or personal experience panels. By giving equal weight to each panel as opposed to each individual participant throughout the Delphi process, individual participants within the

non-neonatal panel will have had a proportionately greater influence on the scoring of outcomes throughout the Delphi process than participants in other panels. At the consensus meeting however, the meeting attendees were treated as one group, not individual panels. Within this setting therefore, where there were less participants from the non-neonatal panel than from other panels, there is potential for the views of members of the non-neonatal panel to have been under-represented in the final COS.

Reduced numbers of non-neonatal stakeholders is also an issue that affected the gastroschisis COS development, and suggests that for development of future paediatric surgical COSs, further consideration may need to be given to the way in which the panels are organised. Additionally, the gastroschisis COS may have been affected by the fact that although there were a good number of parents who completed all three phases of the Delphi process, there were no individuals born with gastroschisis who did so. The difficulty engaging adults treated for gastroschisis as a child may have been due to the fact that many have no on-going active involvement with medical services or charities. It is difficult to know if this population of adults do not have regular contact with medical services because they are symptom free, or because they have become detached from these services. If the former is true, the COS will likely remain fully representative of the outcomes that are important in determining treatment success, as the majority of 'experience' of gastroschisis will be from the parental point of view. However, if it is the latter, and there are differences in opinion of which outcomes are important between parents, and adults who were treated for gastroschisis as a child, then the COS may under-represent the treated adult's opinion.

3.6.4. Incorporating the personal experience voice

Increasingly, there is a move towards undertaking qualitative work with key stakeholders in addition to a systematic review to inform the long-list of outcomes assessed during the Delphi process. This methodology is being promoted as there is a suspicion that outcomes identified through systematic reviews may be biased in favour of clinicians and researchers(84). As opposed to using qualitative methods to inform the Delphi processes presented in this Chapter, they were instead conducted using an adaptive methodology. All participants were asked to recommend additional outcomes of importance to them at the end of phase one, and could suggest modifications to outcomes at all stages of the consensus process. The small number of additional outcomes proposed by the HD personal experience panel suggests that either they felt the initial list covered the majority of outcomes of importance to them, or that they felt unable to propose additional outcomes. As over 50% of comments made in phase one of the HD Delphi process were from members of the personal experience panel, and nearly 60% of the personal experience panel made at least one comment during phase one, the former theory appears more likely. It is also reassuring that there was similarity in the number of outcomes suggested by each panel, and that there was overlap in the domains from which additional outcomes were suggested by each panel.

3.6.5. Implications for Hirschsprung's disease and gastroschisis research

Whilst some of the outcomes included in the COSs such as faecal incontinence, HAE, time on parenteral nutrition, and number of operations were already frequently investigated in the literature, there was significant variation in the way they were defined, or the time-point at

which they were measured(73). This has meant that although researchers were investigating outcomes of importance to patients, the fact that they were doing so in different ways was impeding the development of a meaningful evidence base(18). Developing the COSs has allowed key stakeholders to achieve consensus on definitions and measures that should be used for each of these already commonly investigated core outcomes. Promoting the use of these definitions will improve the quality of the evidence base supporting the management of infants with HD and gastroschisis, without significantly altering the outcomes that researchers are investigating. Other core outcomes including long-term psychological stress, growth, and quality of life were very infrequently investigated in studies(73). It is likely that these have not previously been investigated because it is difficult and expensive to collect data in relation to them. Identifying these outcomes as important to key stakeholders therefore has significant implications for researchers, journal editors and funders, as it will alter the way in which studies are designed, funded and reviewed for publication.

3.6.6. Core outcome set implementation

These development processes have incorporated the views of key stakeholders to generate HD and gastroschisis COSs for use in studies comparing interventions in high-income countries. It is important to promote the use of these COSs in large-scale observational and interventional studies, but also in smaller, retrospective studies that still comprise the vast majority of paediatric surgical research(2). Doing so will ensure studies are relevant to patients and their family, reduce the risk of reporting bias, and importantly, make meta-analysis possible. In the long run, this will improve the evidence-base used to support

clinical management of infants born with HD and gastroschisis, and should eventually allow translation through into improvements in patient care. It is now incumbent on funding bodies, journal editors, and key decision makers in the field of paediatric surgical research to ensure that the COSs are widely implemented, and the benefits of their use realised. Demonstrating the feasibility of using these COSs in large-scale, high quality research to answer clinically meaningful questions will help these organisations in this task.

Chapter Four

A British Isles and Canada-wide cohort study investigating the patient and operative factors that affect core outcomes at 28 days of age in infants born with gastroschisis

4.1. Background

4.1.1. National Confidential Enquiry into Patient Outcomes and Death

In 2011 an NCEPOD review of the organisational and clinical aspects of children's surgery in the UK highlighted two key findings. Firstly, when NEC was excluded, infants who died under the care of paediatric surgeons had most commonly undergone surgery for gastroschisis, exomphalos or malrotation(1, 85), and secondly, two of the drivers for outcomes not being as good as they could be in key paediatric surgical conditions were difficulties and delays in the surgical decision-making process(1). Such difficulties and delays stem in part from the lack of robust evidence that is available to support surgeons in their decision-making, and the infrequency with which an individual surgeon treats many rare neonatal conditions. The end result of these difficulties with decision-making is that there is significant variation in operative management strategies employed for most neonatal surgical conditions (4-6, 8, 49, 86, 87). As it is implausible that all management strategies are equally efficacious, it is highly likely that such widespread variation in management is resulting in some infants experiencing worse outcomes than they should be expected to.

With approximately 140 paediatric surgical consultants practicing across the British Isles, and approximately 260 infants born with gastroschisis in the British Isles each year(4), it will never be possible to satisfactorily increase a surgeon's exposure to the condition to reliably allow surgical-decision making to be based solely on an individual's clinical experience. It is therefore necessary to improve the quality of national management guidelines that are available to help guide surgical decision-making, ideally, basing the recommendations of these guidelines on the results of high quality, well-designed RCTs. Prior to it being possible

to conduct such RCTs however, it is first necessary to demonstrate equipoise between existing treatments, identify the population of infants with gastroschisis in which a trial should be conducted, and finally, due to the low incidence of gastroschisis, determine if an international multi-centre RCT would deliver results that were clinically meaningful in each participating country.

4.1.2. Equipoise between treatments

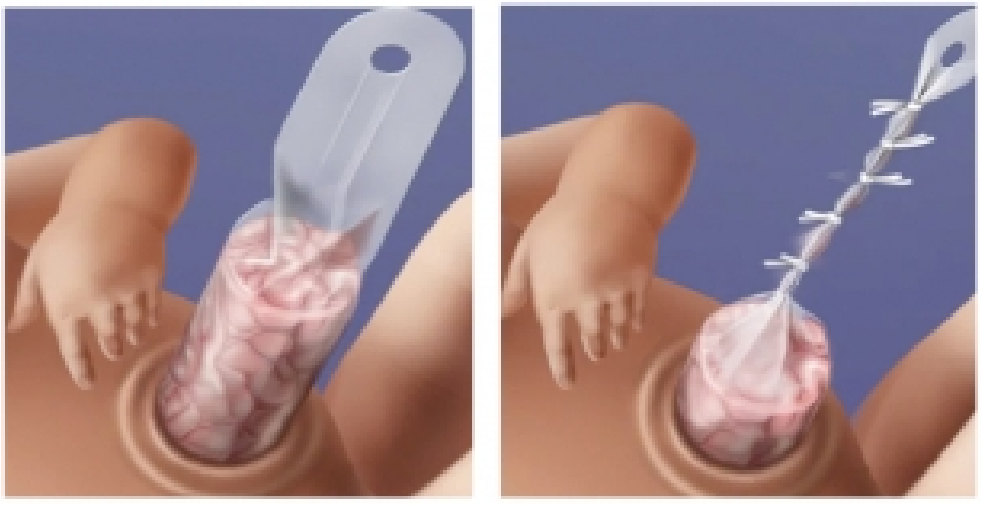
4.1.2.1. Existing treatments for infants born with gastroschisis

The initial management of infants born with gastroschisis involves placement of a nasogastric tube to decompress the gastrointestinal tract, maintenance of hydration with intravenous fluids, antibiotic prophylaxis, and regulation of heat and fluid loss by wrapping the extruded bowel in Clingfilm. Each of these steps is relatively uniformly performed regardless of where or by whom the infant is treated. However, the manner in which the herniated organs are definitively reduced and the abdominal wall defect closed is more variable.

Within the British Isles, the most common definitive reduction and closure strategy is operative primary fascial closure (OPFC)(4), in which the eviscerated abdominal contents are primarily reduced and the fascia sutured to close the defect whilst the infant is under a general anaesthetic. A less common variant of this procedure is where the eviscerated organs are returned to the abdominal cavity under general anaesthetic, but the defect is then closed in a sutureless fashion, using only steri-strips. Following OPFC in frequency of use is silo placement with staged reduction and delayed closure (SR)(4). SiIo placement with

staged reduction and delayed closure involves placement of the eviscerated abdominal organs into a plastic silo which is then suspended above the infant to allow the contents to be gradually returned to the abdominal cavity over a period of days (Figure 9). Silos are commonly applied at the bedside in the NICU, and frequently require only sedation as opposed to general anaesthesia. Once the eviscerated organs have been returned to the abdominal cavity, the fascial defect can then be closed using either steri-strips, or if necessary, fascial sutures under a general anaesthetic. The final technique in common use in the British Isles is ward-based reduction with sutureless closure (WBR), sometimes referred to as the Bianchi technique(4). With WBR, the abdominal contents are reduced on the neonatal unit with the infant under minimal sedation, and the defect is then closed using only steri-strips(88).

Figure 9: Reduction using a spring-loaded silo



4.1.2.2. Evidence to support surgical decision making

Currently, for infants with uncomplicated gastroschisis, most surgeons will have a preferred operative strategy, and will attempt to employ this strategy for all infants unless there are clear contraindications, such as significant abdomino-visceral disproportion in the case of OPFC, or intestinal perforation in the case of SR, or WBR.

Advocates of OPFC suggest that it is associated with shorter times to introducing and fully establishing feeds(89) than SR, whilst advocates of SR suggest that the gentle approach to reducing the abdominal contents decreases the risk of complications associated with increased intra-abdominal pressure(90). The most commonly stated benefit to WBR is that reduction of the mid-gut with an un-anaesthetised infant allows the surgeon to use the infant's reactions to guide the speed of reduction, thereby again reducing the risk of developing abdominal compartment syndrome(91). Each technique has vocal supporters and detractors amongst the paediatric surgical community, but currently, there is little robust evidence to support the use of one technique over the others.

To date, only one RCT has been attempted comparing OPFC to SR(92), and only one RCT attempted comparing sutured closure to sutureless closure(93). Neither trial managed to recruit to target and therefore interpretation of their results is difficult. With the exception of these two RCTs, and studies conducted by either the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS) or Canadian Pediatric Surgery Network (CAPSNet), the vast majority of studies comparing interventions for the treatment of gastroschisis are small, retrospective cohort studies or case series(2). These

small, retrospective studies are so affected by chance, bias and confounding that they cannot reliably be used to inform clinical decision-making. Such a lack of robustness in the primary evidence-base has also prevented systematic reviews from drawing conclusions sufficiently robust to inform management decisions(18, 19).

Whilst it has been demonstrated that many consultant surgeons have a preferred technique for managing infants with gastroschisis (50), and that therefore individual equipoise between interventions probably doesn't exist, the confused picture from the existing literature regarding the relative merits of each treatment, and the common use of all three techniques suggests that at present, community equipoise between treatments probably does exist. What is therefore required now, is conduct of an observational study that is sufficiently robust to convince individual surgeons that equipoise exists, and that it is therefore ethical for them to recruit infants to an RCT.

4.1.3. Existing definitions of complex gastroschisis

As well as there being a lack of clarity around the gold standard management of infants with gastroschisis, there is also a lack of clarity around the patient factors that are associated with outcome. In order to both clinically risk prognosticate, and identify populations of infants who should be studied separately in RCTs, multiple groups have attempted to derive definitions of 'complex' or 'high-risk' gastroschisis. However, in order to be useful both in clinical practice and in research, such definitions need to relate to an outcome which is of interest to key stakeholders, and which could also realistically be utilised for powering an

RCT. Neither of the two most commonly used definitions of 'complex' or 'high-risk' gastroschisis achieves both of these requirements.

In 2001, Molik et al proposed that infants with necrosis, perforation or atresia were at higher risk of mortality than those without any of those features(94). Whilst mortality is undoubtedly an outcome of importance, the relatively high survival rate for infants with gastroschisis, of approximately 96% at one year of age, means that even if every infant born with gastroschisis in the British Isles were recruited to take part in an RCT comparing OPFC to SR, it would take approximately 12 years to recruit sufficient numbers of infants to detect a halving of mortality from 4% to 2%. With recruitment to neonatal trials frequently standing closer to 20% of the eligible population, and a reduction in mortality of 50% implausible, it is likely that recruitment to a trial comparing treatments for gastroschisis on the basis of mortality would take upwards of fifty years to conduct. Mortality is therefore not a viable outcome for powering an RCT comparing treatments for infants with gastroschisis.

Since Molik et al derived their original classification of 'complex' gastroschisis, other groups have conducted work to demonstrate that infants with these features, as well as being at higher risk of mortality, are also at a higher risk of other adverse events, including intestinal failure associated liver disease, and reoperation, both outcomes that have a higher incidence than mortality(5). Re-operation is an outcome that is of importance to key stakeholders(80), and common enough that suitably powered RCTs could plausibly be conducted. Given the ability to identify infants who are at an increased risk of need for re-

operation, it therefore appears that the definition of 'complex' gastroschisis, as described by Molik et al, could be used to help stratify the study population for an RCT comparing treatments for infants with gastroschisis. However, prior to doing so, it is important to understand whether all three patient factors that are included in the definition, necrosis, perforation and atresia are associated with outcome, or only a subset of them.

Following the work by Molik et al, a second group, utilising data collected by CAPSNet between 2005 and 2010 developed the gastroschisis prognostic score (GPS), based upon evidence of bowel injury at six hours of age(95). This group only identified one factor, intestinal necrosis, which independently predicted mortality. Following re-weighting of the investigated features of bowel injury based upon results of the regression analyses, Cowan et al identified that a score of 4 or more on the GPS correctly predicted survival status in 99% of survivors and 75% of non-survivors, and that a score of 2 or more identified infants at a greater risk of complications, or increased duration of parenteral nutrition requirement.

Whilst the GPS can be used to identify infants at increased risk of requiring a prolonged duration of parenteral nutrition, an outcome that is of importance to key stakeholders(72), and which could plausibly be used to power an RCT, it would still be difficult to use it to define inclusion, exclusion and stratification criteria for a trial. This is due to the fact that accurate calculation of the GPS requires correct identification of intestinal atresia at 6 hours of life, something that is notoriously difficult to do with a high degree of accuracy(96, 97). In order to ensure that a future trial is run efficiently, the eligible population must be reliably

identifiable prior to randomisation, and therefore including an absence of intestinal atresia as a requirement for entry to the trial would be difficult to justify.

Both the GPS and Molik et al's definition of complex gastroschisis include only features of bowel injury and do not take account of non-intestinal patient characteristics that may affect an infant's outcome. Multiple physiological factors, including birth weight, gestational age at birth, and birth weight less than the 10th centile for gestational age have been shown to have an association with neonatal outcomes(98-100). Data relating to each of these factors is easily available or calculable at birth, and could be used to help define the population for a trial comparing OPFC to SR for the treatment of gastroschisis. However, prior to doing so, their relationship with appropriate outcomes in infants with gastroschisis should first be investigated.

4.1.4. Trial population size

The two previously attempted RCTs comparing interventions for the treatment of infants with gastroschisis were abandoned due to a failure to recruit to target(92, 93). In order to recruit sufficiently, any future trials will therefore have to be multi-centre, and are likely to have to be international. However, it has previously been demonstrated that mortality for infants born with gastroschisis in Canada is lower than that of infants born in the United States of America, and the determinants of outcome were different in each country(101). It is not known how these countries compare to other high-income Western countries. Prior to conducting an international RCT comparing interventions for gastroschisis, it is therefore

essential to first understand whether the management of, and outcomes for, infants treated in proposed participatory countries are similar.

4.1.5. Existing gastroschisis data

Three large-scale, contemporary, prospectively collected datasets exist containing data relating to infants with gastroschisis. The first of these is a British Isles-wide dataset collected by BAPS-CASS(4), the second is a Canada-wide surgical dataset, containing information collected by CAPSNet(69) and the third is a Canada-wide neonatal dataset, collected by the Canadian Neonatal Network (CNN) (102). These data are the most robustly collected data relating to infants with gastroschisis currently available. The work presented in this chapter therefore focuses on merging these three datasets and utilising them to address the questions that require answering prior to designing an RCT comparing operative strategies for managing infants with gastroschisis.

4.2. Objectives and research questions

The overall objective of the work presented in this chapter was to investigate whether a COS could be applied to existing data so as to inform development of an international, multi-centre RCT comparing reduction and closure strategies for the treatment of infants born with gastroschisis. Within this global objective, four research questions were investigated:

1 Which patient factors affected the number of severe gastrointestinal complications infants developed in the first 28 days of life?
2 Were there differences in core outcomes at 28 days of age between infants who underwent OPFC, infants who underwent SR, and infants who underwent WBR?
3 Was the effect of each intervention on outcome different dependent on the complexity of an infant's gastroschisis?
4 Were there differences in core outcomes at 28 days of age between infants with gastroschisis who were treated in the British Isles and those who were treated in Canada?

4.3. Methods

4.3.1. Study Summary

This study comprised a secondary analysis of data previously collected prospectively by three population-based systems, BAPS-CASS, CAPSNet and the CNN.

Between October 2006 and March 2008, a British Isles-wide cohort study describing outcomes at 28 days of age for children born with gastroschisis was conducted using the BAPS-CASS infrastructure, and from 2005 onwards, CAPSNet collected demographic, early management, operative and pre-discharge outcomes data for all infants diagnosed with gastroschisis in Canada. Infants whose gastroschisis data were collected through CAPSNet also had data relating to any NICU admissions collected through the CNN. The data collected from these three individual systems were merged to create one unified database.

4.3.2. Data collection systems

BAPS-CASS is the main framework through which paediatric surgical research is conducted in the British Isles. This nationwide network of researchers and surgeons has been established for just over a decade, and utilised to collect anonymous data relating to the initial presentation, management and short-term outcomes of infants requiring surgery in the neonatal period or early infancy(4). To date, ten surgical conditions have been studied using the BAPS-CASS infrastructure.

CAPSNet and the CNN are both Canadian population-based neonatal research collaborations consisting of clinicians and academics. The CAPSNet collaboration collects data from hospitals in Canada that have an on-site or functionally linked perinatal diagnostic/high-risk obstetric unit and a level III NICU, and provide paediatric general surgery, paediatric neurosurgery and paediatric general anaesthesia. The CNN is a collaborative of over 200 researchers from 31 hospitals and 17 universities across Canada. The CNN maintains a standardised NICU database collecting data from all infants admitted

to the 31 level III NICUs in Canada. Additionally, the CNN provides database support for CAPSNet. This integration between the two systems allows linkage between an infant's NICU data collected through the CNN, and their surgical data collected through CAPSNet. Two surgical conditions, gastroschisis and congenital diaphragmatic hernia, have been studies using the CAPSNet infrastructure, whilst a range of surgical and neonatal conditions has been studied using the CNN infrastructure.

4.3.3. BAPS-CASS Case Definition

Infants were eligible for inclusion in the original BAPS-CASS study if they were live-born and treated for gastroschisis in one of the 28 paediatric surgical centres in the British Isles between 1st of October 2006 and 31st of March 2008. Gastroschisis was defined as *'A congenital malformation characterized by visceral herniation through an abdominal wall defect lateral to an intact umbilical cord and not covered by a membrane. This excludes infants with aplasia or hypoplasia of abdominal muscles, skin-covered umbilical hernia, exomphalos or omphalocele'.*

4.3.4. CAPSNet Case Definition

Between May 2005 and December 2016, CAPSNet collected data for infants diagnosed with gastroschisis and identified through one of two routes:

1. Mothers referred to a CAPSNet perinatal centre for prenatal care of a fetus with a suspected or confirmed diagnosis of gastroschisis. This included all terminations, stillbirths, and delivery room deaths, regardless of gestational age.

2. Babies admitted to a CAPSNet centre with a diagnosis of gastroschisis. If the infant did not have a prenatal diagnosis, a diagnosis must have been made within the first 7 days of life, regardless of the unit of admission.

4.3.5. Data collection

4.3.5.1. BAPS-CASS

Cases were identified via monthly reporting cards sent to lead clinicians at the 28 paediatric surgical centres in the British Isles, with a detailed data collection form completed at 28 days of age in response to notification of a case. Lead clinicians were asked to return a 'null' card specifying if there had been no cases in their institution that month. If cards were not returned for three months, lead surgeons were contacted by telephone or email to obtain the missing case reports. All data were anonymous, and were double entered into a customised database. Duplicates were excluded by comparing reporting hospital, mother's year of birth, and date of first operation. If any data items were missing or fell outside pre-specified ranges, clinicians were contacted to obtain the required information.

4.3.5.2. CAPSNet

When clinicians identified cases, their details were forwarded to on-site trained research assistants who abstracted data from maternal and infant charts from the point of diagnosis until death or discharge. If an infant was discharged to a community hospital and subsequently readmitted to a CAPSNet centre, then re-operations data were also abstracted. Infants transferred from one CAPSNet centre to another were tracked back to their initial admission. Data were directly entered into a customised Microsoft Access data

entry program with built-in error checking and a standard manual of operations and definitions. From here, data were transferred to a centralised repository for cleaning and storage.

4.3.5.3. Canadian Neonatal Network

The CNN is an admission based system and therefore data are collected every time any infant is admitted or readmitted to a level III NICU. This differs from both CAPSNet and BAPS-CASS, where data collection is diagnosis based. Data abstraction for the CNN is conducted in the same manner as for CAPSNet.

4.3.6. Criteria for inclusion in the secondary analysis

Infants whose data were included in either the BAPS-CASS or CAPSNet databases and who met the case definitions.

4.3.7. Criteria for exclusion from the secondary analysis

CAPSNet collected data relating to terminations of pregnancy, and fetuses with gastroschisis who were not carried to term or who were stillborn, whilst BAPS-CASS only collected data relating to live-born infants. In order to aid comparability between the datasets, terminations of pregnancy, and infants who otherwise met the case definition but were not live-born were excluded from the secondary analysis.

4.3.8. Defining the interventions of interest

4.3.8.1. BAPS-CASS

Treatment allocation was determined based upon the first attempted reduction and closure procedure as reported by the treating surgeon. These were classified as OPFC, WBR, SR, staged reduction and delayed closure facilitated by a custom silo, or mesh repair.

4.3.8.2. CAPSNet

Data were collected relating to whether the treating surgeon intended to primarily reduce the eviscerated abdominal contents and close the defect, or facilitate staged reduction and closure through use of a silo. Secondary questions collected data relating to the timing of the first attempted reduction and closure, whether the intended treatment strategy was successful, whether sutured fascial closure was used, where the reduction and closure was performed, and whether it was conducted with the infant intubated and anaesthetised or not. These data were used for allocating infants to a treatment group, with treatments defined as below.

4.3.8.2.1. Operative primary fascial closure

OPFC was defined as intended primary reduction of the eviscerated abdominal contents, with the first attempted reduction occurring within a day of birth, and sutured fascial closure being employed. If the closure technique was unknown, the surgeon's intent to suture the fascia was assumed if the reduction and closure took place with an intubated or anaesthetised infant.

There are several Canadian paediatric surgical centres that utilise pre-formed silos as bowel protection prior to reducing the abdominal contents and closing the defect in a single procedure. This use of a silo is more akin to OPFC than SR, and therefore, where surgical intent was reported as delayed reduction facilitated by silo, but closure took place within 24 hours of birth, and sutured fascial closure was used, these infants were also deemed to have undergone OPFC.

4.3.8.2.2. Primary reduction with sutureless closure

Primary reduction with sutureless closure was defined as intended primary reduction of the eviscerated abdominal contents, with the first attempted reduction occurring less than 24 hours after birth, and closure being completed without suturing the fascia. If the closure technique was unknown, the surgeon's intent to use a sutureless closure was assumed if the reduction and closure took place with an awake, un-intubated infant.

Where surgical intent was reported as delayed reduction facilitated by silo, but closure took place one day or less after birth, and closure was completed without suturing the fascia, these infants were also deemed to have undergone primary reduction with sutureless closure.

Primary reduction with sutureless closure was sub-classified as operative sutureless closure, and WBR. Infants in whom the reduction and closure took place outside of the operating room without delivery of general anaesthesia were deemed as undergoing WBR, whilst

those in whom the reduction took place in an operating theatre, or under general anaesthetic, were classed as undergoing operative sutureless closure.

Where infants were reported to have undergone successful primary reduction, but closure (either sutured, or sutureless) took place more than 24 hours after birth, their treatment allocation was classified as unknown.

4.3.8.2.3. Silo placement with staged reduction and delayed closure

SR was defined as use of a silo to facilitate delayed closure, with closure taking place more than one day after birth. Where the primary intention was to facilitate staged reduction through use of a silo, the silo was assumed to be a pre-formed, spring loaded silo as opposed to a custom silo. This is because standard practice across Canada is to only use custom silos as a salvage operation where OPFC or use of a pre-formed silo has not been possible. It is therefore highly unlikely that any custom silos were used in cases where staged reduction was the intended treatment strategy.

4.3.8.2.4. Mesh repair

Infants who were reported as undergoing a successful first closure procedure, but in whom a mesh was used to achieve closure were defined as having undergone a mesh repair. However, those in whom another first reduction and closure strategy was unsuccessfully attempted prior to use of a mesh were categorised as having undergone the first attempted reduction and closure strategy, not a mesh repair.

4.3.9. Outcome selection

The outcomes investigated in this secondary analysis were the closest approximations of the NETS[1G] core outcomes that could be achieved from utilising existing BAPS-CASS, CAPSNet and CNN data. Outcome definitions are described in detail in Appendix 13. However, it is important to note that given the data collection methodology used in BAPS-CASS, it was not possible to reliably determine the number of episodes of infection experienced by British and Irish infants, and therefore these infants only contributed data to the outcome *one or more episode of infection,* not the outcome *number of episodes of infection*

Number of severe gastrointestinal complications was investigated as the primary outcome, and number of operations, number of days of parenteral nutrition use, diagnosis of one or more episode of infection, number of episodes of infection, diagnosis of liver disease, z-score for weight, z-score for head circumference, and mortality, were investigated as secondary outcomes. In order to maximise use of the collected data, whilst also meeting the requirements of the COS for reporting outcomes at specific time-points, all outcomes were described at or up to 28 days of age as appropriate.

4.3.10. Creation of a unified dataset

A unified dataset was created containing relevant BAPS-CASS, CAPSNet and CNN data. Creation of the dataset involved five stages:

1. Cleaning of BAPS-CASS data to enable merging with Canadian data using common variable names, codes and definitions.
2. Linkage of CAPSNet data to CNN data using an infant's CNN unique identifier

3. Creation of a master Canadian dataset. See Appendix 14 for mapping of original CAPSNet and CNN data-points to final variables used in the analysis.
4. Merging of the master Canadian dataset with collapsed episode/admission based data collected in additional CNN and CAPSNet datasets
5. Cleaning of the final Canadian dataset to enable merging with the BAPS-CASS dataset using common variable names, codes and definitions. See Appendix 15 for discussion of variables where direct equivalence did not exist between BAPS-CASS and CAPSNet datasets.

See Appendix 16 for details of each stage of the dataset creation process.

4.3.11. Defining missing data for composite outcomes

Data describing the complications experienced by an infant were collected in multiple questions of the CAPSNet, CNN and BAPS-CASS data collection forms. However, none of the data collection forms included a question that would identify those infants who had not experienced any severe gastrointestinal complications. If no data were entered for all questions from which the composite outcome severe gastrointestinal complication was derived, it was therefore difficult to ascertain if the infant had not experienced a complication, or if the data were missing. Therefore, the following rules were applied:

- If no data were entered for all questions from which the composite outcome was derived, infants were assumed to have experienced no complications, unless:

- No data were entered for all questions, including those unrelated to severe gastrointestinal complications, in all sections of the data collection forms containing questions from which the composite outcome was derived. This pattern of data entry suggested the sections had not been completed, as opposed to a negative answer being given, and therefore in this situation, data relating to the number of severe gastrointestinal complications experienced by an infant were assumed to be missing.

Using the above assumptions, only one infant who had sufficient data returned to determine the reduction and closure strategy they had undergone, was classed as missing data relating to the number of severe gastrointestinal complications they had experienced. Similar principles were applied to defining whether infants were missing data for the other composite outcomes, number of operations in the first 28 days of life, and number of episodes of infection in the first 28 days of life.

4.3.12. Impact of data collection methodology on outcome

There are infants in the CAPSNet dataset who did not have 28-day non-operative outcomes data collected due to the fact that they were discharged prior to 28 days of age, and their follow-up therefore ceased. Prior clinical knowledge and evidence from BAPS-CASS suggests that these are likely to be the infants with less complicated gastroschisis and better outcomes. Treating these infants' data as missing in relation to 28-day outcomes would likely therefore artificially worsen outcomes and bias the analysis. It was therefore decided that these infants' data would be retained in the analysis of 28-day outcomes, and the

assumption made that between the point of discharge and 28 days of age, they had experienced no further events of interest. In order to test the security of making this assumption, the following were described:

- Characteristics of infants discharged prior to 28 days of age, and those who remained in a paediatric surgical centre at 28 days of age
- Locations of care at 28 days of age of infants in the BAPS-CASS cohort, the CAPSNet cohort, and the CAPSNet cohort limited to the time period during which the BAPS-CASS study was running (2005-2008).
- Number and proportion of infants in the BAPS-CASS cohort who were discharged prior to 28 days of age and experienced a non-surgical event of interest between discharge and 28 days of age.

4.3.13. Association of patient factors and complications

Counts and proportions were used to describe categorical variables, whilst medians and interquartile ranges or means and standard deviations were used as appropriate to describe continuous variables. Univariable negative binomial regression analysis was used to describe the association between number of severe gastrointestinal complications experienced by an infant prior to 28 days of age and key patient characteristics, including gestational age at birth, birth weight, year of birth, country of treatment, transfer in to a surgical centre, antenatal diagnosis, maternal age at delivery, caesarean section delivery, ethnic group, gender, $<10^{th}$ centile birth weight for gestational age at birth (small for gestational age at birth – SGA), presence of an additional chromosomal or structural anomaly, APGAR score at

five minutes, presence of intestinal necrosis at birth, degree of intestinal matting at birth, presence of an intestinal atresia, presence of an intestinal perforation, and grade of operating surgeon.

Small for gestational age at birth was calculated using the LMS growth add in for excel and the UK 1990 reference charts. See Appendix 16 for a detailed description of the SGA calculation methodology and rationale for using the UK 1990 growth charts.

Additional chromosomal or structural anomalies excluded those that are likely to be directly associated with evisceration of the abdominal contents, including intestinal atresia and undescended testes. Single minor anomalies such as *'accessory skin tags, congenital'* were not included as an additional chromosomal or structural anomaly. See Appendix 17 for full list of included additional chromosomal and structural anomalies.

Characteristics that were shown to be associated with number of severe gastrointestinal complications occurring in the first 28 days of life, as defined by a p-value of ≤0.1 on univariable analysis, were assessed for inclusion in the multivariable negative binomial regression model and retained if they were shown to improve the fit of the model, as defined by a p-value of ≤0.05 on likelihood ratio testing. Due to the weight of existing evidence that they are associated with an infant's outcome, gestational age at birth and birth weight were included in the model *a priori*. Complete case analysis was utilised in the multivariable analysis.

4.3.14. Comparison of reduction and closure strategies

Characteristics of infants who underwent OPFC, SR, and WBR were described using counts and proportions for categorical variables, and medians and inter-quartile ranges or means and standard deviations as appropriate for continuous variables. The Chi^2 test of significance, Wilcoxon-Rank-Sum test and Student's t-test were used as appropriate to compare characteristics between the two groups.

Propensity scores predicting an infant's likelihood of allocation to OPFC, SR or WBR were calculated using multinomial, multivariable logistic regression. The characteristics used to develop the propensity score were gestational age at birth, birth weight, weight $<10^{th}$ centile for gestational age at birth, year of birth, country of treatment, transfer in to a surgical centre, antenatal diagnosis, gender, presence of an additional chromosomal or structural anomaly, intestinal necrosis, intestinal atresia, intestinal perforation, intestinal matting, APGAR score at five minutes, and the composite variable, 'complex' gastroschisis, as per the definition by Molik et al(94).

The impact of treatment choice on outcome was investigated using appropriate regression analyses. Negative binomial regression was used for outcomes with over-dispersed count data, including number of severe gastrointestinal complications and number of episodes of sepsis. Poisson regression was used where the outcome was count data, but was not over-dispersed, including number of operations and number of days of parenteral nutrition use. Logistic regression was used for binary outcomes, including mortality, liver disease and one or more episode of sepsis, and linear regression was used for growth outcomes where the

data were continuous and normally distributed. See Appendix 18 for details of assumption checking for each analysis. Estimates of effect calculated for each outcome were an unadjusted estimate, an estimate adjusted for confounding factors, a propensity score adjusted estimate, and a final estimate adjusted for both propensity score and confounding factors.

4.3.15. Effect of early deaths on conclusions of primary analysis

There is the potential that infants who died may have gone on to experience one or more severe gastrointestinal complication had they survived the event that led to their death. One explanation for a low rate of severe gastrointestinal complications could therefore be a high early mortality rate. In order to investigate whether early deaths were likely to have affected the comparison between treatments, causes of death, and the number of severe gastrointestinal complications experienced by each infant who died were described in each treatment group. Two sensitivity analyses were also conducted to assess the impact of mortality on the conclusions of the primary analysis. Firstly, all infants who died were assumed prior to their death to have experienced the maximum number of severe gastrointestinal complications experienced by any infant in the study, and the negative binomial regression analysis comparing OPFC to SR was then re-run. Secondly, the negative binomial regression analysis was re-run excluding all infants who had died prior to 28 days of age.

4.3.16. Effect of gastroschisis complexity on treatment outcome

Interactions between choice of treatment and intestinal necrosis, intestinal perforation, intestinal matting and intestinal atresia were investigated in the covariate and propensity score adjusted negative binomial regression model in which number of severe gastrointestinal complications was the outcome of interest. Where clinically or statistically significant interactions were identified, these were used to define two sub-groups of infants in which the effect of each reduction and closure strategy on outcomes at 28 days of age was subsequently investigated. A statistically significant interaction was defined as one in which including the interaction term improved the fit of the multivariable model, as defined by a p-value of <0.05 on likelihood ratio testing. A clinically significant interaction was defined as one in which the treatment effects were in opposing directions at each level of the interaction, but where including the interaction term did not meet the level of statistical significance for improving the fit of the model. All analyses comparing the reduction and closure strategies of interest were then re-run in each of the sub-groups defined following interaction testing.

4.3.17. Comparison of infants treated in Canada and the British Isles

Characteristics of infants treated in Canada and infants treated in the British Isles were described using counts and proportions, medians and inter-quartile ranges, and means and standard deviations as appropriate. Outcomes data in each of the British Isles and Canadian cohorts were described as per the comparison between reduction and closure strategies. Unadjusted and covariate-adjusted estimates of effect of country of treatment on outcome were calculated. No comparison was possible for the outcomes number of episodes of

sepsis, weight at 28 days of age, or head circumference at 28 days of age, as these data were not collected in the BAPS-CASS cohort.

4.4. Results

4.4.1. Characteristics of the combined cohort

A total of 1600 live-born infants with gastroschisis were identified during the defined reporting periods, 393 (25%) from the British Isles, and 1207 (75%) from Canada. Overall, 803 infants (50%) were male, 783 (49%) were female, and 14 (1%) had indeterminate sex, or their sex was unknown. The median (IQR) gestational age at birth was 36 weeks (35 weeks to 37 weeks) and the median (IQR) birth weight was 2490g (2160g - 2800g) (Table 15).

Table 15: Characteristics of the combined cohort

	N=1600
	Median (IQR)
Birthweight	
Grams	2490 (2160 – 2800)
Gestational age at birth	
Completed weeks	36 (35 - 37)
	n(%)*
Reporting year	
2005-2008	771 (48.2%)
2009-2012	464 (29.0%)
2013-2016	364 (22.8%)
Transferred in to surgical centre	
No	968 (60.6%)
Yes	629 (39.4%)
Antenatal diagnosis	
No	18 (1.2%)
Yes	1510 (98.8%)
Maternal age	
<25	942 (67.8%)
25-34	414 (29.8%)
35 and above	33 (2.4%)
Caesarean section delivery	
No	921 (65.6%)
Yes	482 (34.4%)
Ethnicity	
White	882 (77.7%)
BME	253 (22.3%)
Sex	
Male	803 (50.6%)
Female	783 (49.4%)
Small for gestational age at birth	
No	1271 (80.5%)
Yes	307 (19.5%)
Additional chromosomal or structural anomaly	
No	1304 (86.1%)
Yes	210 (13.9%)
Intestinal necrosis	
No	1410 (96.8%)
Yes	47 (3.2%)

* Percentage of those with complete data
BME – Black or minority ethnicity

Table 15: Characteristics of the combined cohort - Continued

	N=1600
	n(%)*
Intestinal atresia	
No	1384 (89.6%)
Yes	160 (10.4%)
Intestinal perforation	
No	1418 (96.5%)
Yes	51 (3.5%)
Intestinal matting	
None	645 (44.9%)
Mild	617 (43.0%)
Severe	174 (12.1%)
Complex gastroschisis(94)	
Simple	1258 (78.6%)
Complex	194 (12.1%)
Unknown	148 (9.3%)
APGAR score at five minutes	
≥7	1363 (88.1%)
4-6	151 (9.8%)
0-3	33 (2.1%)

*Percentage of those with complete data

4.4.2. Impact of methodology on outcome ascertainment

4.4.2.1. CAPSNet and CNN linkage

Linkage to CNN data was achieved for 980 (81%) of the 1207 infants in the CAPSNet cohort. There is no evidence that missing links for the remaining 227 infants (19%) affected the conclusions of the study (Appendix 19).

4.4.2.2. Comparison of discharge patterns between countries

The median (IQR) duration of follow-up for the British Isles cohort was 365 days (133 days to 365 days), for the Canadian cohort was 36 days (25 days to 64 days), and for the cohort as a whole was 43 days (28 days to 135 days). In the British Isles cohort, the median (IQR) time to discharge from a paediatric surgical centre was 32 days (22 days to 55 days), which was statistically significantly shorter than in the Canadian cohort, where it was 36 days (25 days to 62 days). A greater proportion of infants in the British Isles cohort (115 infants, 32%) had been discharged home prior to 28 days of age than in the Canadian cohort (302 infants, 25%). However, when the British Isles cohort was compared to the Canadian cohort limited to the time period of 2005-2008, when both the BAPS-CASS and CAPSNet studies were running, the statistical significance of the differences in discharge patterns disappeared (Table 16).

Table 16: Comparison of discharge patterns between countries

	British Isles	Canada 2005 to 2008		Canada entire cohort	
	N=393	N=378		N=1207	
	n(%)	n(%)	p-value*	n(%)	p-value*
Location of care at 28 days of age			0.13		0.039
Died	6 (1.7%)	7 (1.9%)		26 (2.2%)	
Home	115 (32.4%)	94 (25.0%)		302 (25.4%)	
Other Hospital	24 (6.8%)	35 (9.3%)		73 (6.1%)	
Other e.g. Hospice	0 (0.0%)	0 (0.0%)		10 (0.8%)	
Paediatric Surgical Centre	210 (59.2%)	240 (63.8%)		778 (65.4%)	
	Median (IQR)	Median (IQR)	p-value*	Median (IQR)	p-value*
Time from admission to discharge			0.2		0.019
Number of days	32 (22, 55)	36 (23, 62)		36 (25, 62)	

*p-value for difference to British Isles

4.4.2.3. Comparison of infants discharged pre- and post-28 days of age

In the cohort as a whole, there were 988 infants (62%) who remained alive and cared for in a paediatric surgical centre at 28 days of age, 524 (33%) who had been discharged home or were cared for in a community/district general hospital at 28 days of age, and 32 (2%) who had died prior to 28 days of age. The location of care at 28 days of age was unknown for 56 infants (4%).

Compared to those who remained in a paediatric surgical centre at 28 days of age, those infants who had been discharged home or transferred out to a community/district general hospital had a statistically significantly higher birth weight and gestational age at birth, and were statistically significantly less likely to have an additional chromosomal or structural anomaly, intestinal necrosis at presentation, intestinal perforation at presentation, intestinal matting at presentation, or an intestinal atresia. They were also statistically significantly more likely to have been transferred into a paediatric surgical centre prior to treatment and to have undergone OPFC than those who remained in a paediatric surgical centre at 28 days of age (Table 17)

Table 17: Characteristics of infants who remained alive and in a paediatric surgical centre at 28 days of age, and those who had been transferred or discharged home

	Paediatric Surgical Centre	Other	
	N=988	N=524	
	Median (IQR)	Median (IQR)	p-value
Gestational age at birth			<0.001
Completed weeks	36 (35, 37)	37 (36, 37)	
Birthweight			<0.001
Grams	2405 (2080, 2760)	2610 (2280, 2890)	
	n(%)*	n(%)*	
Reporting year			0.11
2005-2008	450 (45.5%)	268 (51.1%)	
2009-2012	303 (30.7%)	146 (27.9%)	
2013-2016	235 (23.8%)	110 (21.0%)	
Transferred in to surgical centre			<0.001
No	566 (57.4%)	347 (66.2%)	
Yes	420 (42.6%)	177 (33.8%)	
Antenatal diagnosis			0.083
No	13 (1.4%)	2 (0.4%)	
Yes	933 (98.6%)	497 (99.6%)	
Maternal age			0.65
<25	577 (67.7%)	315 (67.5%)	
25-34	258 (30.3%)	139 (29.8%)	
35 and above	17 (2.0%)	13 (2.8%)	
Caesarean section delivery			0.36
No	581 (66.6%)	290 (64.0%)	
Yes	292 (33.4%)	163 (36.0%)	
Ethnicity			0.42
White	531 (76.6%)	297 (78.8%)	
BME	162 (23.4%)	80 (21.2%)	
Sex			0.57
Male	502 (51.1%)	258 (49.5%)	
Female	481 (48.9%)	263 (50.5%)	
Small for gestational age at birth			0.18
No	777 (79.6%)	429 (82.5%)	
Yes	199 (20.4%)	91 (17.5%)	

*Percentage of those with complete data
BME – Black or minority ethnicity

Table 17: Characteristics of infants who remained alive and in a paediatric surgical centre at 28 days of age, and those who had been transferred or discharged home - Continued

	Paediatric Surgical Centre	Other	
	N=988	N=524	
	n(%)	n(%)	p-value
Additional chromosomal or structural anomaly			0.001
No	783 (83.7%)	443 (89.9%)	
Yes	153 (16.3%)	50 (10.1%)	
Necrosis at admission			<0.001
No	874 (96.4%)	465 (99.4%)	
Yes	33 (3.6%)	3 (0.6%)	
Intestinal atresia			<0.001
No	822 (86.1%)	493 (97.6%)	
Yes	133 (13.9%)	12 (2.4%)	
Intestinal perforation			<0.001
No	875 (95.7%)	469 (99.2%)	
Yes	39 (4.3%)	4 (0.8%)	
Intestinal Matting			<0.001
None	354 (39.4%)	258 (56.3%)	
Mild	405 (45.1%)	179 (39.1%)	
Severe	139 (15.5%)	21 (4.6%)	
Complex gastroschisis			<0.001
Simple	749 (75.8%)	449 (85.7%)	
Complex	157 (15.9%)	14 (2.7%)	
Unknown	82 (8.3%)	61 (11.6%)	
APGAR score at five minutes			0.45
≥7	838 (87.6%)	460 (89.7%)	
4-6	98 (10.2%)	45 (8.8%)	
0-3	21 (2.2%)	8 (1.6%)	
First attempted reduction/closure procedure			<0.001
OPFC	387 (40.4%)	242 (47.5%)	
Operative primary reduction, sutureless closure	42 (4.4%)	55 (10.8%)	
SR	441 (46.1%)	139 (27.3%)	
Mesh	5 (0.5%)	6 (1.2%)	
WBR	82 (8.6%)	67 (13.2%)	

*Percentage of those with complete data
OPFC – Operative Primary Fascial Closure
SR – Silo placement with staged reduction and delayed closure
WBR – Ward-based reduction with sutureless closure

4.4.2.4. Events occurring between discharge and 28 days of age

Of the 139 infants who were discharged prior to 28 days of age, but in whom 28-day outcomes data were available, i.e. those from the BAPS-CASS cohort who had been discharged prior to 28 days of age, there was only one infant (1%) who experienced a severe gastrointestinal complication between discharge and 28 days of age, and one infant (1%) who experienced an episode of sepsis between discharge and 28 days of age. No infants were reported as dying, developing liver disease or being readmitted for administration of parenteral nutrition between the time of discharge and 28 days of age.

4.4.2.5. Handling of data from Canadian infants discharged prior to 28 days

The data described in sections 4.4.2.2 to 4.4.2.4 support the hypothesis that infants discharged prior to 28 days of age are likely to be those with less complex gastroschisis and better outcomes, and that they are unlikely to experience further adverse events between the point of discharge and 28 days of age. Excluding these infants from analysis of 28-day outcomes would likely artificially worsen the described results. Therefore, as described in section 4.3.12, data from these infants was utilised in assessment of 28-day outcomes, with the assumption made that they experienced no events of interest between the time of discharge and 28 days of age.

4.4.3. Association of patient characteristics with outcome

There were 1430 infants (89%) who experienced no severe gastrointestinal complications in the first 28 days of life, 127 (8%) who experienced one, 30 (2%) who experienced two, and 12 (1%) who experienced three or more.

Gestational age at birth, birth weight, year of birth, country of treatment, ethnic group, intestinal necrosis at presentation, degree of intestinal matting at presentation, intestinal perforation at presentation and presence of an intestinal atresia met criteria for assessment in the multivariable model. Four factors, gestational age at birth, birth weight, intestinal perforation and intestinal atresia then met the criteria for retention in the multivariable model. Overall, 1435 infants (90% of the total cohort) had data recorded for all four of these factors and their data were therefore utilised to derive the effect estimates in the complete case analysis (Table 18).

Following adjustment in the multivariable model, higher birthweight was associated with a 4% reduction in incidence of severe gastrointestinal complications in the first 28 days of life, IRR 0.96 (95% CI 0.95-0.98, $p<0.001$) per 50g higher birthweight, and presence of intestinal atresia and intestinal perforation were statistically significantly associated with an increased incidence of severe gastrointestinal complications in the first 28 days of life, IRRs respectively 2.4 (95% CI 1.5-3.7, $p<0.001$) and 3.7 (95% CI 2.0-7.2 $p<0.001$). Gestational age at birth showed no statistically significant association with the number of severe gastrointestinal complications in the first 28 days of life (Table 18).

Table 18: Association of patient characteristics with number of severe gastrointestinal complications

	Number of severe gastrointestinal complications in the first 28 days of life							
	0	**1**	**2**	**≥3**				
	N=1430	**N=127**	**N=30**	**N=12**				
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**IRR (95% CI)**	**p-value**	**Adjusted IRR (95% CI)**	**p-value**
Gestational Age at Birth						<0.001		0.5
Completed weeks	36 (35-37)	36 (34-37)	35.5 (35-36)	36 (35-37)	0.8 (0.75-0.89) per week increase		0.97 (0.88-1.10) per week increase	
Birthweight						<0.001		<0.001
Grams	2500 (2185-2830)	2260 (1910-2600)	2210 (1860-2420)	2243 (2000-2600)	0.96 (0.94-0.97) per 50g increase		0.96 (0.95-0.98) per 50g increase	
	n(%)*	**n(%)***	**n(%)***	**n(%)***				
Reporting year						0.005		
2005-2008	672 (47.0%)	70 (55.1%)	19 (63.3%)	9 (75.0%)	Ref.		Not retained	
2009-2012	425 (29.7%)	33 (26.0%)	3 (10.0%)	3 (25.0%)	0.56 (0.38-0.84)			
2013-2016	332 (23.2%)	24 (18.9%)	8 (26.7%)	0 (0.0%)	0.60 (0.39-0.92)			
Country of treatment						<0.001		
British Isles	331 (23.1%)	41 (32.3%)	13 (43.3%)	7 (58.3%)	Ref.		Not retained	
Canada	1099 (76.9%)	86 (67.7%)	17 (56.7%)	5 (41.7%)	0.47 (0.33-0.66)			
Transferred in to surgical centre						0.808		
No	860 (60.2%)	87 (69.0%)	17 (56.7%)	4 (33.3%)	Ref.		Not retained	
Yes	568 (39.8%)	39 (31.0%)	13 (43.3%)	8 (66.7%)	1.04 (0.74-1.46)			
Antenatal diagnosis						0.538		
No	15 (1.1%)	2 (1.6%)	1 (3.6%)	0 (0.0%)	Ref.		Not retained	
Yes	1349 (98.9%)	122 (98.4%)	27 (96.4%)	12 (100.0%)	0.65 (0.16-2.56)			

*Percentage of those with complete data
IRR – Incidence Rate Ratio

Table 18: Association of patient characteristics with number of severe gastrointestinal complications - Continued

	Number of severe gastrointestinal complications in the first 28 days of life							
	0	**1**	**2**	**≥3**				
	N=1430	**N=127**	**N=30**	**N=12**				
	n(%)*	n(%)*	n(%)*	n(%)*	**IRR (95% CI)**	**p-value**	**Adjusted IRR (95% CI)**	**p-value**
Maternal Age						0.357		
<25	843 (67.5%)	73 (69.5%)	14 (60.9%)	11 (91.7%)	1.21 (0.8-1.82)		Not retained	
25-34	374 (30.0%)	30 (28.6%)	9 (39.1%)	1 (8.3%)	Ref.			
35 and above	31 (2.5%)	2 (1.9%)	0 (0.0%)	0 (0.0%)	0.49 (0.10-2.47)			
Caesarean Section Delivery						0.417		
No	830 (66.2%)	66 (60.0%)	16 (59.3%)	9 (75.0%)	Ref.		Not retained	
Yes	424 (33.8%)	44 (40.0%)	11 (40.7%)	3 (25.0%)	1.16 (0.81-1.68)			
Ethnicity Grouped						0.099		
White	779 (76.6%)	79 (92.9%)	14 (66.7%)	9 (81.8%)	Ref.		Not retained	
BME	238 (23.4%)	6 (7.1%)	7 (33.3%)	2 (18.2%)	0.65 (0.38-1.09)			
Sex						0.727		
Male	721 (50.8%)	60 (48.4%)	15 (50.0%)	6 (50.0%)	Ref.		Not retained	
Female	698 (49.2%)	64 (51.6%)	15 (50.0%)	6 (50.0%)	1.06 (0.76-1.48)			
Small for gestational age						0.564		
No	1141 (80.8%)	100 (80.6%)	20 (69.0%)	10 (83.3%)	Ref.		Not retained	
Yes	272 (19.2%)	24 (19.4%)	9 (31.0%)	2 (16.7%)	1.13 (0.75-1.70)			

* Percentage of those with complete data
IRR – Incidence Rate Ratio
BME – Black or minority ethnicity

Table 18: Association of patient characteristics with number of severe gastrointestinal complications - Continued

	Number of severe gastrointestinal complications in the first 28 days of life							
	0	1	2	≥3				
	N=1430	N=127	N=30	N=12				
	n(%)*	n(%)*	n(%)*	n(%)*	IRR (95% CI)	p-value	Adjusted IRR (95% CI)	p-value
Additional chromosomal or structural anomaly						0.544		
No	1170 (86.3%)	99 (83.9%)	25 (89.3%)	10 (83.3%)	Ref.		Not retained	
Yes	186 (13.7%)	19 (16.1%)	3 (10.7%)	2 (16.7%)	1.16 (0.72-1.87)			
APGAR score at five minutes						0.466		
≥7	1220 (88.0%)	107 (89.2%)	24 (85.7%)	12 (100.0%)	Ref.		Not retained	
4-6	135 (9.7%)	13 (10.8%)	3 (10.7%)	0 (0.0%)	0.87 (0.48-1.57)			
0-3	32 (2.3%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0.42 (0.09-2.02)			
Necrosis at admission						0.001		
No	1276 (97.6%)	101 (91.8%)	23 (82.1%)	10 (90.9%)	Ref.		Not retained	
Yes	32 (2.4%)	9 (8.2%)	5 (17.9%)	1 (9.1%)	3.61 (1.71-7.59)			
Intestinal matting						0.014		
None	588 (45.5%)	45 (42.5%)	7 (25.0%)	5 (45.5%)	Ref.		Not retained	
Mild	559 (43.3%)	42 (39.6%)	13 (46.4%)	3 (27.3%)	1.09 (0.73-1.61)			
Severe	144 (11.2%)	19 (17.9%)	8 (28.6%)	3 (27.3%)	2.12 (1.26-3.54)			
Intestinal atresia						<0.001		<0.001
No	1267 (91.7%)	91 (74.6%)	18 (64.3%)	8 (66.7%)	Ref.		Ref.	
Yes	115 (8.3%)	31 (25.4%)	10 (35.7%)	4 (33.3%)	3.47 (2.28-5.28)		2.36(1.50-3.71)	

* Percentage of those with complete data
IRR – Incidence Rate Ratio

Table 18: Association of patient characteristics with number of severe gastrointestinal complications - Continued

	Number of severe gastrointestinal complications in the first 28 days of life							
	0	**1**	**2**	**≥3**				
	N=1430	**N=127**	**N=30**	**N=12**				
	n(%)*	**n(%)***	**n(%)***	**n(%)***	**IRR (95% CI)**	**p-value**	**Adjusted IRR (95% CI)**	**p-value**
Intestinal Perforation						<0.001		<0.001
No	1286 (97.7%)	102 (89.5%)	23 (82.1%)	7 (63.6%)	Ref.		Ref.	
Yes	30 (2.3%)	12 (10.5%)	5 (17.9%)	4 (36.4%)	5.40(2.86-10.12)		3.75(1.96-7.15)	
Grade of surgeon						0.315		
Consultant	609 (56.8%)	40 (49.4%)	9 (56.3%)	4 (80.0%)	Ref.		Not retained	
Trainee	358 (33.4%)	27 (33.3%)	4 (25.0%)	1 (20.0%)	0.92 (0.58-1.46)			
Consultant and Trainee	106 (9.9%)	14 (17.3%)	3 (18.8%)	0 (0.0%)	1.54 (0.83 - 2.86)			
Complex gastroschisis(94)						<0.001		
Simple	1159 (81.0%)	78 (61.4%)	16 (53.3%)	5 (41.7%)	Ref.		Not assessed#	
Complex	138 (9.7%)	38 (29.9%)	12 (40.0%)	6 (50.0%)	3.96 (2.71-5.80)			
Unknown	133 (9.3%)	11 (8.7%)	2 (6.7%)	1 (8.3%)	1.18 (0.66-2.09)			

* Percentage of those with complete data

Not assessed for inclusion in the multivariable model, as characteristic is a composite of other assessed markers of bowel injury

IRR – Incidence Rate Ratio

4.4.4. Comparison of reduction and closure strategies

4.4.4.1. First reduction and closure strategies

Of the 1600 infants in the combined cohort, 671 (42%) underwent OPFC as their first attempted reduction and closure strategy, 597 (37%) underwent SR, 16 (1%) underwent staged reduction facilitated by a custom silo, 183 (11%) underwent WBR, 71 (4%) underwent operative primary reduction with suture-less closure, and 11 infants (1%) had a mesh sutured in place at their first reduction and closure procedure. The first reduction and closure strategy was unknown for 51 infants (3%). All infants who underwent staged reduction with a custom silo were in the British Isles cohort.

4.4.4.2. Characteristics of infants in each reduction and closure group

Infants who underwent OPFC were more likely than either those who underwent SR or those who underwent WBR to have been treated in the earliest time period in the study (2005-2008), treated in the British Isles, have intestinal necrosis or perforation at presentation, have an intestinal atresia, and have their operation performed by a consultant (Table 19). These same infants were less likely to have been transferred in to a paediatric surgical centre, be of Black or Minority Ethnicity (BME), and have an additional chromosomal or congenital structural anomaly than either of the other groups. Infants who underwent SR were more likely than both infants who underwent OPFC, and those who underwent WBR, to have matted intestines at delivery. Differences in maternal age at delivery also existed across the three intervention groups. There were no other significant differences between the three groups of infants, including in sex distribution, median birthweight, and median gestational age at birth (Table 19).

Table 19: Characteristics of infants in each treatment group

	OPFC	SR	WBR	
	N=671	N=597	N=183	
	Median (IQR)	Median (IQR)	Median (IQR)	p-value[#]
Birthweight				0.48
Grams	2490 (2140-2820)	2450 (2170-2790)	2510 (2207-2850)	
Gestational age at birth				0.87
Completed weeks	36 (35-37)	36 (35-37)	37 (35-37)	
	n(%)*	n(%)*	n(%)*	
Reporting year				<0.001
2005-2008	408 (60.9%)	266 (44.6%)	35 (19.1%)	
2009-2012	151 (22.5%)	202 (33.8%)	53 (29.0%)	
2013-2016	111 (16.6%)	129 (21.6%)	95 (51.9%)	
Country of treatment				<0.001
British Isles	203 (30.3%)	138 (23.1%)	26 (14.2%)	
Canada	468 (69.7%)	459 (76.9%)	157 (85.8%)	
Transferred in to surgical centre				<0.001
No	497 (74.1%)	240 (40.2%)	128 (69.9%)	
Yes	174 (25.9%)	357 (59.8%)	55 (30.1%)	
Antenatal diagnosis				0.23
No	5 (0.8%)	9 (1.6%)	4 (2.2%)	
Yes	642 (99.2%)	555 (98.4%)	178 (97.8%)	
Maternal age				0.036
<25	421 (69.1%)	333 (65.7%)	100 (69.9%)	
25-34	169 (27.8%)	168 (33.1%)	37 (25.9%)	
35 and above	19 (3.1%)	6 (1.2%)	6 (4.2%)	
Caesarean section delivery				0.49
No	364 (65.0%)	357 (65.3%)	118 (69.8%)	
Yes	196 (35.0%)	190 (34.7%)	51 (30.2%)	
Ethnicity				<0.001
White	424 (84.8%)	285 (70.4%)	91 (70.5%)	
BME	76 (15.2%)	120 (29.6%)	38 (29.5%)	
Sex				0.16
Male	349 (52.5%)	297 (50.3%)	81 (44.5%)	
Female	316 (47.5%)	294 (49.7%)	101 (55.5%)	

#p-value for overall difference between the three reduction and closure groups
*Percentage of those with complete data
BME – Black or minority ethnicity, OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction

Table 19: Characteristics of infants in each treatment group - Continued

	OPFC	SR	WBR	
	N=671	N=597	N=183	
	Median (IQR)	Median (IQR)	Median (IQR)	p-value[#]
Small for gestational age at birth				0.45
No	542 (81.9%)	466 (79.5%)	151 (83.0%)	
Yes	120 (18.1%)	120 (20.5%)	31 (17.0%)	
Additional chromosomal or structural anomaly				0.018
No	566 (88.6%)	469 (82.9%)	149 (85.6%)	
Yes	73 (11.4%)	97 (17.1%)	25 (14.4%)	
APGAR score at five minutes				0.98
≥7	570 (88.4%)	513 (88.8%)	157 (87.7%)	
4-6	61 (9.5%)	53 (9.2%)	17 (9.5%)	
0-3	14 (2.2%)	12 (2.1%)	5 (2.8%)	
Necrosis at admission				<0.001
No	571 (95.0%)	552 (98.7%)	177 (99.4%)	
Yes	30 (5.0%)	7 (1.3%)	1 (0.6%)	
Intestinal matting				<0.001
None	257 (43.5%)	205 (37.2%)	120 (68.2%)	
Mild	265 (44.8%)	256 (46.5%)	56 (31.8%)	
Severe	69 (11.7%)	90 (16.3%)	0 (0.0%)	
Intestinal atresia				<0.001
No	577 (86.1%)	546 (92.5%)	176 (96.7%)	
Yes	93 (13.9%)	44 (7.5%)	6 (3.3%)	
Intestinal Perforation				0.020
No	578 (95.1%)	551 (97.9%)	174 (97.8%)	
Yes	30 (4.9%)	12 (2.1%)	4 (2.2%)	
Complex gastroschisis				<0.001
Simple	499 (74.4%)	510 (85.4%)	170 (92.9%)	
Complex	110 (16.4%)	53 (8.9%)	8 (4.4%)	
Unknown	62 (9.2%)	34 (5.7%)	5 (2.7%)	
Grade of surgeon				<0.001
Consultant	290 (62.5%)	233 (52.2%)	73 (46.5%)	
Trainee	139 (30.0%)	166 (37.2%)	52 (33.1%)	
Consultant and Trainee	35 (7.5%)	47 (10.5%)	32 (20.4%)	

#p-value for overall difference between the three reduction and closure groups
*Percentage of those with complete data
BME – Black or minority ethnicity, OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction

4.4.4.3. Primary outcome - severe gastrointestinal complications

There were no statistically significant differences between the three treatment modalities in number of severe gastrointestinal complications using any of the four estimates of effect. The crude and covariate plus propensity score adjusted estimates of effect are displayed in Table 20, and the covariate and propensity score alone adjusted estimates of effect are displayed in Appendix 20. A breakdown of the types of severe gastrointestinal complication experienced by infants in each reduction and closure group is given in Table 21.

When the sensitivity analyses were conducted to assess the effect of early deaths on number of severe gastrointestinal complications, no clinically or statistically significant differences were identified from the primary analysis. See Appendix 21 for details.

Table 20: Core outcomes at or up to 28 days of age in each reduction and closure group

	OPFC	SR	WBR	Crude estimate of effect in comparison to OPFC				Propensity score and covariate[#] adjusted estimate of effect in comparison to OPFC			
	N=671	N=597	N=183	SR		WBR		SR		WBR	
	n(%)*	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Severe gastrointestinal complications											
None	586 (87.5)	549 (92.0%)	164 (89.6%)	0.73 (0.5-1.06)	0.094	0.91 (0.53-1.55)	0.719	0.72 (0.45-1.13)	0.149	1.74 (0.91 - 3.32)	0.093
One	67 (10.0%)	35 (5.9%)	13 (7.1%)								
Two	13 (1.9%)	9 (1.5%)	5 (2.7%)								
Three or more	4 (0.6%)	4 (0.7%)	1 (0.5%)								
Operations											
One	0 (0.0%)	1 (0.2%)	0 (0.0%)	1.4(1.3-1.5)	<0.001	1.1 (1.02-1.3)	0.012	1.34 (1.23-1.46)	<0.001	1.14 (1.01 - 1.29)	0.033
Two	461 (71.1%)	6 (1.1%)	64 (35.4%)								
Three	149 (23.0%)	476 (83.4%)	111 (61.3%)								
Four or more	38 (5.9%)	88 (15.4%)	6 (3.3%)								
Episodes of infection											
None	286 (83.1%)	317 (80.3%)	120 (86.3%)	1.13 (0.80-1.62)	0.472	0.76 (0.45-1.29)	0.314	1.25 (0.83-1.90)	0.29	1.34 (0.72-2.49)	0.356
One	46 (13.4%)	61 (15.4%)	14 (10.1%)								
Two	9 (2.6%)	14 (3.5%)	5 (3.6%)								
Three or more	3 (0.9%)	3 (0.8%)	0 (0.0%)								
	n(%)*	n(%)*	n(%)*	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Mortality											
No	657 (98.1%)	582 (98.1%)	175 (97.2%)	0.96 (0.4-2.1)	0.9	1.4 (0.5-4.1)	0.5	1.22 (0.44-3.41)	0.701	1.33 (0.38 - 4.68)	0.652
Yes	13 (1.9%)	11 (1.9%)	5 (2.8%)								

OPFC – Operative Primary Fascial Closure, SR – Silo repair with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

IRR – incidence rate ratio, OR- Odds ratio

[#]Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation

*Percentage of those with complete data

Table 20: Core outcomes at or up to 28 days of age in each reduction and closure group - Continued

	OPFC	SR	WBR	Crude estimate of effect in comparison to OPFC				Propensity score and covariate[#] adjusted estimate of effect in comparison to OPFC			
	N=671	N=597	N=183	SR		WBR		SR		WBR	
	n(%)*	n(%)*	n(%)*	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
One or more Infection											
No Yes	460 (84.1%) 87 (15.9%)	426 (80.4%) 104 (19.6%)	144 (87.3%) 21 (12.7%)	1.29 (0.94-1.77)	0.111	0.77 (0.46-1.29)	0.32	1.60 (1.10-2.34)	0.015	1.14 (0.62-2.10)	0.674
Liver Disease											
No Yes	610 (95.8%) 27 (4.2%)	568 (99.1%) 5 (0.9%)	173 (97.7%) 4 (2.3%)	0.2 (0.07-0.5)	0.001	0.5 (0.2-1.5)	0.2	0.38 (0.14 - 1.06)	0.065	0.77 (0.22 - 2.64)	0.677
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value
Head circumference											
z-score	-.595(-0.81 to -0.38)	-0.686 (-0.896 to - 0.476)	-0.587 (-1.0 to -0.168)	-0.91 (-0.39 to 0.21)	0.55	0.008 (-0.42 to 0.44)	0.97	0.04 (-0.27 to 0.35)	0.784	0.03 (-0.39 to 0.46)	0.876
Weight											
z-score	-0.9 (-1.0 to -0.76)	-1.05 (-1.198 to -0.903)	-1.115 (-1.371 to 0-.859)	-.148 (-0.348 to 0.051)	0.1	-0.212 (-0.502 to 0.078)	0.2	0.01 (-0.13 to 0.14)	0.918	-0.12 (-0.31 to 0.08)	0.242
	Median (IQR)	Median (IQR)	Median (IQR)	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Parenteral nutrition											
Number of days use	26 (17, 28)	28 (21, 28)	23 (17, 28)	1.08 (1.06-1.11)	<0.001	0.96 (0.93 - 0.997)	0.035	1.07 (1.04 - 1.10)	<0.001	0.97 (0.93 - 1.01)	0.165

OPFC – Operative Primary Fascial Closure, SR – Silo repair with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure
IRR – incidence rate ratio, OR- Odds ratio
[#]Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation
*Percentage of those with complete data

Table 21: Number of each component severe gastrointesintal complication

	OPFC		SR		WBR	
	N=105 complications		N=68 complications		N=26 complications	
	n(%)*	n/100 infants	n(%)*	n/100 infants	n(%)*	n/100 infants
Type of complication						
Mechanical obstruction	7 (6.7%)	1.04	7 (10.3%)	1.17	2 (7.7%)	1.09
Intestinal perforation	19 (18.1%)	2.83	10 (14.7%)	1.67	3 (11.5%)	1.64
Unplanned Intestinal resection	41 (39.0%)	6.11	22 (32.4%)	3.68	4 (15.4%)	2.19
Abdominal compartment syndrome	10 (9.5%)	1.49	8 (11.8%)	1.34	3 (11.5%)	1.64
Enterocolitis	28 (26.7%)	4.17	21 (30.9%)	3.51	14 (53.8%)	7.65

* Percentage of total number of severe gastrointestinal complications
OPFC – Operative Primary Fascial Closure,
SR – Silo placement with staged reduction and delayed closure
WBR - Ward Based Reduction

4.4.4.4. Mortality

Numbers and proportions of infants who died are shown in Table 20, along with crude and propensity score plus covariate adjusted estimates of effect. Covariate only and propensity score only estimates of effect are shown in Appendix 20. There were nine infants who it was not known whether they died prior to 28 days of age or not. If these nine infants were assumed to have also died, then there would have been 15 deaths (2.2%, 95% CI 1.3% - 3.7%) in the OPFC group, 15 deaths (2.5%, 95% CI 1.4% - 4.1%) in the SR group, and 8 deaths (4.4%, 95% CI 1.9% - 8.4%) in the WBR group. These proportions were not statistically significantly different from those where only confirmed deaths were included.

Cause of death data were only reliably collected in the BAPS-CASS dataset, not the CAPSNet or CNN datasets, and therefore only BAPS-CASS data are presented. The causes of death in the six BAPS-CASS infants who died prior to 28 days of age were intestinal ischaemia (three infants, 50%), mucus plugging of the airway (one infant, 20%), Patau's syndrome (one infant, 20%), and Herpes Simplex Hepatitis (one infant, 20%).

4.4.4.5. Number of procedures

Overall numbers and types of procedures conducted in the first 28 days of life are shown in Tables 20 and 22. Infants who underwent either SR or WBR underwent a statistically significantly greater number of operations in the first 28 days of life than infants who underwent OPFC. Respective covariate and propensity score adjusted IRRs were 1.34 (95 CI 1.23-1.46, $p<0.001$) and 1.14 (95% CI 1.01-1.29, $p=0.033$). Of note, there were seven infants (1.2%) in the SR group who underwent fewer procedures than would be expected. One of these infants died shortly after silo placement and prior to any other procedures, two

infants died after silo placement and central venous catheter insertion, but prior to closure of their abdominal wall defect, and four infants survived, but had their abdominal wall defect closed more than 28 days after birth.

Table 22: Types of operations performed

	OPFC		SR		WBR	
	N=1537 operations		N=1839 operations		N=489 operations	
	n(%)*	n/100 infants	n(%)*	n/100 infants	n(%)*	n/100 infants
Under general anaesthetic						
Abdominal operation	780 (50.7%)	116.2	817 (44.4%)	136.9	57 (11.7%)	31.1
Central venous catheter insertion	31 (2.0%)	4.6	70 (3.8%)	11.7	1 (0.2%)	0.5
Other	20 (1.3%)	3	10 (0.5%)	1.7	2 (0.4%)	1.1
Without general anaesthetic						
Abdominal operation	73 (4.7%)	10.9	401 (21.8%)	67.2	249 (50.9%)	136.1
Central venous catheter insertion	624 (40.6%)	93	518 (28.2%)	86.8	180 (36.8%)	98.4
Unknown anaesthetic status						
All	9 (0.6%)	1.3	23 (1.3%)	3.9	0 (0%)	0

* Percentage of total number of operations performed
OPFC – Operative Primary Fascial Closure,
SR – Silo placement with staged reduction and delayed closure
WBR - Ward Based Reduction

4.4.4.6. Parenteral nutrition

The median (IQR) number of days on which parenteral nutrition was received in the OPFC group was 26 (17 days to 28 days), in the silo placement and staged reduction group was 28 (21 days to 28 days) and in the WBR group was 23 days (17 days to 28 days). Infants in the SR group received parenteral nutrition on a statistically significantly greater number of days in the first 28 days of life than infants in the OPFC group, covariate and propensity score adjusted IRR 1.07 (95% CI 1.04 – 1.10, p<0.001) (Table 20 and Appendix 20).

4.4.4.7. Infections

Of the 1451 infants that underwent one of the three reduction and closure strategies of interest, 878 (61%) had data collected relating to the number of episodes of infection that they experienced in the first 28 days of life. No statistically significant differences in number of infections were identified between the three groups (Table 20 and Appendix 20). In addition to the 878 CAPSNet infants whose data were utilised in the 'number of episodes of infection' analysis, there were another 364 infants from the BAPS-CASS cohort whose data were used in the 'one or more episodes of infection' analysis, giving a total of 1242 infants (86%). Infants who underwent SR were significantly more likely to experience one or more infection in the first 28 days of life than those who underwent OPFC, propensity score and covariate adjusted OR 1.60 (95% CI 1.10-2.34, p=0.015) (Table 20 and Appendix 20).

4.4.4.8. Liver disease

Liver disease was diagnosed in 27 infants (4%) who had undergone OPFC, six infants (1%) who had undergone SR, and 4 infants (2.3%) who had undergone WBR. Prior to adjustment for propensity score, SR was associated with a statistically significantly reduced odds of liver

disease in comparison to OPFC, covariate adjusted OR 0.2 (95% CI 0.1-0.6, p=0.002). However, following adjustment for propensity score, this result was no longer statistically significant, although the direction remained the same, with a covariate and propensity score adjusted OR of 0.38 (95% CI 0.14-1.06, p=0.065). There was no difference in odds of liver disease between infants who underwent WBR, and infants who underwent OPFC (Table 20 and Appendix 20).

4.4.4.9. Growth

Data relating to head circumference at 28 days of age were only available for 292 infants (20%), and data relating to weight at 28 days of age were only available for 443 infants (31%). No differences in z-score at 28 days of age for either weight or head circumference were identified between the treatment groups (Table 20 and Appendix 20).

4.4.4.10. Differences in treatment effect according to complexity of gastroschisis

Interactions between treatment strategy, and presence of intestinal necrosis, presence of intestinal perforation, diagnosis of intestinal atresia, and degree of intestinal matting were investigated in the propensity score and covariate adjusted negative binomial regression model describing the relationship between treatment type and number of severe gastrointestinal complications in the first 28 days of life.

A clinically plausible interaction was identified between intestinal perforation and treatment, with SR associated with an IRR of severe gastrointestinal complications of 0.65 in those without perforation, and an IRR of 1.96 in those with perforation. Similarly, a clinically plausible interaction was identified between presence of intestinal matting and treatment,

with SR associated with an IRR of severe gastrointestinal complications of 0.31 in those without intestinal matting, and 1.10 in those with severe matting. Finally, a clinically plausible interaction was also identified between intestinal necrosis and treatment, with SR associated with an IRR of severe gastrointestinal complications of 0.66 in those without intestinal necrosis, and 2.54 in those with intestinal necrosis. No interaction was identified between intestinal atresia and treatment type, with SR associated with an IRR of severe gastrointestinal complications of 0.70 in those without intestinal atresia, and 0.75 in those with intestinal atresia.

As the effect of SR on number of severe gastrointestinal complications differed between infants with and without intestinal perforation, matting or necrosis, two sub-group analyses were conducted. The first sub-group analysis was conducted in infants without intestinal necrosis, perforation or matting, and the second was in infants with one or more of these features of bowel injury.

4.4.5. Infants without intestinal necrosis, perforation or matting

In the sub-group of 560 infants without intestinal necrosis, perforation or matting, infants who underwent SR experienced statistically significantly fewer severe gastrointestinal complications in the first 28 days of life than those who underwent OPFC, covariate and propensity score adjusted IRR 0.25 (95% CI 0.09-0.67, p=0.006), but underwent a greater number of operations, covariate and propensity score adjusted IRR 1.40 (95% CI 1.22-1.60, p<0.001), and required a marginally greater number of days of parenteral nutrition, covariate and propensity score adjusted IRR 1.08 (95% CI 1.03-1.13, p<0.001), and were more likely to experience one or more infection, covariate and propensity score adjusted OR

2.06 (95% CI 1.10-3.87 p=0.025) (Table 25 and Appendix 22). There were no differences in any other outcomes between infants who underwent SR, and those who underwent OPFC.

When outcomes for infants who underwent WBR were compared to those for infants who underwent OPFC, the only difference was that infants who underwent WBR underwent a greater number of procedures in the first 28 days of life than those who underwent OPFC, covariate and propensity score adjusted IRR 1.19 (95% CI 1.01-1.40, p=0.037).

Table 23: Outcomes in infants without intestinal necrosis, perforation or matting

	OPFC	SR	WBR	Crude estimate of effect in comparison to OPFC				Propensity score and covariate# adjusted estimate of effect in comparison to OPFC			
	N=241	N=202	N=117	SR		WBR		SR		WBR	
	n(%)*	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Severe gastrointestinal complications											
None	215 (89.2%)	194 (96.0%)	107 (91.5%)	0.29 (0.12-0.68)	0.005	1.00 (0.47-2.11)	0.997	0.25 (0.09-0.67)	0.006	1.13 (0.48-2.67)	0.774
One	21 (8.7%)	8 (4.0%)	5 (4.3%)								
Two	3 (1.2%)	0 (0.0%)	4 (3.4%)								
Three or more	2 (0.8%)	0 (0.0%)	1 (0.9%)								
Operations											
One	0 (0%)	0 (0%)	0 (0%)	1.42 (1.26-1.59)	<0.001	1.22 (1.06-1.40)	0.006	1.40 (1.22-1.60)	<0.001	1.19 (1.01 - 1.40)	0.037
Two	192 (81.0%)	2 (1.0%)	41 (35.0%)								
Three	39 (16.5%)	168 (86.6%)	72 (61.5%)								
Four or more	6 (2.5%)	24 (12.4%)	4 (3.4%)								
Number of episodes of infection											
None	107 (86.3%)	93 (77.5%)	75 (86.2%)	1.55 (0.82-2.94)	0.179	0.89 (0.41-1.91)	0.767	1.57 (0.76-3.23)	0.219	1.52 (0.63-3.68)	0.353
One	14 (11.3%)	23 (19.2%)	9 (10.3%)								
Two	2 (1.6%)	3 (2.5%)	3 (3.4%)								
Three or more	1 (0.8%)	1 (0.8%)	0 (0.0%)								
	n(%)*	n(%)*	n(%)*	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Mortality											
No	237 (98.3%)	201 (99.5%)	111 (97.4%)	0.29 (0.03 - 2.66)	0.276	1.60 (0.35-7.28)	0.542	Too few events to calculate adjusted estimate of effect			
Yes	4 (1.7%)	1 (0.5%)	3 (2.6%)								
Infection in first 28 days											
No	180 (87.0%)	149 (81.0%)	92 (87.6%)	1.57 (0.91-2.71)	0.108	0.94 (0.46-1.91)	0.869	2.06 (1.10-3.87)	0.025	1.29 (0.55-3.01)	0.559
Yes	27 (13.0%)	35 (19.0%)	13 (12.4%)								
Liver disease											
No	215 (95.1%)	193 (99.5%)	110 (97.3%)	0.10 (0.013 - 0.79)	0.029	0.53 (0.15-1.95)	0.342	0.14 (0.017-1.23)	0.076	0.65 (0.14-2.96)	0.576
Yes	11 (4.9%)	1 (0.5%)	3 (2.7%)								

IRR – incidence rate ratio, OR- Odds ratio, OPFC – Operative Primary Fascial Closure, SR – Silo Placement with staged reduction and delayed closure, WBR – ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

*Percentage of those with complete data

Table 23: Outcomes in infants without intestinal necrosis, perforation or matting - Continued

	OPFC	SR	WBR	Crude estimate of effect in comparison to OPFC				Propensity score and covariate# adjusted estimate of effect in comparison to OPFC			
	N=241	N=202	N=117	SR		WBR		SR		WBR	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value
Head circumference											
z-score	-0.35 (-2.62 to 1.92)	-.68 (-2.42 to 1.06)	-.46 (-2.30 to 1.38)	-0.33 (-0.77 to 0.11)	0.147	-0.11 (-0.59 to 0.37)	0.658	-0.32 (-0.72 to 0.09)	0.127	-0.10 (-0.55 to 0.35)	0.665
Weight											
z-score	-.87 (-2.87 to 1.13)	-1.04 (-2.49 to 0.41)	-1.17 (-2.80 to 0.46)	-0.18 (-0.50 to 0.15)	0.285	-0.31 (-0.67 to 0.05)	0.091	-0.08 (-0.30 to 0.13)	0.448	-0.16 (0.-0.41 to 0.08)	0.199
	Median (IQR)	Median (IQR)	Median (IQR)	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Parenteral nutrition											
Number of days use	23 (16, 28)	27 (20, 28)	22 (16, 28)	1.10 (1.06 - 1.15)	<0.001	0.997 (0.95 - 1.05)	0.913	1.08 (1.03-1.13)	0.001	0.97 (0.91-1.02)	0.220

IRR – incidence rate ratio, OR- Odds ratio, OPFC – Operative Primary Fascial Closure, SR – Silo Placement with staged reduction and delayed closure, WBR – ward-based reduction with sutureless closure
#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

4.4.6. Infants with intestinal necrosis, perforation or matting

When outcomes for the group of 756 infants with intestinal necrosis, perforation or matting were compared between OPFC and SR, only two statistically significant differences were identified. Use of SR was associated with a greater number of operations in the first 28 days of life, covariate plus propensity score adjusted IRR 1.30 (95% CI 1.17 – 1.45, p<0.001), and a marginally greater number of days on which parenteral nutrition was used in the first 28 days of life, covariate plus propensity score adjusted IRR 1.06 (95% CI 1.02-1.10, p=0.003). No statistically significant differences in outcome were identified between OPFC and WBR, although the small number of infants who underwent WBR limited the power of this comparison to detect differences as statistically significant (Table 24 and Appendix 23).

Table 24: Outcomes in infants with intestinal necrosis, perforation or matting

	OPFC	SR	WBR	Crude estimate of effect in comparison to OPFC				Propensity score and covariate# adjusted estimate of effect in comparison to OPFC			
	N=349	N=348	N=59	SR		WBR		SR		WBR	
	n(%)*	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Number of severe GI complications											
None	300 (86.0%)	316 (90.8%)	50 (84.7%)	0.78 (0.49-1.24)	0.298	0.94 (0.40-2.19)	0.884	1.02 (0.60-1.74)	0.950	1.89 (0.68-5.28)	0.222
One	37 (10.6%)	21 (6.0%)	8 (13.6%)								
Two	10 (2.9%)	8 (2.3%)	1 (1.7%)								
Three or more	2 (0.6%)	3 (0.9%)	0 (0.0%)								
Number of operations											
One	0 (0%)	0(0%)	0(0%)	1.29 (1.18-1.42)	<0.001	1.08 (0.91-1.28)	0.395	1.30 (1.17-1.45)	<0.001	1.10 (0.90-1.34)	0.366
Two	208 (62.1%)	4 (1.2%)	19 (33.3%)								
Three	96 (28.7%)	273 (82.2%)	36 (63.2%)								
Four or more	31 (9.3%)	55 (16.6%)	2 (3.5%)								
Number of episodes of infection											
None	158 (81.4%)	202 (80.8%)	41 (85.4%)	1.1 (0.65-1.57)	0.975	0.77 (0.35-1.73)	0.533	1.07 (0.65-1.79)	0.782	1.33 (0.54-3.31)	0.538
One	29 (14.9%)	36 (14.4%)	5 (10.4%)								
Two	5 (2.6%)	11 (4.4%)	2 (4.2%)								
Three or more	2 (1.0%)	1 (0.4%)	0 (0.0%)								
	n(%)*	n(%)*	n(%)*	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Mortality											
No	342 (98.3%)	336 (97.4%)	57 (96.6%)	1.53 (0.54-4.33)	0.427	2.0 (0.39-10.15)	0.403	2,37 (0.71-7.92)	0.161	2.12 (0.35-13.05)	0.416
Yes	6 (1.7%)	9 (2.6%)	2 (3.4%)								
Infection in first 28 days											
No	247 (82.6%)	240 (78.7%)	47 (85.5%)	1.29 (0.86-1.92)	0.224	0.81(0.36-1.81)	0.606	1.41 (0.88 - 2.27)	0.159	1.20 (0.47 - 3.06)	0.697
Yes	52 (17.4%)	65 (21.3%)	8 (14.5%)								
Liver Disease											
No	321 (95.3%)	331 (98.8%)	58 (98.3%)	1.24 (0.08-0.73)	0.012	0.35 (0.04-2.66)	0.308	0.60 (0.18-2.06)	0.420	1.43 (0.14-14.42)	0.760
Yes	16 (4.7%)	4 (1.2%)	1 (1.7%)								

IRR – incidence rate ratio, OR- Odds ratio, OPFC – Operative Primary Fascial Closure, SR – Silo Placement with staged reduction and delayed closure, WBR – ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

*Percentage of those with complete data

Table 24: Outcomes in infants with intestinal necrosis, perforation or matting - Continued

	OPFC	SR	WBR	Crude estimate of effect in comparison to OPFC				Propensity score and covariate# adjusted estimate of effect in comparison to OPFC			
	N=349	N=348	N=59	SR		WBR		SR		WBR	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value
Head circumference											
z-score	-.74 (-3.15 to 1.67)	-.0.62 (-3.12 to 1.89)	-.84 (-4.61 to 2.95)	0.12 (-0.32 to 0.55)	0.597	-0.09 (-0.87 to 0.68)	0.809	0.32 -0.11 to 0.76)	0.145	0.06 (-0.72 to 0.84)	0.878
Weight											
z-score	-..90 (-2.84 to 1.04)	-1.03 (-3.21 to 1.15)	-1.01 (-3.40 to 1.38)	-.032 (-0.19 to 0.12)	0.675	0.01 (-0.28 to 0.29)	0.968	0.05 (-0.12 to 0.22)	0.541	-0.96 (-0.42 to 0.22)	0.555
	Median (IQR)	Median (IQR)	Median (IQR)	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Parenteral nutrition											
Number of days use	28 (20, 28)	28 (22, 28)	24 (18, 28)	1.06 (1.02-1.09)	<0.001	0.97 (0.91-1.03)	0.267	1.06 (1.02-1.10)	0.003	0.98 (0.92-1.05)	0.572

IRR – incidence rate ratio, OR- Odds ratio, OPFC – Operative Primary Fascial Closure, SR – Silo Placement with staged reduction and delayed closure, WBR – ward-based reduction with sutureless closure
#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

4.4.7. Comparison of outcomes between the British Isles and Canada

4.4.7.1. Characteristics of Canadian and British and Irish infants

When compared to those treated in the British Isles, infants treated in Canada had a higher median birth weight, were less likely to be small for gestational age at birth and delivered via caesarean section, and were more likely to be from a BME background, be born to a woman aged 25 or over, have an additional chromosomal or structural anomaly, and have severe intestinal matting. Infants treated in Canada were also more likely to have undergone WBR, and be ventilated post-operatively than infants treated in the British Isles (Table 25).

One of the biggest differences between the two cohorts of infants was in rates of additional congenital anomalies, which was 5% in British and Irish infants, and 17% in Canadian infants. Of the 190 Canadian infants who had an additional congenital anomaly, one (0.5%) had a chromosomal anomaly, 53 (27.8%) had cardiac anomalies, five (2.6%) had central nervous system anomalies, 39 (20.5%) had genitourinary or renal anomalies, three (1.6%) had pulmonary anomalies, 15 (7.9%) had skeletal anomalies, 18 (9.5%) had another single major anomaly, and 56 (29.5%) had multiple anomalies. Of the 20 British and Irish infants who had an additional congenital anomaly, 7 (35%) had cardiac anomalies, 2 (10%) had central nervous system anomalies, 4 (20%) had genitourinary or renal anomalies, 3 (15%) had skeletal anomalies, 2 (10%) had another single major anomaly, and 2 (10%) had multiple anomalies.

Table 25: Characteristics and management strategies of infants treated in the British Isles and infants treated in Canada

	British Isles	Canada 2005 - 2008		Canada entire cohort	
	N=393	N=378		N=1207	
	Median (IQR)	Median (IQR)	p-value*	Median (IQR)	p-value*
Birthweight			<0.001		<0.001
Grams	2386 (2060, 2690)	2580 (2190, 2930)		2508 (2182, 2860)	
Gestational age at birth			0.25		<0.001
Completed weeks	37 (35, 37)	36 (35, 37)		36 (35, 37)	
	n(%)#	n(%)#	p-value	n(%)#	p-value
Reporting year			N/A		<0.001
2005-2008	393 (100.0%)	N/A		378 (31.3%)	
2009-2012	0 (0.0%)	N/A		464 (38.5%)	
2013-2016	0 (0.0%)	N/A		364 (30.2%)	
Transferred in to surgical centre			0.29		0.038
No	255 (65.1%)	232 (61.4%)		713 (59.2%)	
Yes	137 (34.9%)	146 (38.6%)		492 (40.8%)	
Antenatal diagnosis			0.35		0.83
No	5 (1.3%)	2 (0.6%)		13 (1.1%)	
Yes	385 (98.7%)	334 (99.4%)		1125 (98.9%)	
Maternal age			0.19		0.007
<25	282 (74.2%)	240 (68.8%)		660 (65.4%)	
25-34	92 (24.2%)	99 (28.4%)		322 (31.9%)	
35 and above	6 (1.6%)	10 (2.9%)		27 (2.7%)	
Caesarean section delivery			0.08		0.029
No	238 (61.2%)	222 (67.5%)		683 (67.4%)	
Yes	151 (38.8%)	107 (32.5%)		331 (32.6%)	
Ethnicity			<0.001		<0.001
White	343 (91.2%)	136 (69.4%)		539 (71.0%)	
Other	33 (8.8%)	60 (30.6%)		220 (29.0%)	
Sex			0.014		0.012
Male	177 (45.2%)	201 (54.0%)		626 (52.4%)	
Female	215 (54.8%)	171 (46.0%)		568 (47.6%)	
Small for gestational age at birth			<0.001		<0.001
No	277 (71.4%)	304 (82.4%)		994 (83.5%)	
Yes	111 (28.6%)	65 (17.6%)		196 (16.5%)	
Additional chromosomal or congenital structural anomaly			<0.001		<0.001
No	369 (94.9%)	256 (74.0%)		935 (83.1%)	
Yes	20 (5.1%)	90 (26.0%)		190 (16.9%)	
APGAR score at five minutes			0.037		0.056
≥7	339 (91.6%)	315 (86.1%)		1024 (87.0%)	
4-6	25 (6.8%)	45 (12.3%)		126 (10.7%)	
0-3	6 (1.6%)	6 (1.6%)		27 (2.3%)	
Necrosis at admission			0.82		0.31
No	363 (97.6%)	325 (97.3%)		1047 (96.5%)	
Yes	9 (2.4%)	9 (2.7%)		38 (3.5%)	
Intestinal Matting			0.006		<0.001
None	173 (49.1%)	160 (47.3%)		472 (43.5%)	
Mild	157 (44.6%)	133 (39.3%)		460 (42.4%)	
Severe	22 (6.3%)	45 (13.3%)		152 (14.0%)	

* p-value for comparison to the British Isles, # Percentage of those with complete data

Table 25: Characteristics and management strategies of infants treated in the British Isles and infants treated in Canada - Continued

	British Isles	Canada 2005 - 2008		Canada entire cohort	
	N=393	N=378		N=1207	
	n(%)#	n(%)#	p-value *	n(%)#	p-value *
Intestinal atresia			0.48		0.5
No	338 (88.7%)	326 (90.3%)		1046 (89.9%)	
Yes	43 (11.3%)	35 (9.7%)		117 (10.1%)	
Intestinal perforation			0.93		0.78
No	365 (96.3%)	324 (96.4%)		1053 (96.6%)	
Yes	14 (3.7%)	12 (3.6%)		37 (3.4%)	
Complex gastroschisis			0.39		0.38
Simple	329 (88.0%)	283 (85.8%)		929 (86.2%)	
Complex	45 (12.0%)	47 (14.2%)		149 (13.8%)	
First attempted reduction/closure procedure			0.004		<0.001
OPFC	203 (52.2%)	205 (57.1%)		468 (40.3%)	
Operative primary reduction, suture-less closure	0 (0%)	15 (4.2%)		71 (6.1%)	
Silo placement and staged reduction	154 (39.6%)	128 (35.7%)		459 (39.6%)	
Mesh	6 (1.5%)	2 (0.6%)		5 (0.4%)	
WBR	26 (6.7%)	9 (2.5%)		157 (13.5%)	
Ventilated post-operatively			<0.001		<0.001
No	84 (21.4%)	16 (4.3%)		78 (6.7%)	
Yes	308 (78.6%)	354 (95.7%)		1093 (93.3%)	
	Median (IQR)	**Median (IQR)**	**p-value**	**Median (IQR)**	**p-value**
Ventilated post-operatively			<0.001		<0.001
Number of days	2 (1, 5)	4 (3, 5)		3 (2, 5)	

* p-value for comparison to the British Isles, # Percentage of those with complete data

4.4.7.2. Number of severe gastrointestinal complications

Of the 393 British and Irish infants, 331 (84%) experienced no severe gastrointestinal complications prior to 28 days of age, 41 (11%) experienced one, 13 (3%) experienced two, and 7 (2%) experienced three or more. Within the Canadian cohort, 1099 infants (91%) experienced no severe gastrointestinal complications prior to 28 days of age, 86 (7%) experienced one, 17 (1%) experienced two, and 5 (0.5%) experienced three or more. Prior to adjusting for covariates this difference was statistically significant, IRR 0.47 (95% CI 0.33-0.66, $p<0.001$). However, following adjustment for the previously identified covariates of birth-weight, gestational age at birth, intestinal perforation at birth, and presence of an intestinal atresia, the result was no longer statistically significant, IRR 0.65 (95% CI 0.40-1.08, $p=0.096$) (Table 26). The types of complication occurring in each country are described in Table 27.

Table 26: Outcomes for infants treated in the British Isles and infants treated in Canada

	British Isles	Canada				
	N=393	N=1207	Crude Estimate of effect		Covariate[#] adjusted Estimate of effect	
	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Severe gastrointestinal complications						
None	331 (84.4%)	1099 (91.1%)	0.47 (0.33-0.66)	<0.001	0.65 (0.40-1.08)	0.096
One	41 (10.5%)	86 (7.1%)				
Two	13 (3.3%)	17 (1.4%)				
Three or more	7 (1.8%)	5 (0.4%)				
Operations						
One	1 (0.3%)	0 (0.0%)	1.01(0.94-1.08)	0.821	1.02 (0.93-1.13)	0.619
Two	173 (44.5%)	471 (40.9%)				
Three	173 (44.5%)	584 (50.7%)				
Four or more	42 (10.8%)	96 (8.3%)				
	n(%)	n(%)	OR (95% CI)	p-value	OR (95% CI)	p-value
Mortality						
No	387 (98.5%)	1171 (97.7%)	1.54 (0.63-3.75)	0.34	0.69 (0.22-2.21)	0.535
Yes	6 (1.5%)	28 (2.3%)				
One or more infection						
No	329 (84.4%)	807 (82.3%)	1.16 (0.84-1.59)	0.372	1.32 (0.85-2.04)	0.213
Yes	61 (15.6%)	173 (17.7%)				
Liver disease						
No	371 (95.1%)	1120 (98.2%)	0.37 (0.19-0.69)	0.002	0.49 (0.19 - 1.24)	0.131
Yes	19 (4.9%)	21 (1.8%)				
	Median (IQR)	Median (IQR)	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Parenteral nutrition						
Number of days use	26 (18, 28)	27 (19, 28)	1.04 (1.02-1.07)	0.001	1.09 (1.06-1.13)	<0.001

*Percentage of those with complete data

[#]Covariates are gestational age at birth, birth-weight, intestinal perforation at presentation and diagnosis of intestinal atresia

Table 27: Number of component severe gastrointesintal complications

	British Isles		Canada	
	N=94 Complications		N=135 Complications	
	n(%)	n/100 infants (95% CI)	n(%)	n/100 infants (95% CI)
Type of complication				
Mechanical obstruction requiring repeat laparotomy	11 (11.7%)	2.8 (1.4-4.9)	8 (5.9%)	0.7 (0.3-2.8)
Intestinal perforation	19 (20.2%)	4.8 (2.9-7.4)	19 (14.1%)	1.6 (1.0-2.4)
Intestinal resection regardless of length or indication	26 (27.7%)	6.6 (4.4-9.5)	53 (39.3%)	4.4 (3.3-5.7)
Abdominal compartment syndrome	3 (3.2%)	0.8 (0.2-2.2)	20 (14.8%)	1.7 (1.0-2.5)
Enterocolitis	35 (37.2%)	8.9 (6.3-12.2)	35 (25.9%)	2.9 (2.0-4.0)

* Percentage of total number of severe gastrointestinal complications

4.4.7.3. Secondary outcomes

The median (IQR) number of days that an infant treated in the British Isles received parenteral nutrition for in the first 28 days of life was 26 (18 days to 28 days) whilst for infants treated in Canada it was 27 (19 days to 28 days). Univariable Poisson regression analysis showed this to be a statistically significant difference, IRR 1.04 (95% CI 1.02-1.07, p=0.001), and this difference remained after adjustment for covariates, IRR 1.09 (95% CI 1.06-1.13, p<0.001) (Table 26).

Before adjustment for covariates, rates of liver disease prior to 28 days of age appeared lower in the Canadian cohort (21 infants, 1.8%) than in the British Isles cohort (19 infants, 4.9%), OR 0.375 (95% CI 0.19-0.69, p=0.002. However, following covariate adjustment, the results were no longer statistically significant, adjusted OR 0.49 (95 % CI 0.19-1.24, p=0.131). Growth and number of episodes of sepsis were not compared between infants treated in Canada and infants treated in the British Isles, as data relating to these outcomes were only collected in the Canadian cohort. No statistically significant differences were identified for the remaining outcomes of mortality and number of procedures (Table 26).

4.5. Discussion

This secondary analysis of data from 1600 infants, collected prospectively from population-based studies conducted in two countries, has described key information needed for the design of an international, multi-centre RCT comparing reduction and closure strategies for the treatment of infants born with gastroschisis. It has described findings that could be used to influence development of current management guidelines.

4.5.1. Impact of reduction and closure strategy on outcome

4.5.1.1. Key message

In comparison to OPFC, use of SR in infants without intestinal necrosis, perforation, or matting was associated with an approximately 75% reduction in the incidence of severe gastrointestinal complications in the first 28 days of life, but at the expense of a 40% increase in number of operations, a doubling in the risk of experiencing one or more infections, and potentially an 8% increase in number of days on which parenteral nutrition was received over the same time period. In contrast to its effect in infants without intestinal perforation, necrosis or matting, the use of SR in infants with any of these features was associated with a 30% increase in the number of operations infants undergo in the first 28 days of life, and potentially a 6% increase in the number of days on which they receive parenteral nutrition, but no reduction in number of severe gastrointestinal complications. Interpretation of the clinical significance of the differences in duration of parenteral nutrition use is harder than for the other outcomes due to the fact that follow-up was terminated at 28 days of age, and the median duration of parenteral nutrition use in the OPFC and SR groups was 26 days and 28 days respectively.

The only differences identified in outcome between infants who underwent WBR and those who underwent OPFC, was that in the cohort as a whole, use of WBR was associated with an approximately 14% increase in number of operations that an infant underwent in the first 28 days of life, and in those without necrosis, perforation or matting, it was associated with an approximately 19% increase in number of operations. No other differences between the two reduction and closure strategies were identified. The ability to detect any differences as statistically significant may however have been limited by the relatively small number of infants who underwent WBR.

4.5.1.2. Placing the results in context

4.5.1.2.1. Silo placement with staged reduction and delayed closure

Two recently conducted systematic reviews(18, 19) reported that multiple outcomes, including length of stay, time to feeding, and time on a ventilator were better for infants who underwent OPFC than for those who underwent SR. However, there were significant limitations with the primary data upon which those conclusions were based, and when Kunz et al limited their review to only studies with a lower risk of selection bias, they drew the opposite conclusion, that outcomes from SR were better than those from OPFC. Given the uncertain conclusions, it is very difficult to use these reviews to influence management of infants with gastroschisis.

Unfortunately, it is also impossible to use the one RCT that has been conducted comparing OPFC to SR to guide management decisions for infants with gastroschisis(92). This trial needed to recruit approximately 90 infants to detect a statistically significant difference in

the primary outcome, days on a ventilator. However, after 5 years of recruitment, the trial was stopped early; only fifty infants had been randomised. It is therefore very difficult to determine if the lack of difference they demonstrated between OPFC and SR was genuine, or due to limited statistical power(92).

In contrast to the existing literature, the work described in this chapter was able to at least in part address issues arising from selection bias and confounding that weaken the published systematic reviews (18, 19), and also achieve sufficient statistical power to detect differences in meaningful outcomes, something that was not possible in Pastor et al's RCT (92). The conclusions of this work, that the use of SR in infants without intestinal perforation, necrosis or matting is associated with a decrease in severe gastrointestinal complications, but an increase in parenteral nutrition use, number of operations and risk of infection, are therefore likely the most robust currently available, and should be used for counselling parents and developing management guidelines.

4.5.1.2.2. Ward-based reduction with sutureless closure

In a similar manner to SR, little evidence exists to compare and contrast the outcomes of WBR against those of OPFC. In 2002, a Cochrane review comparing ward-based reduction without general anaesthesia to primary repair under general anaesthesia was attempted by Davies et al, but no RCTs were identified for inclusion(103). Since that review, a series of small, retrospective cohort studies and case series have been conducted, reporting both harms and benefits to WBR. In 2005, the authors of the Cochrane review reported that, based upon their experience with 31 infants, the use of WBR appeared to be associated with reduced duration of ventilation and intensive care stay (104), a finding that was

broadly supported by a similar retrospective cohort study conducted in 2006 by Cauchi et al(105). In contrast to these optimistic studies however, other retrospective reviews by Rao and Dolgin sound a more cautionary note, suggesting the use of WBR may be associated with an increase in number of complications, including intestinal necrosis and death(106, 107). None of these studies however, are sufficiently large or free from bias and confounding to allow sound conclusions to be drawn.

One RCT, conducted by Bruzoni et al has compared sutured to sutureless closure for infants with gastroschisis, but in this study, no restrictions were placed on the reduction technique used, such that both closure groups contained infants who had undergone primary and staged reduction of the viscera(93). As with the study by Pastor et al, this RCT also failed to recruit to target, and was abandoned after five years. Prior to abandoning the trial, the authors identified that sutureless closure was associated with a statistically significant increase in length of stay, and time to half and full feeds, but no differences in time on a ventilator or rate of complications were identified. Given the heterogeneity of the intervention groups compared in this trial however, it is difficult to determine how applicable the results are to infants who have undergone WBR.

Whilst it is likely that the work presented in this chapter is still insufficiently large to detect statistically significant differences in many outcomes between OPFC and WBR, it has suggested that the use of WBR is associated with a greater number of operations in the first 28 days of life than OPFC. This does not seem to be a finding that has been previously reported in the literature. Although the overall number of operations per hundred infants reported in the work described in this chapter is higher at 267.2 for those who have

undergone WBR than it is at 229.1 for those who have undergone OPFC, the nature of the operations undertaken appears to be less invasive in the former treatment group than in the latter. Going forward, it is therefore important to undertake further work with key stakeholders to develop a better understanding of whether the reduced invasiveness of the operations conducted for infants undergoing WBR counters the fact that more operations are necessary.

4.5.1.2.3. Characteristics of infants in each reduction and closure group

It is important to bear in mind that key differences existed in the characteristics of infants who underwent OPFC and those who underwent SR or WBR. Infants who underwent SR were less likely to be born to a woman aged less than 25 years old at the time of delivery, be white, have an intestinal perforation, have intestinal atresia, have intestinal necrosis or have their operation performed by a consultant surgeon, and more likely to be transferred in to a paediatric surgical centre, have an additional congenital anomaly, and have moderately to severely matted bowel at the time of presentation. Similar differences were seen between infants undergoing OPFC and WBR, as between infants undergoing OPFC and SR. The presence of fewer features of bowel injury in infants who underwent SR, or WBR than in infants who underwent OPFC implies that at present, surgeons are selecting treatment options based at least in part upon an infant's characteristics.

Whilst similar differences in the characteristics of the treatment groups have also been demonstrated in previously published studies (108-110), what is less clear from the existing literature is which of these characteristics are associated with outcome, and hence should

be used to define whether an infant has 'simple' or 'complex' gastroschisis(5, 18, 19, 89, 92).

4.5.2. Patient factors associated with outcome

4.5.2.1. Key message

Three patient factors were identified in the work described in this chapter as associated with the number of severe gastrointestinal complications occurring in the first 28 days of life. Intestinal perforation at presentation was associated with an approximately 3.7-fold increase in incidence of severe gastrointestinal complications in the first 28 days of life, and intestinal atresia was associated with an approximately 2.4-fold increase in incidence of severe gastrointestinal complications in the first 28 days of life. Each 50g increase in birth weight was associated with an approximately 4% reduction in incidence of severe gastrointestinal complications in the first 28 days of life.

4.5.2.2. Placing the results in context

By merging BAPS-CASS, CAPSNet, and CNN data, this work has created a dataset that is larger than any other contemporary, prospectively established dataset that is available in the current literature. This size allowed for investigation of associations between outcomes of interest and individual patient factors, including the three components of the definition of complex gastroschisis described by Molik et al; intestinal necrosis, intestinal perforation and intestinal atresia(94). On univariable analysis, all three components of this definition were associated with the outcome of interest, the number of severe gastrointestinal complications in the first 28 days of life. Of the three features, intestinal perforation was the most strongly associated with outcome, followed by intestinal necrosis and then intestinal

atresia. However, following adjustment in the multivariable model, only intestinal perforation and intestinal atresia remained significantly association with the number of severe gastrointestinal complications. It is likely that intestinal necrosis was not retained in the multivariable model as both it and the presence of an intestinal perforation are identifying a similar sub-set of infants at increased risk of adverse outcome, and the presence of an intestinal perforation has a stronger association than intestinal necrosis.

When Cowan et al used univariable logistic regression analysis to identify candidate factors for inclusion in the GPS, they did not detect a statistically significant association between either intestinal perforation or intestinal atresia and mortality (95). Identification of an association between these factors and outcome in the work described in this chapter, but not in the work by Cowan et al could have occurred for two reasons.

Firstly, the work by Cowan et al is based on a sample size of approximately a third of the dataset reported here, and their analysis may therefore have lacked the statistical power required to detect a significant association between a rare outcome such as mortality and intestinal perforation or intestinal atresia, features that are less common than intestinal necrosis, defined as it was by Cowan et al, to include both diffuse and focal necrosis. Secondly however, it is also plausible that the presence of intestinal atresia may be more strongly associated with the number of severe gastrointestinal complications experienced by an infant than it is with mortality.

If not corrected at the first operation, there is a clear, direct causal pathway between intestinal atresia and two of the components of the outcome severe gastrointestinal

complication, namely mechanical intestinal obstruction requiring repeat laparotomy, and intestinal resection. The presence of an intestinal atresia may also increase the risk of two other severe gastrointestinal complications, intestinal perforation, and enterocolitis. There is a much less clearly defined causal pathway between intestinal atresia and mortality. It is therefore biologically plausible that presence of an intestinal atresia would have a much stronger association with the number of severe gastrointestinal complications than it does with mortality.

Work by Arnold et al, interrogating the *National Inpatient Sample* database and the *Kids' Inpatient Database* in America, supports the theory that intestinal atresia may be more strongly associated with the number of severe gastrointestinal complications than with mortality(111). In the Arnold et al study of 4310 cases of gastroschisis, the association between mortality and key international classification of diseases listed co-morbidities was investigated. One of the factors identified as having a statistically significant association with mortality was intestinal atresia. However, the association described was significantly weaker than that seen between intestinal atresia and number of severe gastrointestinal complications in the work described in this chapter. It is likely therefore, that no association was seen between intestinal atresia and mortality in the work by Cowan et al, due to a combination of a lack of statistical power, and the weaker association between intestinal atresia and mortality than between intestinal atresia and number of severe gastrointestinal complications.

In addition to investigating whether the number of severe gastrointestinal complications was associated with key markers of bowel injury, the work described in this chapter also

investigated the association between number of severe gastrointestinal complications and key physiological parameters, including birth weight, gestational age at birth, birth weight less than the 10th centile for gestational age, and APGAR score at five minutes. Of these, only birth weight was shown to be associated with outcome, with each 50g increase in birth weight associated with an approximately 4% reduction in incidence of severe gastrointestinal complications in the first 28 days of life.

This finding differs from previous works, where associations have been identified between gestational age at birth and a range of outcomes in infants with gastroschisis, including jaundice, time to full enteral feeds, sepsis and mortality (95, 112, 113). APGAR score at five minutes has also previously been demonstrated to be associated with mortality in infants with gastroschisis(114). It is unclear why, following adjustment in the multivariable model, these associations were not seen in the work presented in this chapter. However, one theory relates to the differing nature of the outcomes previously investigated from the outcome number of severe gastrointestinal complications. The composite outcome, number of severe gastrointestinal complications, is comprised of five individual complications, mechanical intestinal obstruction requiring laparotomy, intestinal resection, intestinal perforation, abdominal compartment syndrome, and enterocolitis. The occurrence of the first four of these complications will be determined to a great degree by factors directly affecting the intestines, and to a much lesser degree by systemic factors. It is plausible therefore, that in contrast to outcomes investigated in previous works, which are determined by a great many characteristics affecting a neonates physiological responses, that the number of severe gastrointestinal complications will have a much stronger association with factors that directly determine how successfully the infant's intestines are

returned to the abdominal cavity, than it does to factors determining outcome through more systemic mechanisms of action.

In contrast to the other physiological parameters investigated, birth weight potentially has a stronger association with number of severe gastrointestinal complications because of the way in which infants with gastroschisis are treated. Treatment of gastroschisis is reliant on returning eviscerated abdominal contents to the abdominal cavity, which, because the infant's in utero development has occurred without the intestines inside the cavity, has a smaller volume than normal. Returning the intestines to the abdominal cavity therefore almost by default results in increased intra-abdominal pressure. The implications of such an increase in intra-abdominal pressure are, however, dependent upon the ability of the infant to maintain perfusion of the abdominal organs. Low birth weight has previously been shown to be associated with pathological changes to the vasculature in guinea pigs(115), to endothelial dysfunction in children and young adults(116, 117) and for a long time, has been known to be associated with a range of cardiovascular diseases(118). It is highly plausible therefore that infants' with lower birth weight have a less robust vascular supply to the abdominal organs than infants of normal birth weight. Maintaining perfusion of the abdominal organs in the face of increased intra-abdominal pressure may therefore be more challenging for infants of lower birth weight. Such impaired perfusion puts the infant at risk of intestinal ischaemia, which in turn can lead to enterocolitis, intestinal perforation, and intestinal stricture formation, with resultant mechanical obstruction and need for intestinal resection. At the most extreme end of the spectrum, the combination of increased intra-abdominal pressure and inadequate vascular supply would result in abdominal

compartment syndrome. Each of these events is a contributor to the number of severe gastrointestinal complications experienced by an infant.

4.5.3. Comparison of outcomes between countries

4.5.3.1. Key Message

British and Irish infants were more likely to undergo OPFC, less likely to be ventilated post-operatively, and had a shorter length of stay in a paediatric surgical centre, than their Canadian counterparts. Significant differences also existed in the demographics of infants treated in each country. When compared to infants treated for gastroschisis in Canada, infants treated in the British Isles had a higher gestational age at birth but a lower birth weight, and were therefore more likely to be small for gestational age at birth. These same infants were also less likely to have an additional congenital anomaly, have severely matted bowel, or have been transferred in to a surgical centre, but more likely to be white, be female, and have been born to a woman aged less than 25 at the time of delivery.

Following adjustment for known confounding factors, the only difference in outcome between infants treated in the British Isles and infants treated in Canada, was that infants treated in Canada received parenteral nutrition for longer. As with the comparison between reduction and closure strategies, the interpretation of the clinical significance of this difference is difficult to make due to the proximity of the median duration of parenteral nutrition use in each group to the maximal duration of follow-up. No differences in number of severe gastrointestinal complications, number of operations, mortality rate, rate of infection or rate of liver disease were identified.

4.5.3.2. Placing the results in context

4.5.3.2.1. Congenital anomalies

One of the most marked differences in characteristics between British and Irish infants with gastroschisis, and Canadian infants with gastroschisis, was in the rate of additional chromosomal or structural anomalies. In British and Irish infants this was 5%, whilst in Canadian infants it was 17%. Previous studies have estimated the proportion of infants with gastroschisis and an additional congenital anomaly as ranging from 5% to 27% dependent upon setting, year of data collection, country and methodology used(119-122). The only international study, conducted by Mastroiacovo in 2007 combined data from 24 registries, each a member of the International Clearing House for Birth Defects Surveillance and Research, and estimated the rate of additional congenital anomalies for infants with gastroschisis at 14.1%.

In the work described in this chapter, the difference seen in additional chromosomal or structural anomaly rate between British and Irish infants, and Canadian infants, is potentially due to differences in data collection methodology used. For British and Irish infants, surgeons or members of staff within the surgical department were responsible for data reporting, and the focus of the data collection forms was on the surgical procedure and surgical outcomes. In contrast, for Canadian infants, abstractors working for CAPSNet reported surgical data, and abstractors working for the CNN reported neonatal data. The CNN data collection forms placed a far greater emphasis on the reporting of non-surgical information than the BAPS-CASS data collection forms did, and there is therefore the potential that the lower rates seen in the British and Irish Infants were due to under-reporting of congenital anomalies. However, previous work, including that by Rankin et al

using data collected between 1986 and 1996 from the Northern Congenital Abnormality Survey (NorCAS) has also put the additional congenital anomaly rate for British infants with gastroschisis at approximately 5%(123). This suggests that if under reporting is the cause of the low rates of additional anomalies seen in British and Irish infants, that it is a systemic problem, not something specific to the BAPS-CASS study.

In 2014, the British and Irish Network of Congenital Anomaly Researchers (BINOCAR) published work based upon data collected from five congenital anomalies registers covering 36% of British and Irish births, describing a prevalence of congenital anomalies in the general population of 227 per 10,000 live births (95% CI 221 – 232) (124). This prevalence is significantly lower than that reported by the Public Health Agency of Canada in their 2013 report, where prevalence of congenital anomalies in the general population is 371.1 per 10,000 live births (95% CI not supplied)(125). In calculating the overall prevalence of congenital anomalies, the report by the Public Health Agency of Canada only includes six defined congenital anomalies: neural tube defects, Down's syndrome, congenital heart defects, orofacial clefts, limb deficiency defects and gastroschisis. In comparison, the overall prevalence reported by BINOCAR includes the six congenital anomalies reported by the Public Health Agency of Canada, and then also respiratory anomalies, digestive system anomalies, urinary anomalies, genital anomalies, skeletal anomalies, four other chromosomal anomalies and three other neurological anomalies. Given the greater number of conditions included by BINOCAR when calculating the overall prevalence of congenital anomalies, it would be reasonable to anticipate this to be greater, not lower than the figure reported by the Public Health Agency of Canada. As case ascertainment has previously been demonstrated to be good for BINOCAR(126), under-reporting of congenital anomalies in the

British Isles is unlikely to fully explain this difference. A focus of future research should therefore be on trying to understand whether other factors such as differences in congenital anomaly screening practices, or attitudes towards termination of pregnancy might also contribute to the apparent differences in congenital anomaly rates seen between the British Isles and Canada.

4.5.3.2.2. Sex differences

The other major difference in demographics between Canadian infants and British and Irish infants was in the proportion of infants that were male. In the British Isles, the proportion of male infants was 45% whilst in Canada it was 52%. There is no clear rationale why the sex ratios would be different between the British Isles and Canada, and large previous studies describing the epidemiology of infants born with gastroschisis have reported both male and female predispositions(112, 119, 120). It would therefore appear most likely that this difference is due to chance.

4.5.3.2.3. Other infant characteristics

As well as differences in additional congenital anomaly rates and sex ratios between Canadian infants and British and Irish infants, differences were also seen in a range of other demographics, including birthweight, gestational age at birth, maternal age at delivery, and ethnicity. These remaining differences are likely to either reflect underlying differences between the British and Irish, and Canadian populations as a whole, or differences in data collection methodology utilised in each country.

In Canada, the proportion of infants in the general population live-born prior to 37 weeks gestation is 7.7% (95% CI 7.6% - 7.8%) and the proportion of live-born infants weighing less than 2500g is 6.1% (95% CI 6.0%-6.2%)(Source: Statistics Canada, 2012, Births, Catalogue number: 84F0210X, Issue number: 2009000, Reference period: 2008-2009). In Comparison, in the British Isles, the proportion of infants live-born prior to 37 weeks gestation is 7.8% (95% CI 7.7%-7.9%) and the proportion of live-born infants weighing less than 2500g is 6.96% (6.9%-7.0%)(127). It is therefore not unexpected to see a slightly lower median birth weight and greater proportion of small for gestational age at birth infants in the British Isles cohort than in the Canadian cohort. Differences in maternal age at delivery and ethnicity may also reflect differences in the underlying population. However, these are variables that are unreliably collected by both CAPSNet and CNN, and for which there are large amounts of missing data. It would therefore be unreliable to draw conclusions from them.

4.5.3.2.4. Management strategy

Infants treated in Canada were less likely to undergo OPFC, more likely to undergo WBR, more likely to be ventilated post-operatively, and had a longer length of stay in a paediatric surgical centre than infants treated in the British Isles. Whilst the differences in length of stay and post-operative ventilation were statistically significant, at four days and one day respectively, they are unlikely to be clinically meaningful, and the differences in operative strategy appear to be related to the time-period over which the original studies were conducted, as opposed to necessarily reflecting differences in current practice.

When the Canadian cohort was limited to infants born during the period of the BAPS-CASS study, the differences in operative strategy were less marked, suggesting a change over

time in preferred operative strategy in Canada. Although there do not appear to be any large-scale studies describing similar changes in the British Isles, a survey conducted at the European Paediatric Surgeon's Association (EUPSA) annual congress in 2011 suggested that WBR was the closure technique of choice for approximately 20% of Western European, including British and Irish, surgeons (50). This figure is much closer to the 13.5% of the overall Canadian cohort who underwent WBR in the work presented in this chapter, reinforcing the theory that the differences described between the British Isles and Canadian cohorts are due to changes over time as opposed to current differences in management strategy. Anecdotally, there also appears to be an increasing number of groups conducting studies comparing sutureless to sutured closure for infants with gastroschisis, again, suggesting that interest in use of the technique may be increasing (128) (93, 129).

4.5.3.2.5. Outcomes

Only one difference in outcome was identified between British and Irish infants, and Canadian infants, with the number of days on which parenteral nutrition was received in the first 28 days of life being approximately 10% higher for Canadian infants. However, given that the median number of days on which parenteral nutrition was received in British and Irish infants was 26 (IQR 18 days – 28 days) and in Canadian infants was 27 (IQR 19 days -28 days), and the maximum number of days parenteral nutrition that any infant could possibly have received in the defined period of follow-up was 28, it is not clear that this is a meaningful difference. In order to develop an understanding of whether clinically meaningful differences in duration of parenteral nutrition use exist between the two countries, longer follow-up will be required.

4.5.4. Strengths and limitations of the study

4.5.4.1. Strengths

Three key strengths of the work described in this chapter are the size of the cohort, the patient-centred nature of the outcomes investigated, and the detailed, prospective data collection methodology that was utilised.

In 2007, Abdullah and Arnold each published articles based on the same cohort of just over 4000 infants with gastroschisis(111, 119), and whilst their cohort is larger than that described here, only high level data collected by the National Inpatient Sample database and the Kids' Inpatient Database in America were available for their analysis. These studies were therefore useful for describing the epidemiology of gastroschisis, but the lack of nuanced data available prevented investigation of any association between key patient factors, management factors and outcome. In contrast, the work presented in this chapter collected detailed, nuanced data relating to an infant's physiology, the degree of bowel injury they had sustained, their operative management, and outcomes that are important to clinicians and patients. Such data, combined with the size of the study allowed identification of key patient and operative factors that affect short-term outcomes for infants with gastroschisis. As the outcomes investigated were identified as important by clinicians, people born with gastroschisis and parents of children born with gastroschisis, the results of the comparison between OPFC and SR hold direct relevance to clinical practice and can therefore be used to inform clinical decision-making and counsel parents regarding the pros and cons of each treatment option.

4.5.4.2. Limitations

The two major limitations of the work presented in this chapter arise from the fact that it is comprised of a secondary analysis of data that have been collected in a non-randomised manner using three different data collection systems, none of which were designed to investigate the outcomes identified as important in the NETS[1G] gastroschisis COS.

4.5.4.2.1. Variability of outcome definition

The first limitation is that the definitions of some outcomes, including liver disease, infection, enterocolitis, and abdominal compartment syndrome varied between the BAPS-CASS and CAPSNet studies, making it difficult to ensure comparability when creating the unified dataset. Inevitably, as the definitions in each individual dataset were different, it was also not possible to match the overall study definition for these outcomes to that which was specified in the NETS[1G] gastroschisis COS. It must therefore be borne in mind that the outcomes *number of infections* and *liver disease* reported in this work are approximations, and not exact representations of the outcomes *number of episodes of sepsis*, and *liver disease* that are included in the NETS[1G] COS. The primary outcome investigated, *number of severe gastrointestinal complications*, is also affected to a degree by this problem, as the definitions used for *abdominal compartment syndrome* and *enterocolitis,* two of the constituent complications, were different from those utilised in the NETS[1G] COS. Again therefore, this outcome is an approximation of that derived in the NETS[1G] COS, but would appear close enough to the original definition to allow conclusions to remain valid and relevant to clinical practice.

As the reported outcomes will not therefore necessarily be equivalent to outcomes reported in other studies using the COS, it is likely that some of the benefit of reporting core outcomes has been lost. Making comparisons with other studies, and conducting meta-analysis must therefore be undertaken with caution.

4.5.4.2.2. Confounding by intention

Many leaders in biomedical research are now recognising the cost-effective nature of using well-designed observational studies and secondary analyses of existing data to guide management decisions in rare conditions, or those conditions in which RCTs are difficult to conduct. In their elegant series in the Lancet detailing waste in biomedical research, Chalmers and colleagues detail a series of steps including investigation of outcomes relevant to key stakeholders, and appropriate use of existing data, that can be implemented to reduce unnecessary expenditure and increase the speed with which knowledge is translated into clinical practice(38, 39, 41, 130). However, when used for comparison of interventions, a key limitation of observational studies is that they are prone to confounding by intention, and unless such confounding is controlled for, the results can be misleading. Within the work described in this chapter, key differences in characteristics were demonstrated between infants who underwent OPFC and those who underwent SR, clearly highlighting how allocation to treatment had been confounded by intention.

Over recent years, propensity score matched analyses have gained popularity as a method of accounting for confounding by intention(131, 132). Such analyses replicate as close as is possible in observational studies the conditions that would be seen in an RCT. Within the work presented here, a large range of patient characteristics proposed to be associated with

both treatment and outcome were used to develop the propensity score. Adjusting for this score alongside known confounding factors in a multivariable model will in theory have produced the most robust estimate of treatment effect possible from the existing observational data(133). Therefore, whilst like much of the previously published literature(110, 134-137), allocation to treatment in this work is undoubtedly confounded by intention, the use of a covariate and propensity score adjusted analysis should, if sufficient factors have been taken account of and accurately measured, have accounted for much of this confounding.

4.5.4.3. Limitations of statistical analysis strategy

In addition to the two limitations described above, there were two potential limitations arising from the choice of statistical analysis strategy. Firstly, Cox proportional hazards analysis would have provided more robust conclusions than the negative binomial regression analysis used for the primary outcome, however, accurate time to event data were not collected and therefore it was not possible to utilise a survival-type analysis. Secondly, the use of complete case analysis in regression models may have introduced type two errors and potential biases. This limitation is discussed further below.

4.5.4.4. Complete case analysis

Due to Canadian data protection laws, it was not possible to remove CAPSNet or CNN data from the servers of the Maternal Infant Care (MiCARE) institute in Toronto. Remote access and Virtual Private Network (VPN) access to these servers had also not been established, and therefore, all analysis of Canadian data had to take place within the MiCARE institute. Data protection rules governing handling of the BAPS-CASS data allowed transfer of fully

anonymised data to Canada for the purposes of analysis, but prevented retention of this data after completion of the analysis. Therefore, the only situation in which the BAPS-CASS and Canadian data could be brought together for a combined analysis was through temporary merging of the datasets on the MiCARE institute servers, conduct of all analyses, and then destruction of the merged dataset following completion of the analyses. Due to limitations of funding and timing, only a six-week block was available in which to merge the datasets and conduct the required analyses. It was therefore necessary to design analyses with time-efficiency and pragmatism in mind.

In comparison to more advanced techniques for handling missing data such as multiple imputation or use of dummy variables, complete case analysis represents a simple, time-efficient method for handling missing data. Previous work on BAPS-CASS datasets, including those for gastroschisis, necrotising enterocolitis, and oesophageal atresia by an experienced statistician and health services researcher, has also suggested that use of complete case analysis is likely to be appropriate and associated with no more significant biases in these datasets than other methods of handling missing data(5, 78, 138, 139). The decision was therefore made to conduct all regression analyses on the merged dataset using complete case analysis. It is probable that such use of complete case analysis reduced the power of the conducted analyses to detect associations with statistical significance, and potentially introduced a degree of bias if the data were not missing completely at random. However, the benefits of not utilising a large proportion of the relatively limited time available to conduct more complex analyses, or multiple sensitivity analyses using other techniques, was felt to outweigh these potential limitations.

4.5.5. Implications for clinical practice

Results of the work described in this chapter provide the most robust and comprehensive assessment available to date of the relative merits of different reduction and closure strategies for the treatment of infants born with gastroschisis. These results should therefore be used for the counselling of parents and for informing clinical decision-making.

Based upon the results of this work, parents of infants born with gastroschisis who do not have intestinal perforation, intestinal necrosis or matted bowel at delivery should be counselled that both OPFC and SR have their pros and cons. They should be advised that in the first 28 days of life, treatment with silo placement and staged reduction appears to reduce the number of severe gastrointestinal complications their child is likely to develop, but increase the number of operations they are likely to require, increase the risk of them developing a serious infection, and marginally increase the number of days on which they will require parenteral nutrition. Conversely, they should be advised that treatment with OPFC appears to increase the number of severe gastrointestinal complications their child is likely to develop in the first 28 days of life, but reduce the number of operations they are likely to require and the risk of them developing a serious infection, and marginally reduce the number of days on which they will require parenteral nutrition. Taking account of the facilities and expertise available in the treating hospital, and in partnership with the treating surgeon and neonatologist, parents should then be involved in the decision as to which intervention is most appropriate for their child.

In contrast to parents of children without intestinal perforation, intestinal necrosis, or matted bowel, parents of children with any of those characteristics should be advised that

at present, it appears that OPFC is the operation of choice, as there are demonstrable drawbacks to treatment with silo placement and staged reduction, but no demonstrable benefits.

Parents of children in either complexity group should be advised that whilst WBR is a treatment that is used in approximately 10% of infants, there is currently not sufficient evidence to determine which infants it is most appropriate for use in, or how outcomes following it compare to either of the other reduction and closure strategies. Unfortunately, there are also not sufficiently large numbers of infants who have undergone WBR in the work presented in this chapter to provide the observational data that is required to appropriately design an RCT to provide this evidence, and therefore, further large-scale observational studies must be conducted.

This work does however provide the information required to inform development of a joint British Isles-Canada, multi-centre RCT, comparing OPFC to SR. Conducting such a trial in which the effect of these reduction and closure strategies on all outcomes in the NETS[1G] gastroschisis COS, including quality of life, is described, should still be the aim. Such a trial should only be conducted in infants without intestinal perforation, necrosis or matting, and should ensure that balance is achieved between groups in regards to median birth weight and proportion of participants with intestinal atresia. As it appears probable that such a trial would reveal advantages and disadvantages to both treatments, a cost-utility analysis should be included in this future work, and preliminary qualitative studies should be undertaken to allow key stakeholders to weigh the relative importance of each outcome in the NETS[1G] COS.

4.5.6. Implications for use of core outcome sets

This work has demonstrated that whilst there are limitations to utilising COSs in secondary analyses where the data were not designed for use with the COS, that it is still possible to do so and reach meaningful conclusions relating to clinical questions.

Chapter Five

A British Isles-wide cohort study assessing the impact of choice of surgical intervention on core outcomes at five to seven years of age in children with Hirschsprung's disease

5.1. Background

5.1.1. Parent experiences

By conducting in depth interviews with 44 parents of children who underwent neonatal surgery, including parents of children with HD, Hinton et al identified six key aspects of care that affected a parent's experience(140). Central to this experience was the ability of surgeons to help parents understand their child's diagnosis and the journey ahead. In general, feedback from the parents interviewed was that the hospitals were not able to supply them with sufficient information to address their concerns, and they therefore sought out further information from the Internet and parent forums. One way to improve the experience of parents of children who undergo surgery for HD is therefore to increase the amount of reliable, easily understandable information that hospitals are able to give them regarding their child's diagnosis and likely journey(140).

At present however, with the exception of a few notable pieces of work by Risto Rintalla's group in Finland, which provide outcomes data for adults previously treated for HD(48, 141, 142), there is little information available on which to base counselling of parents. The vast majority of available information is from small, single institution studies, and relates to hospital metrics as opposed to patient-centred outcomes (73). A series of systematic reviews have also highlighted that there is currently insufficient data available to allow reliable comparisons to be drawn between the multiple different operative strategies that are in use to treat children with HD(16, 17, 143-146). It is therefore currently very difficult for surgeons to identify reliable information to use to help parents understand their child's diagnosis and probable treatment course.

5.1.2. Explaining the limitations of existing data

There are many reasons for the lack of available data that could be used for counselling of parents. Primarily however, it is due to the fact that HD has a low incidence, making it impossible for single centre studies to recruit sufficient infants to answer clinically relevant questions over a sensible period of time. Most studies therefore either represent small, but contemporary cohorts of patients, or larger, but historical cohorts, collected over time-periods where there have been multiple changes in practice(16). The retrospective nature of the majority of these studies(2) means that limited data-points are available to researchers, and hence analysis focuses on those that are easily identified from case records, as opposed to those which are relevant to patients, their families, or service provision. Provision of reliable, easily relatable information to help parents understand their child's diagnosis and likely outcomes will only be possible once studies are describing patient-centred outcomes from large, contemporary cohorts of children at multiple time-points in infancy, childhood, adolescence and adulthood.

5.1.3. The pull-through procedure

There are multiple components to the definitive surgical intervention for HD, the 'pull-through' procedure, including the number of stages over which it is performed, the approach, and the rectal dissection technique used. Each component can be performed in multiple ways, and little evidence exists to differentiate the relative merits of each method (16, 17, 143-146). However, work undertaken with the members of the United Kingdom Paediatric Colorectal Group (UKPCG) when designing the study described in this chapter

suggested that the area in greatest need of further investigation was comparison of the rectal dissection techniques.

5.1.4. Rectal dissection and anastomotic techniques

Since the original rectal dissection and anastomotic technique was described by Swenson in 1948 (46), Duhamel(44), and Soave(45) have described modifications that have gained wide-spread acceptance, and subsequently over-taken the Swenson technique in popularity in the UK(49).

5.1.4.1. The Swenson technique

The Swenson technique begins with identification of the point where aganglionic, abnormal bowel transitions to ganglionic, normal bowel. This area is referred to as the transition zone. Following identification of the transition zone, the sigmoid colon is mobilised, and the normal colon is divided from the abnormal colon. The peritoneal reflection is then divided anteriorly and laterally to expose the muscular coat of the rectum, before the bowel is divided at the recto-sigmoid junction. Dissection then continues close around the rectum into the pelvis for a sufficient distance to allow the rectum to be intussuscepted through the anus. An incision is made in the anterior wall of the intussuscepted rectum, allowing the mobilised normal colon to be grasped and pulled through the anus with an anastomosis made between the normal colon and the anterior wall of the native rectum. This anastomosis is then allowed to retract inside the anus, completing the pull-through. Figure 10 shows the pre-operative anatomy, and Figure 11 shows the end result of the Swenson procedure.

Figure 10: Pre-operative anatomy

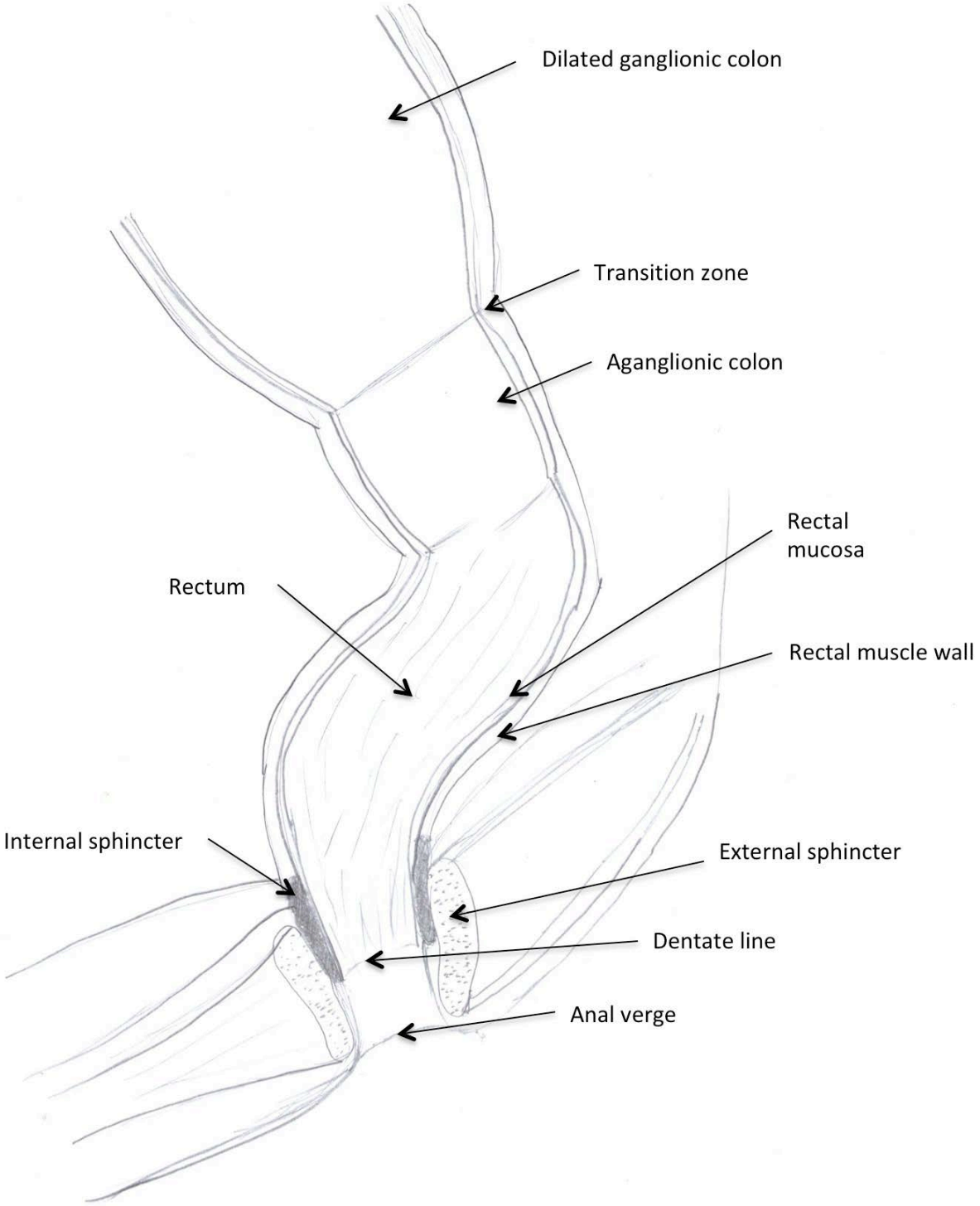
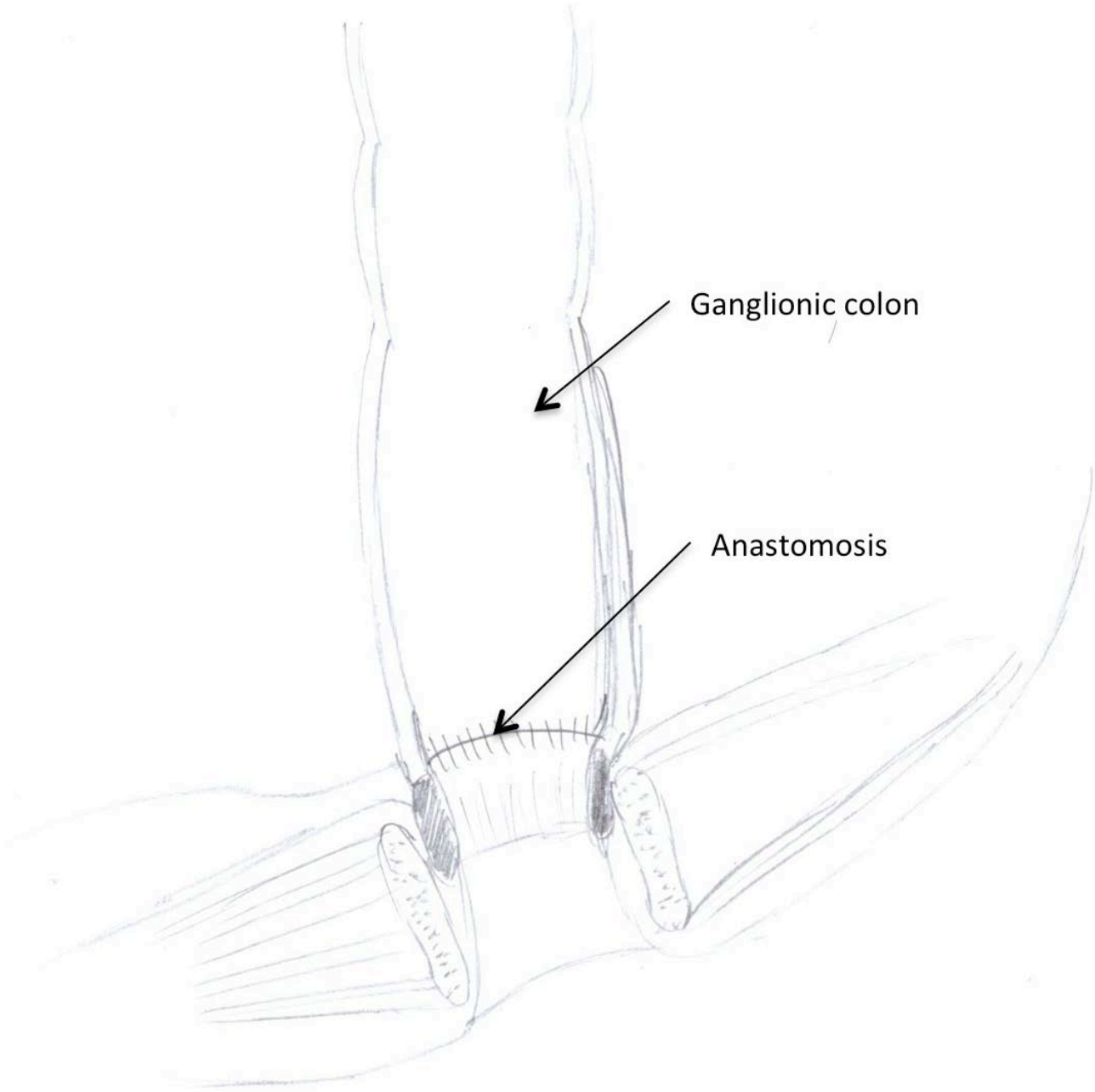


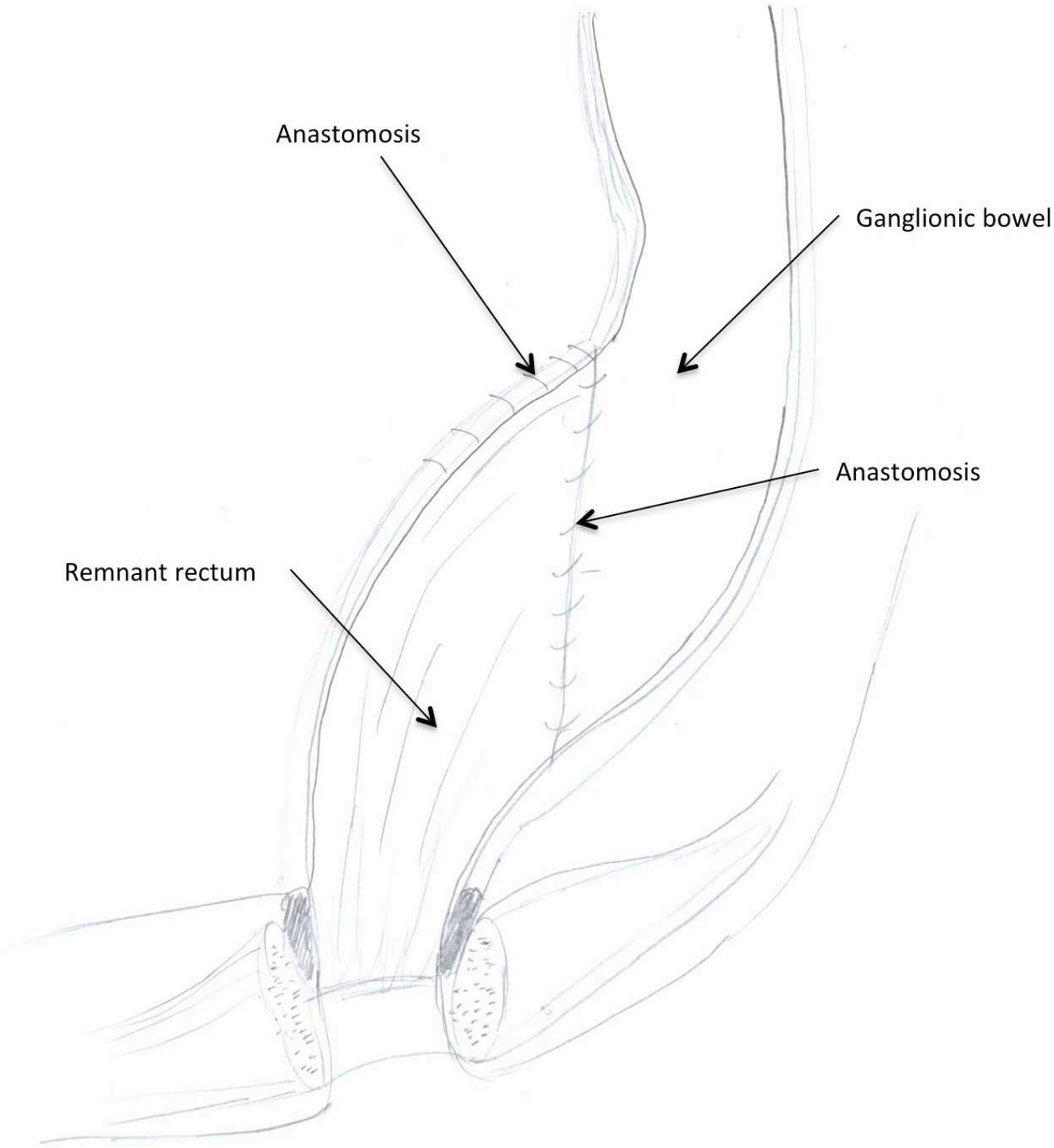
Figure 11: End result of the Swenson procedure



5.1.4.2. The Duhamel technique

Approximately fifteen years after Swenson described his technique, Duhamel proposed a series of modifications. The basic principles involve division of the colon proximal to the transition zone, resection of the abnormal sigmoid colon, mobilisation of the normal colon so that the distal portion can be placed in the pelvis, and formation of an end to side anastomosis between the normal colon and remnant abnormal rectum(44). More commonly nowadays however, the Duhamel technique is performed with the addition of the Lester Martin modification, whereby the spur between the posterior rectum and anterior portion of the mobilised colon is divided to create one large rectal space where the posterior half is formed from the mobilised normal colon, and the anterior half is formed from the remnant aganglionic rectum(147) (Figure 12).The primary difference between the Duhamel and Swenson techniques is that with the Duhamel technique, the rectum is not dissected or removed, thereby reducing the risk of damage to surrounding nerves and vessels. Proponents of the Duhamel technique suggest that when compared to the Swenson technique, rectal sensation is better preserved, and the risk of anastomotic stricture and post-operative enterocolitis are reduced(44, 148).

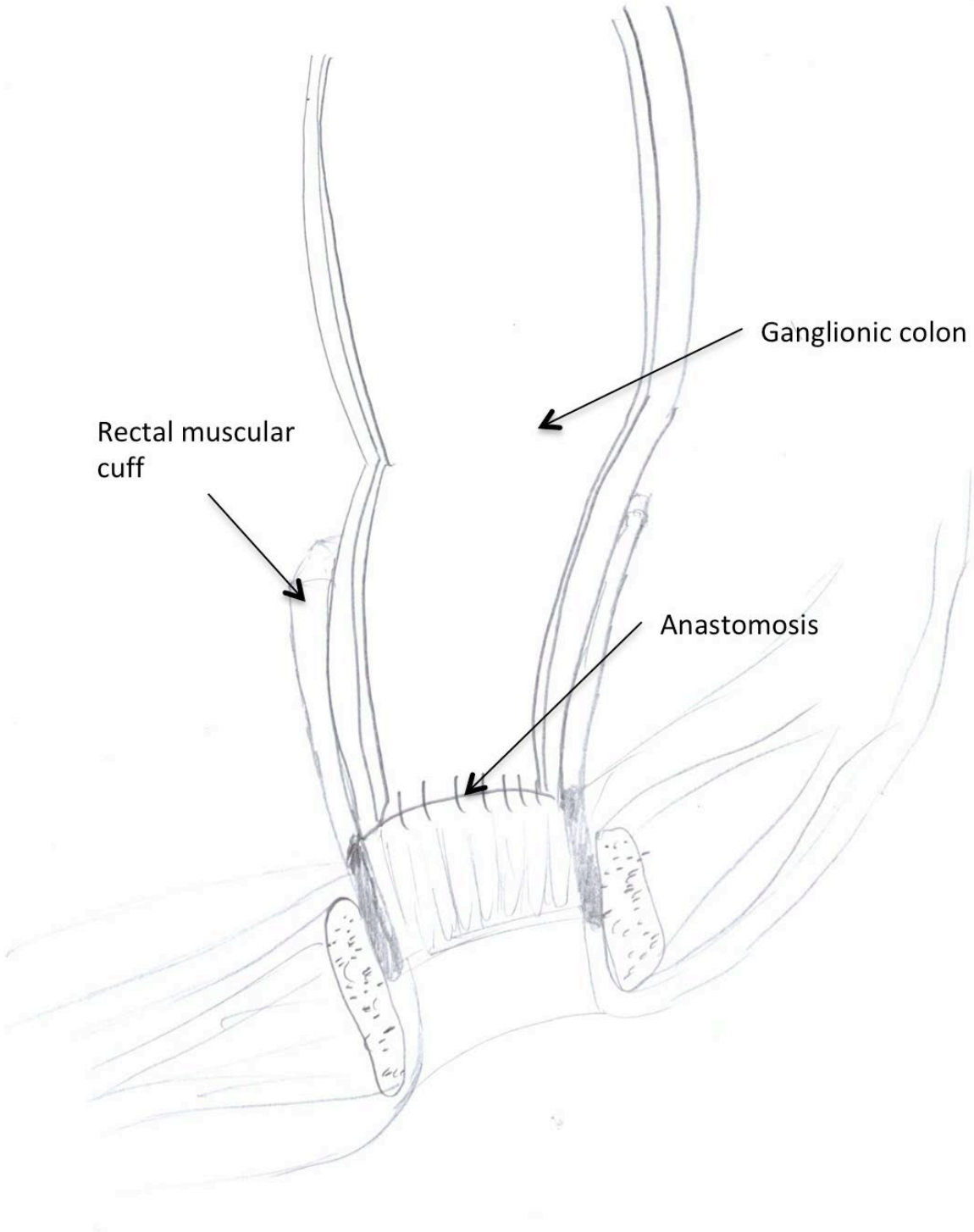
Figure 12: End result of the Duhamel procedure



5.1.4.3. The Soave technique

The final major variant of the pull-through procedure utilises Soave's technique(45). Soave's technique proceeds initially in the same manner as the Swenson or Duhamel techniques, with identification of the transition zone and mobilisation of the proximal colon via an abdominal incision. However, at this stage, instead of dividing the normal from abnormal colon, a local anaesthetic solution is infiltrated into the intestinal wall between the seromuscular layers and the mucosal layer, at a point just above the pelvic peritoneal reflection. This hydro-dissection allows an incision to be made in the seromuscular layers of the rectum, which can then be circumferentially dissected free from the underlying mucosa. This dissection can be continued distally to separate the rectal mucosa from the seromuscular layers as far as the ano-rectal junction. A perineal stage of the operation is then undertaken, whereby an incision is made via the anus in the distal rectal mucosa, just superior to the dentate line, allowing dissection between the mucosa and serosa to proceed superiorly to meet that which has been undertaken from the abdomen. The rectal mucosal layer is thereby completely freed from the outer seromuscular coat, and can be prolapsed through the anus along with the proximal abnormal colon. Once the abnormal colon and transition zone have been prolapsed, they are resected, and in the commonly used Boley modification of the original Soave procedure, anastomosed to the anal verge(149) (Figure 13). As with the Duhamel technique, proponents of Soave's modification would suggest that its use is associated with reduced risk of damage to the pelvic nerves(45).

Figure 13: End result of the Soave procedure



5.1.5. Approaches to the pull-through

Each rectal dissection technique can be performed via multiple different approaches, including the open approach, the laparoscopic approach(150), the trans-anal approach(151), and a combined laparoscopic/trans-anal approach. Traditionally, the open approach, where an operation is performed through a single incision on the abdomen, has been the standard for HD surgery(49). As minimally invasive surgery has evolved however, the laparoscopic approach, in which the operation is performed in a keyhole manner through multiple small incisions on the abdominal wall, and the purely trans-anal approach, in which the entire operation is performed through the anus without making any abdominal incisions, have gained popularity(49). A combined laparoscopic/trans-anal approach is also utilised, where varying degrees of colonic mobilisation are performed laparoscopically, prior to completing the operation trans-anally. Benefits and drawbacks to each approach are discussed in Appendix 24.

5.1.6. Other variations in the operative strategy

As well as being defined by the approach taken and the rectal dissection technique used, the overall surgical package that a child undergoes is also defined by a myriad of other factors, including whether a pre-operative stoma is created, the age and weight of the child at which the surgery is performed, the distance that the anastomosis is made from the dentate line, and a host of other modifications to each rectal dissection technique that individual surgeons have developed over their years of practice. The relationship between each of these operative variations is complex, and defining the effect of any individual component is therefore difficult.

5.1.7. Investigating patient centred outcomes

Utilising the BAPS-CASS infrastructure described in section 4.3.2 to conduct paediatric surgical research in the British Isles, identifiable information is never removed from the child's treating hospital, and therefore consent from parents for use of their child's data is not required. This methodology was intended to maximise case ascertainment and therefore allow accurate calculation of incidences for many of the rare conditions studied. However, the lack of consent prevents the infrastructure in its current form from being used to collect data relating to many patient or parent-centred outcomes. Specifically, there are three outcomes that were identified as important in the NETS^{1HD} COS described in Chapter Three that it is not possible to investigate using the current BAPS-CASS infrastructure. These outcomes are quality of life, psychological stress for the individual with HD, and objective score of bowel function.

5.1.7.1. Quality of life and psychological stress

Quality of life and psychological stress can be measured in multiple ways, but the measure proposed for use by the NETS^{1HD} COS was the PedsQL (152). The PedsQL is available in age-specific child and parent-proxy reported questionnaires, and consists of 23 items scored from 0 (never) to 4 (almost always), that are designed to measure the World Health Organisation (WHO)'s four core dimensions of health: physical functioning, emotional functioning, social functioning and school functioning. Answers from the 23 constituent questions are reverse scored and linearly transformed to a 0-100 scale, such that higher scores indicate a better health related quality of life. The mean score of all 23 items represents the child's Total Scale Score, i.e. a measure of their overall health related quality of life, whilst the mean score of the 15 items in the school functioning, emotional

functioning and social functioning sub-scales represents the child's Psychosocial Health Summary Score, i.e. a measure of the psychological and emotional quality of life of the child.

5.1.7.2. Objective measure of bowel function

The Paediatric Incontinence and Constipation Score (PICS) (153) was proposed in the NETS[1HD] COS as the most appropriate objective measure of a child's bowel function. Evaluation of bowel function using the PICS is achieved through parent completion of thirteen questions that contribute to calculation of two scores, one for incontinence, and one for constipation. The maximum incontinence score, representing complete continence is 32, and the maximum constipation score, representing no constipation, was 29. Age-specific mean values for children with no health problems have previously been derived for each of the constipation and incontinence scores. Children with scores below the lower 95% confidence limit in the incontinence score are classified as having incomplete continence, whilst those with scores below the lower 95% confidence limit on the constipation score are classed as having constipation.

5.1.8. Information required to improve clinical care

In order to improve the care of children who are diagnosed with HD, and the experience of parents of children with HD, evidence from the existing literature suggests that further knowledge needs to be developed in three key areas. Firstly, more information is needed regarding the 'journey' that a child with HD is likely to take as they grow, secondly, the characteristics of a child that influence whether they are likely to have a good or poor outcome need to be better understood, and thirdly, the relative merits of different forms of surgical intervention must be more robustly described. In order to address these

deficiencies in the current evidence-base, it is necessary to collect robust data at multiple time-points throughout a child's life, from both clinicians and parents, relating to large, representative cohorts of children with HD. This is something that has not previously been achieved.

5.2. Objectives and research questions

The overall objective of the work presented in this chapter was to investigate if it was possible to describe school-age core outcomes for a British Isles-wide cohort of children with HD by collecting data from clinicians and parents, subsequently link this data to existing anonymised operative and early outcomes data, and by doing so, inform the development of national management guidelines. Within this global objective, the following specific research questions were addressed.

1. What were core outcomes at five to seven years of age for children diagnosed with HD in the British Isles between 2010 and 2012?
2. For children who were diagnosed with HD in the British Isles between 2010 and 2012, which characteristics and early management factors were associated with variation in risk of unplanned reoperation following definitive surgery?
3. For children who were diagnosed with HD in the British Isles between 2010 and 2012, was the type of pull-through procedure they underwent associated with variation in core outcomes at five to seven years of age?

5.3. Methods

5.3.1. Ethics committee approval

Approval for the work presented in this chapter was obtained from the South Central (Berkshire) Research Ethics Committee (REC reference: 17/SC/0152), and the Confidentiality Advisory Group of the Health Research Authority (England and Wales) (reference: 17/CAG/0052).

5.3.2. Summary

Between October 2010 and October 2012, BAPS-CASS was utilised to collect data relating to the presentation and early management of children diagnosed with HD at less than six months of age in the 28 paediatric surgical centres in the British Isles. The work presented in this chapter describes the follow-up of children from 20 of these 28 paediatric surgical centres at five to seven years of age. The study comprised two arms, one that collected data from parents, and one that collected data from clinicians. Data from both sources were combined with data collected 28 days and one year after diagnosis by the original BAPS-CASS study. These amalgamated data were used to describe core outcomes for this cohort of children, investigate the association of key child and management factors with outcome, and investigate whether the type of rectal dissection and anastomosis used in a child's pull-through procedure affected their outcomes.

5.3.3. Stakeholder involvement in study design

The research questions and design of the work presented in this chapter were informed through consultation and collaboration with two stakeholder groups. Firstly, a parental

advisory group comprising families of children requiring early surgery; and secondly, the UKPCG, a special interest group for paediatric colorectal surgeons based in the British Isles. Parents of children with HD, people with HD, and representatives of patient interest groups were involved in development of the study materials and methodology, in particular, the participant information leaflet, consent form, data collection form, and the recruitment and consenting process. Two parents of children with HD were members of the Study Steering Committee. The outcomes investigated were identified through the robust Delphi process involving key stakeholder groups that was described in Chapter Three.

5.3.4. Case definition

Any live-born infant who was diagnosed with HD between the 1st of October 2010 and 31st of September 2012, and was less than six months of age at the time of diagnosis. HD was defined as an absence of ganglia in the enteric nervous system of the distal bowel (aganglionosis).

5.3.5. Case identification, consenting and data collection

5.3.5.1. BAPS-CASS study

Case identification and data collection for the original BAPS-CASS study was performed using standard BAPS-CASS methodology as described in Chapter Four, section 4.3.4.1.

5.3.5.2. Re-identification of infants

At each participating site, NHS numbers of infants whose data were included in the original BAPS-CASS study were identified by paediatric surgeons, clinical nurse specialists and NIHR

research nurses through the use of locally held BAPS-CASS study registers. Where study registers were no longer available, local researchers used anonymised data supplied by BAPS-CASS to identify infants based upon matching the gender and date of definitive operation, date of suction rectal biopsy, or date of stoma formation, to local operative logs. The NHS central register was then used to obtain up-to-date contact information and survival status for identified infants.

5.3.5.3. Parent reported outcomes

Parents of children whose data were included in the original BAPS-CASS study and who survived to five years of age were contacted by telephone by researchers based in their child's treating hospital to seek consent for sharing of their contact details with central research staff based in the NPEU. If parents were un-contactable after three telephone attempts, then written contact was attempted. Where consent was obtained for sharing of contact details, parents were sent either electronically, or by post (dependent on their preference) a study information pack and consent form. Where no response was received, parents were followed-up by telephone or text message two and four weeks after posting the study pack. Following receipt of consent to participate, parents were sent a link by email and text message to an electronic data collection form hosted on OpenClinica (OpenClinica open source software, version 3.1. © OpenClinica LLC and collaborators, Waltham, MA, USA). Alternative methods of completing the data collection form were made available to parents if required, including in paper format, over the telephone with a member of the research team, or through a translator, and data collected in this manner were then entered into OpenClinica by research staff based in the NPEU. Where the data collection form had

not been completed at two and four weeks after sending the link, parents were followed-up by telephone or text message.

5.3.5.4. Clinician reported outcomes

Children whose parents had actively opted out of participating in the study by declining to share their contact details, returning a blank consent form to the NPEU, or verbally informing a member of the research team that they did not wish to participate were neither included in the parent reported outcomes arm, nor the clinician reported outcomes arm of the study. All other children, including those in whom it had not been possible to make contact with their parents, and those who had not survived to five years of age, were included in the clinician reported outcomes arm of the study. In order to allow parents the opportunity to decline to participate, clinician reported outcomes questionnaires were completed a minimum of six weeks after posting of the study pack to parents. Clinicians entered all data directly into OpenClinica. Site Principal Investigators were sent regular updates regarding the number of data collection forms remaining for completion at their site. Where there were discrepancies or missing data, local researchers were contacted by email or telephone for clarification.

5.3.6. Study initiation and site inclusion

The original BAPS-CASS study involved collection of data for infants treated in the 28 paediatric surgical centres in the British Isles. The work presented in this chapter was designed to follow-up children from all of these centres. However, after 16 months of attempting to obtain relevant permissions, it was not possible to initiate the study in eight

of the 28 centres. Therefore, the decision was made to proceed with data collection and analysis from the 20 centres where approvals had been obtained.

5.3.7. Outcomes of interest

5.3.7.1. Primary outcome

The primary outcome was unplanned reoperation with the indication for re-operation specified. Unplanned was defined as any procedure not considered part of routine post-intervention practice. This therefore excluded stoma closures performed separately as part of a planned three-stage pull-through procedure, but included all anal dilatations/calibrations performed under anaesthesia, as opinion varies as to whether these are to be considered part of routine care or not. As per the definition from the NETS[1HD] COS, re-operation included all procedures performed as a direct result of the diagnosis or treatment of the child's HD, ***and*** all episodes of general anaesthesia that were required as a direct result of the diagnosis or treatment of the child's HD, regardless of whether an operative intervention was undertaken, e.g. examinations under anaesthesia. As the outcome of interest was ***re***-operation, not operation, only those operations occurring after the definitive pull-through were included. Where multiple procedures were undertaken at the same time, these were counted as one additional unplanned reoperation, and classified as the most significant procedure performed. Indications for the operations were classified according to NICE criteria as minor, intermediate or major/complex (NICE Guideline NG45 – Routine preoperative tests for elective surgery).

5.3.7.2. Secondary outcomes

The secondary outcomes investigated were the remaining nine outcomes from the NETS[1HD] COS. These were:

- Death with cause classified as due to:
    - A complication of treatment (excluding HAE)
    - HAE
    - An associated anomaly
    - Other condition.
- Faecal incontinence, defined as involuntary passage of faecal matter in an inappropriate place, and with the severity graded as:
    - Occasionally (e.g. once to twice per week) either with or without causing social problems
    - Every day but without social problems, or
    - Constant and causing social problems.
- Urinary incontinence, defined as involuntary voiding of urine that was constant, associated with social problems, or requiring catheterisation.
- Permanent stoma as a direct result of the diagnosis or treatment of the child's HD, including where the decision for a stoma had been made out of child or parental preference, or for continence management. Permanent stoma was defined as one that was created without the intention of later reversal. Indication for stoma formation was reported.
- Clinician decision to admit and treat for HAE.
- Objective score of bowel function, as measured by the PICS.

- Voluntary bowel movements without need for enemas or rectal or colonic irrigation.
- Quality of life for the child with HD, as measured by the total scale score for the parent proxy reported PedsQL questionnaire for five to seven year olds.
- Psychological stress for the child with HD, as measured by the psychosocial health summary score for the parent proxy reported PedsQL questionnaire for five to seven year olds.

Discrepancies between clinician and parent reports for each outcome were handled as described in Appendix 25.

5.4. Statistical analyses

5.4.1. Representativeness of the cohort

Data relating to baseline demographics and early outcomes for infants with HD treated in the 20 participating NETS^{2HD} sites and the eight non-participating sites were collected in the original BAPS-CASS HD cohort study. Based upon these data the following infant characteristics and management strategies were described for infants treated in each group of sites.

- Infant characteristics: Ethnicity, gestational age at birth, birthweight, sex, family history of HD, presence of an associated anomaly, age at presentation, age at diagnosis, and location of transition zone identified at surgery.
- Management characteristics: Formation of a stoma prior to definitive surgery, weight at stoma formation, staged definitive procedure, weight at definitive

procedure, rectal dissection technique used, and approach to the pull-through procedure used.

The following outcomes were also described for infants in the participating and non-participating sites who had survived to one year post-diagnosis, had undergone definitive surgery, and had one year data returned for the BAPS-CASS study.

- Revision surgery within a year of diagnosis, formation of a stoma post-pull-through within a year of diagnosis, post-operative enterocolitis within a year of diagnosis, one or more unplanned operation within a year of diagnosis, and total number of unplanned operations within a year of diagnosis.

5.4.2. Completeness of follow-up

Infant characteristics, management characteristics, and early outcomes were described for children treated in the participating sites with and without return of parent and/or clinician data collection forms. The denominator for calculating percentage of parent questionnaires returned was the number of infants who were known to be alive at the time contact was first attempted with the parents. As per the comparison between participating and non-participating hospitals, early outcomes were only compared for infants who had undergone definitive surgery, who had survived to one year post-diagnosis, and for whom one-year outcomes data had been returned to the BAPS-CASS study.

5.4.3. Core outcomes at five to seven years of age

5.4.3.1. Data description

Counts and proportions, means and 95% confidence intervals, medians and interquartile ranges, and event rates and 95% confidence intervals were used as appropriate to describe the ten outcomes of interest. Outcomes were described in the population as a whole and in two sub-groups of infants, those with short segment HD, and those with either long-segment or total colonic HD.

5.4.3.2. Unplanned reoperation

Counts and proportions of children who had undergone none, one, two, three and four or more unplanned reoperations between the time of their definitive operation and five to seven years of age were described. A multiple events Cox proportional hazards model was used to calculate rates of unplanned reoperation per person-year follow-up, and to graphically represent the Kaplan-Meier survival function for undergoing an unplanned reoperation. Children were censored at the point of death or loss to follow-up, whichever occurred first.

5.4.3.3. Quality of life

A PedsQL total scale score, and a PedsQL psychosocial health summary score were calculated for each infant. Scale and summary scores were calculated as the sum of the items divided by the number of items answered, and were only calculated for infants where 50% or more of the questions in the scale had been answered. The mean (SD) total scale score was calculated, and compared using an unpaired t-test to the mean parent proxy-

reported total scale score for an established reference population(154). The mean (SD) psychosocial health summary score was also calculated and compared to the mean parent proxy-reported psychosocial health summary score for an established reference population(154). The number and proportion of infants with reduced health related quality of life, and reduced psychosocial health related quality of life, defined as more than one standard deviation below the mean for the appropriate scale, were calculated and described.

5.4.3.4. Paediatric incontinence and constipation score

Medians and interquartile ranges for the incontinence and constipation scores derived from the PICS were described. The counts and proportions of infants with constipation or impaired continence, as evidenced by a score of less than the age specific lower 95% confidence limit on the appropriate score were also described. For children aged five to seven, these lower 95% confidence levels were 23.2 on the incontinence score and 20.1 on the constipation score(153).

5.4.4. Association of patient and management factors with outcome

5.4.4.1. Univariable analysis

Multiple event univariable Cox proportional hazards models, with censoring of children at the point of death or loss to follow-up were used to investigate the association of key patient factors with unplanned reoperation. The following patient factors were investigated: ethnicity, gestational age at birth, birthweight, sex, family history of HD, age at presentation, age at diagnosis, associated anomaly or syndrome, pre-operative enterocolitis

and site of transition zone. The proportional hazards assumption for each variable was assessed using log-log plots of survival, and estimation of Schoenfeld residuals, based upon a model without calculation of robust standard errors. Associations of each patient factor with unplanned reoperation were then remodelled including a time-varying covariate if appropriate, and with robust standard errors calculated in order to account for the clustered nature of the data. Variables that were shown to have a statistically significant association with unplanned reoperation, as evidenced by a p-value of <0.1 were subsequently assessed for inclusion in the multi-variable model.

5.4.4.2. Multivariable model development

Patient characteristics were added into the multivariable model in a forward stepwise manner in order of statistical significance. Proportional hazards assumptions were assessed following addition of each variable, and time varying covariates included if necessary. Each subsequent multivariable model was then re-assessed including calculation of robust standard errors, and those variables that were shown to significantly improve the fit of the model as evidenced by a p-value of <0.05 on Wald testing were retained in the model. Following development of the final model, proportional hazards assumptions were reassessed and time-varying covariates included as required.

5.4.4.3. Operative factors

Operative factors that potentially confounded the relationship between rectal dissection technique and unplanned reoperation were identified through use of a Directed Acyclic Graph (DAG) (155).

DAGs are graphical models that represent the hypothetical causal processes that result in development of a set of variables of interest. They are frequently utilised to demonstrate the pathways that link an exposure, multiple potentially confounding variables and an outcome of interest. Variables are linked to one another via arrows, with an arrow directed from X → Y suggesting that X plays a role in the development of Y. By analysing the relationships between variables of interest, it is possible to identify factors that lie on biasing pathways between an exposure of interest and an outcome of interest. These variables represent the sufficient adjustment set, i.e. the set of variables which should be adjusted for or which participants should be matched on, in order to most accurately estimate the effect of the exposure of interest on the outcome of interest.

It was hypothesised that there would be more confounding factors identified through use of the DAG than it would be feasible to adjust for given the size of the available dataset. Therefore, identified confounding factors were prioritised for adjustment by investigating the strength of their relationship with unplanned reoperation using a univariable, multiple event Cox proportional hazards model in the same population of infants as used in section 5.4.4.2 Those operative factors that were shown to have a statistically significant relationship with unplanned re-operation, as evidenced by a p-value of <0.1 on univariable analysis were added to the multi-variable model developed in 5.4.4.2 in a forward stepwise manner in order of statistical significance. Those factors that improved the fit of the model as evidenced by a p-value of <0.05 on Wald testing were retained in the model. Continuous variables were mean centred prior to univariable analysis. Investigation of the proportional hazards assumption and adjustment for clustering were handled as in 5.4.4.1 and 5.4.4.2.

5.4.5. Comparison of pull-through procedures

Characteristics of infants who underwent the Soave procedure, the Swenson procedure, and the Duhamel procedure were described using counts and proportions for categorical variables, and medians and inter-quartile ranges or means and standard deviations as appropriate for continuous variables. The Chi^2 test for significance, Wilcoxon-Rank-Sum test and Student's t-test were used as appropriate to compare characteristics between the three groups.

Due to the limited size of the available dataset, the most statistically economical way to adjust for differences in patient characteristics between children who had undergone different rectal dissection techniques was to adjust for a child's probability of having been allocated to each of the different techniques utilised, as opposed to adjusting for a series of confounding patient characteristics. Therefore, propensity scores predicting an infant's likelihood of allocation to the Soave, the Swenson or the Duhamel rectal dissection techniques were calculated using multinomial multivariable logistic regression. The infant characteristics used to develop the propensity scores were ethnicity, gestational age at birth, birthweight, sex, family history of HD, age at presentation, age at diagnosis, associated anomaly or syndrome, pre-operative enterocolitis and the site of transition zone.

A multiple-event Cox proportional hazards model was used to investigate the association between method of rectal dissection and unplanned reoperations. An unadjusted hazard ratio (HR), as well as an HR adjusted for the child's propensity score and the operative factors identified as confounders on the DAG and shown to have a statistically significant association with unplanned reoperation, were calculated. Logistic regression analysis was

used to investigate the association between method of rectal dissection and binary outcomes, again with unadjusted ORs, and ORs adjusted for propensity score and operative confounders calculated. Due to the high proportion of missing data, no comparison was made between groups for quality of life or PICS scores. Due to the low number of children who underwent the Swenson procedure and who had five to seven year follow-up data collected, statistical comparison was only made between this group and the other rectal dissection techniques for the primary outcome, unplanned reoperation.

5.4.6. Changes to pre-specified protocol

5.4.6.1. Comparison of interventions

When the work presented in this chapter was originally conceived, it was anticipated that the primary clinical question that clinicians would want addressing would be whether there were differences in outcome between the open, laparoscopic, and trans-anal approaches to the pull-through procedure. However, following wider consultation with the UKPCG, it became apparent that the majority of surgeons base their treatment decisions around which rectal dissection technique they feel is most appropriate, and then determine the approach to the pull-through secondarily to the rectal dissection technique. The majority of surgeons therefore expressed the preference that the primary comparison for the study was between rectal dissection techniques as opposed to between approaches to the pull-through. The analysis strategy was therefore revised to make this the primary comparison.

5.4.6.2. Selection of primary outcome

Non-participation of eight sites meant that the population of infants available for analysis was smaller than anticipated, and therefore the study would likely be under-powered to detect associations between the proposed primary outcome of faecal incontinence, and key patient and management factors. In order to maximise the power of the study to detect clinically meaningful differences in outcome with statistical significance, the association of patient and management factors with outcome was investigated based on one of the proposed secondary outcomes, unplanned reoperation, as opposed to the proposed primary outcome, faecal incontinence. Faecal incontinence was still investigated as one of the secondary outcomes when comparing rectal dissection techniques, and a sensitivity analysis was conducted whereby the multivariable model describing the association of key patient factors with outcome was developed using faecal incontinence as the outcome of interest instead of unplanned reoperation.

5.5. Results

5.5.1. Participating and non-participating sites

Of the 28 British and Irish paediatric surgical centres, there were two Irish centres (7%), one Welsh centre (4%), and five English centres (18%) who did not participate in the NETS^{2HD} study. Reasons for non-participation were varied. Hull Royal Infirmary, King's College Hospital, Queen's Medical Centre, and the Royal London Hospital did not manage to find staff with sufficient time to collect the data, and the Royal Victoria Infirmary and the University Hospital of Wales were unable to identify appropriate Principal Investigators. The Children's University Hospital (Crumlin), and Our Lady's Hospital for Sick Children (Dublin) were not covered by national research ethics committee approvals, and local approvals were only obtained in August 2018, nearly two years after beginning the process.

Fifty-three (17%) of the 305 infants in the original BAPS-CASS cohort were treated in one of the non-participating sites, 39 (74%) of whom had one year BAPS-CASS data collected. There were therefore 252 children (83%) from the original BAPS-CASS cohort who were treated in a participating site, and 221 (91%) of these had one-year BAPS-CASS data returned. Children from non-participating sites were more likely to have been treated in a low-volume HD centre, were more likely to have a family history of HD, more likely to have undergone a combined laparoscopic and trans-anal procedure, and more likely to have undergone a Swenson procedure than those children treated in a participating site (Table 28). Despite the differences in management strategy and family history of HD between infants treated in participating and non-participating sites, for those infants who had undergone definitive surgery within a year of diagnosis, and for whom one year BAPS-CASS data had been

returned, there were no differences in early outcomes (Table 29). However, the low number of infants in non-participating sites may have affected detection of differences as statistically significant.

Table 28: Characteristics and management of infants treated in participating and non-participating sites

	Non-participating sites	Participating sites	
	N=53	N=252	
	n(%)*	n(%)*	p-value
Diagnosed in a low volume centre (< national median number of cases/year)			<0.001
No	0 (0.0%)	141 (56.0%)	
Yes	53 (100.0%)	111 (44.0%)	
Ethnicity			0.68
White	44 (84.6%)	216 (86.7%)	
BME	8 (15.4%)	33 (13.3%)	
Gestational age at birth			0.1
Term	49 (94.2%)	215 (86.0%)	
Pre-term	3 (5.8%)	35 (14.0%)	
Birthweight			0.06
2500g or more	49 (96.1%)	211 (86.8%)	
Less than 2500g	2 (3.9%)	32 (13.2%)	
Sex			0.46
Male	38 (73.1%)	196 (77.8%)	
Female	14 (26.9%)	56 (22.2%)	
Family history of HD			<0.001
No	41 (78.8%)	234 (94.0%)	
Yes	11 (21.2%)	15 (6.0%)	
Associated anomaly			0.063
Isolated HD	47 (88.7%)	184 (73.6%)	
Syndromic	4 (7.5%)	47 (18.8%)	
Isolated additional anomaly	2 (3.8%)	19 (7.6%)	
Age at presentation			0.94
1-7 days	47 (88.7%)	219 (86.9%)	
8-28 days	2 (3.8%)	11 (4.4%)	
More than 28 days	4 (7.5%)	22 (8.7%)	

* Percentage of those with complete data

Table 28: Characteristics and management of infants treated in participating and non-participating sites - Continued

	Non-participating sites	Participating sites	
	N=53	N=252	
	n(%)*	n(%)*	p-value
Age at diagnosis			0.82
<31 days	47 (88.7%)	213 (85.2%)	
31-60 days	2 (3.8%)	10 (4.0%)	
61-90 days	3 (5.7%)	13 (5.2%)	
91-120 days	1 (1.9%)	4 (1.6%)	
121-150 days	0 (0.0%)	2 (0.8%)	
>150 days	0 (0.0%)	8 (3.2%)	
Transition zone (as defined at surgery)			0.35
Rectosigmoid	31 (67.4%)	168 (74.3%)	
Long segment (proximal to sigmoid colon)	11 (23.9%)	49 (21.7%)	
Total colonic aganglionosis	4 (8.7%)	9 (4.0%)	
Stoma created prior to pull-through			0.18
No	38 (71.7%)	156 (61.9%)	
Yes	15 (28.3%)	96 (38.1%)	
Definitive surgery prior to one year			1
No	4 (7.8%)	19 (7.9%)	
Yes	47 (92.2%)	223 (92.1%)	
Staged definitive procedure	**n(%)**	**n(%)**	0.14
No	38 (77.6%)	153 (66.8%)	
Yes	11 (22.4%)	76 (33.2%)	
First approach to the pull-through			0.032
Definitive surgery not performed prior to one year	2 (4.0%)	13 (5.4%)	
Open	18 (36.0%)	91 (37.8%)	
Laparoscopic	9 (18.0%)	41 (17.0%)	
Trans-anal	3 (6.0%)	50 (20.7%)	
Combined laparoscopic and trans-anal	18 (36.0%)	46 (19.1%)	
Rectal dissection technique			0.008
Submucosal (Soave)	29 (60.4%)	119 (52.4%)	
Peri-rectal (Swenson)	9 (18.8%)	17 (7.5%)	
Posterior (Duhamel)	10 (20.8%)	91 (40.1%)	
	Median (IQR)	**Median (IQR)**	
Weight at stoma formation			0.23
Grams	3800 (3340, 4200)	3500 (3000, 4000)	
Weight at definitive surgery			0.052
Kilograms	6.12 (5.2, 6.92)	5.43 (4.21, 6.55)	

* Percentage of those with complete data

Table 29: Outcomes for infants who underwent definitive surgery in participating and non-participating sites

	Non-participating site	Participating site	
	N=36	N=202	
	n(%)*	n(%)*	p-value
Revision surgery within a year of diagnosis			0.42
No	30 (100.0%)	187 (97.9%)	
Yes	0 (0.0%)	4 (2.1%)	
Post pull-through stoma within a year of diagnosis			0.11
No	25 (80.6%)	160 (90.4%)	
Yes	6 (19.4%)	17 (9.6%)	
Post-operative HAE suspected			0.70
No	25 (71.4%)	137 (68.2%)	
Yes	10 (28.6%)	64 (31.8%)	
One or more unplanned reoperation within a year of diagnosis			0.72
No	31 (88.6%)	164 (86.3%)	
Yes	4 (11.4%)	26 (13.7%)	
Total number of unplanned operations within a year of diagnosis			0.81
None	31 (88.6%)	164 (86.3%)	
One	3 (8.6%)	14 (7.4%)	
Two	1 (2.9%)	8 (4.2%)	
Three	0 (0.0%)	4 (2.1%)	

*Percentage of those with complete data

5.5.2. Loss to follow-up

Of the 252 children in participating NETS^{2HD} sites, clinician questionnaires were completed between five and seven years of age for 185 (73%). Twelve (5%) of the children treated in these sites were known to have died prior to five years of age, and there were therefore 240 (95%) who were eligible for participation in the parent reported outcomes arm of the study. Contact details were obtained for parents of 186 of these children (78%), 107 of whom (58%) returned completed consent forms. Eighty-one parents (76% of those who consented to participate) returned a completed study questionnaire. There were 67 children (28% of those eligible) who had ***both*** clinician and parent reported outcomes questionnaires returned between five and seven years of age, and 199 (79% of those eligible) who had ***either*** clinician or parent reported outcomes questionnaires returned between five and seven years of age (Figure 14).

Of the 187 children who survived to five years of age and had outcomes data returned, the child's age at completion of the questionnaire was known for 185 (99%), and for these 185, the median (IQR) age at completion of data collection forms was six years and seven months (six years and one month to seven years and two months). The youngest child who had a questionnaire completed was aged five years and six months, and the oldest was seven years and nine months.

Children from the participating sites who did not have either a clinician or parent questionnaire returned between five and seven years of age were more likely to be from a BME background, more likely to be male, and less likely to have undergone the Swenson procedure than infants who had at least one questionnaire returned (Table 30). The pattern

of differences in characteristics between those children with and without ***clinician*** follow-up was the same as for those with and without ***any*** follow-up (Appendix 26), except that those without clinician follow-up were additionally less likely to have been diagnosed in a low-volume paediatric surgical centre, and more likely to have undergone an open or combined laparoscopic/trans-anal pull-through than those without clinician follow-up. The only differences between children without parent follow-up and children with parent follow-up, was that those without follow-up were more likely to have been diagnosed in a low-volume centre, more likely to have undergone definitive surgery prior to one year of age, more likely to have undergone a trans-anal pull-through, and less likely to have undergone a laparoscopic pull-through (Appendix 27).

Figure 14: Data return for the NETS^{2HD} study

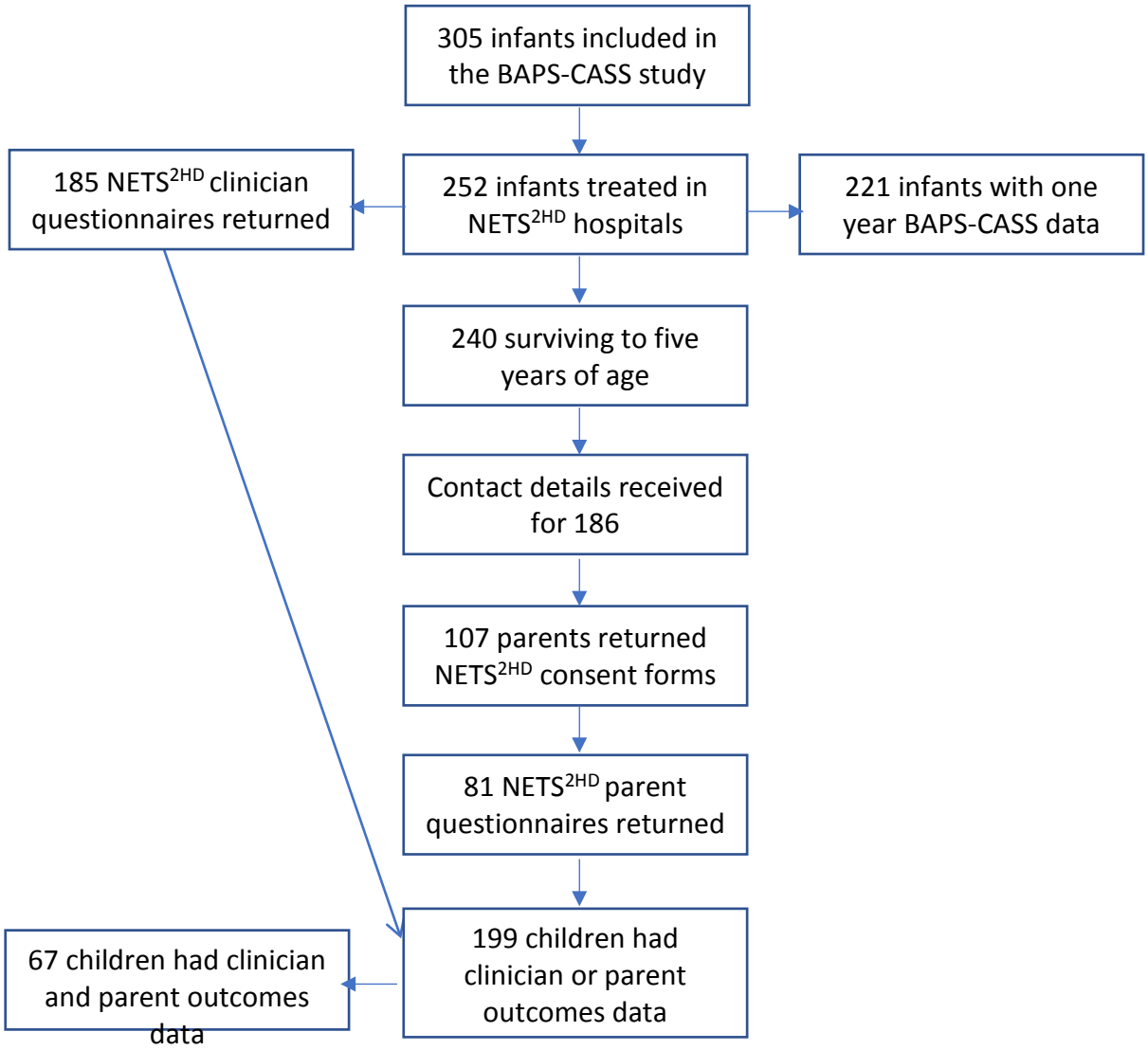


Table 30: Characteristics and management of infants treated in participating sites with and without five to seven year data

	No data returned	Data returned	
	N=53	N=199	
	n(%)*	n(%)*	p-value
Diagnosed in a low volume (< median) centre			0.26
No	27 (50.9%)	84 (42.2%)	
Yes	26 (49.1%)	115 (57.8%)	
Ethnicity			0.023
White	41 (77.4%)	175 (89.3%)	
BME	12 (22.6%)	21 (10.7%)	
Gestational age at birth			0.44
Term	43 (82.7%)	172 (86.9%)	
Pre-term	9 (17.3%)	26 (13.1%)	
Birthweight			0.78
2500g or more	44 (88.0%)	167 (86.5%)	
Less than 2500g	6 (12.0%)	26 (13.5%)	
Sex			0.032
Male	47 (88.7%)	149 (74.9%)	
Female	6 (11.3%)	50 (25.1%)	
Family history of HD			0.46
No	50 (96.2%)	184 (93.4%)	
Yes	2 (3.8%)	13 (6.6%)	
Associated anomaly			0.74
Isolated HD	39 (75.0%)	145 (73.2%)	
Syndromic	10 (19.2%)	37 (18.7%)	
Isolated additional anomaly	3 (5.8%)	16 (8.1%)	
Age at presentation (days)			0.74
1-7 days	45 (84.9%)	174 (87.4%)	
8-28 days	2 (3.8%)	9 (4.5%)	
More than 28 days	6 (11.3%)	16 (8.0%)	
Age at diagnosis			0.59
<31 days	42 (79.2%)	171 (86.8%)	
31-60 days	2 (3.8%)	8 (4.1%)	
61-90 days	5 (9.4%)	8 (4.1%)	
91-120 days	1 (1.9%)	3 (1.5%)	
121-150 days	1 (1.9%)	1 (0.5%)	
>150 days	2 (3.8%)	6 (3.0%)	
Transition zone (as defined at surgery)			1.0
Rectosigmoid	37 (74.0%)	131 (74.4%)	
Long segment (proximal to sigmoid colon)	11 (22.0%)	38 (21.6%)	
Total colonic aganglionosis	2 (4.0%)	7 (4.0%)	

* Percentage of those with complete data
BME – Black or minority ethnicity

Table 30: Characteristics and management of infants treated in participating sites with and without five to seven year data - Continued

	No data returned	Data returned	
	N=53	N=199	
	n(%)*	n(%)*	p-value
Stoma created prior to pull-through			0.18
No	37 (69.8%)	119 (59.8%)	
Yes	16 (30.2%)	80 (40.2%)	
Definitive surgery confirmed as occurring prior to one year of age			0.53
No	3 (5.8%)	16 (8.4%)	
Yes	49 (94.2%)	174 (91.6%)	
Staged definitive procedure			0.22
No	37 (74.0%)	116 (64.8%)	
Yes	13 (26.0%)	63 (35.2%)	
First approach to the pull-through			0.052
Definitive surgery not performed prior to one year	2 (3.8%)	11 (5.8%)	
Open	25 (48.1%)	66 (34.9%)	
Laparoscopic	4 (7.7%)	37 (19.6%)	
Trans-anal	7 (13.5%)	43 (22.8%)	
Combined laparoscopic and trans-anal	14 (26.9%)	32 (16.9%)	
Rectal dissection technique			0.004
Submucosal (Soave)	21 (42.0%)	98 (55.4%)	
Peri-rectal (Swenson)	0 (0.0%)	17 (9.6%)	
Posterior (Duhamel)	29 (58.0%)	62 (35.0%)	
	Median (IQR)	Median (IQR)	
Weight at stoma formation			0.069
Grams	4000 (3300-4700)	3400 (2980-3950)	
Weight at definitive surgery			0.68
Kilograms	5.5 (4.5-6.91)	5.4 (4.2-6.45)	

*Percentage of those with complete data

Of the 199 infants treated in a participating hospital who had either clinician or parent reported outcome data returned between five and seven years of age, 172 (86%) also had one-year BAPS-CASS data returned, and of those, 156 (91%) had undergone definitive surgery within a year of diagnosis. For the 53 infants treated in a participating hospital who had neither parent nor clinician reported outcomes data returned between five and seven years of age, 49 (92%) also had one-year BAPS-CASS data returned, and of those, 46 (94%) had undergone definitive surgery within a year of diagnosis. Within this group of 202 infants who had undergone definitive surgery within a year of diagnosis, and who had one year BAPS-CASS data returned, there were no differences in early outcomes between children with ***any*** five to seven year data returned, and children with ***no*** five to seven year data returned (Table 31). Similarly, there were no differences in outcomes between children with and without clinician follow-up, and children with and without parent follow-up (appendices 26 to 29).

Table 31: Outcomes at one year post diagnosis for children with and without five to seven year data returned

	No data returned	Data returned	
	N=46	N=156	
	n(%)*	n(%)*	p-value
Revision surgery within a year of diagnosis			0.95
No	44 (97.8%)	143 (97.9%)	
Yes	1 (2.2%)	3 (2.1%)	
Post pull-through stoma within a year of diagnosis			0.68
No	31 (88.6%)	129 (90.8%)	
Yes	4 (11.4%)	13 (9.2%)	
Post-operative HAE suspected			0.82
No	32 (69.6%)	105 (67.7%)	
Yes	14 (30.4%)	50 (32.3%)	
One or more unplanned reoperation within a year of diagnosis			0.16
No	36 (80.0%)	128 (88.3%)	
Yes	9 (20.0%)	17 (11.7%)	

* Percentage of those with complete data

5.5.3. Sub-populations for reporting outcomes

Data relating to the children whose outcomes are described in this chapter were collected using the BAPS-CASS birth form, the BAPS-CASS one year form, the NETS^{2HD} five to seven year parent form, and the NETS^{2HD} five to seven year clinician form. Not all children whose data are used in the analysis described in this chapter had data returned for all four data collection forms. The numbers of children on which each analysis was conducted therefore varied. The data sources utilised in each analysis and the sizes of the resulting populations are described below, and all results are presented grouped according to the population in which the analysis was undertaken.

5.5.3.1. Bowel and bladder function related outcomes

Data relating to faecal incontinence, urinary incontinence, HAE, presence of a permanent stoma, and voluntary bowel movements without need for enemas or rectal or colonic washouts, were collected using both the NETS^{2HD} five to seven year clinician data collection form and the NETS^{2HD} five to seven year parent data collection form. The first four of these outcomes are therefore described in the population of 187 children who were alive at five years of age and had either NETS^{2HD} five to seven year data collection form returned. Voluntary bowel movements is described in the population of 160 children who were alive at five years of age, had either NETS^{2HD} five to seven year data collection form returned, and who did not have a stoma at the time of completion of the data collection form.

5.5.3.2. Unplanned reoperations survival analyses

All survival analyses were conducted in the population of 256 children who had undergone their definitive surgical operation, had at least one day of post-operative follow-up, and

were not missing data relating to the outcome unplanned reoperation. Where multivariable survival analyses were conducted, complete case analyses were used, and therefore the population of children was restricted to those who had data returned for all variables utilised in the analysis.

5.5.3.3. Numbers of unplanned reoperations in the first five to seven years of life

Describing the number of unplanned reoperations experienced by a child in the first five to seven years of life required return of data from the NETS^{2HD} five to seven year clinician data collection form. Therefore, numbers of unplanned reoperations are described in the cohort of 164 children who had undergone definitive surgery, were alive at five years of age, and had a NETS^{2HD} five to seven year clinician data collection form returned.

5.5.3.4. Mortality

Five-year mortality can be determined from both NETS^{2HD} five to seven year data collection forms, and is therefore described in the cohort of 199 children who had either form returned. Minimum and maximum estimates of mortality are also described for the population of 305 children whose data were used in the original BAPS-CASS study.

5.5.3.5. Quality of life, psychological stress and objective score of bowel function

Quality of life, psychological stress and the PICS data were only collected using the NETS^{2HD} five to seven year parent form. Quality of life and psychological stress are therefore described in the population of 81 children who had a NETS^{2HD} five to seven year parent data collection form returned, and the PICS is described in the 70 children who had a NETS^{2HD} five

to seven year data collection form returned and who did not have a stoma at time of completion of the form.

5.5.4. Outcomes of the 199 children with either NETS^{2HD} form returned

5.5.4.1. Mortality

Eight infants (4%) died prior to one year of age and a further four infants (2%) died between one and five years of age, giving an overall case-fatality for those children with complete follow-up of 6% (95% CI 3% - 10%) (Table 32). Based on the proportion of children who were known to have died between one year of age and five years of age, it would be anticipated that two of the 106 children who were lost to follow-up would also have died between one year of age and five years of age. In the entire cohort of 305 children, the maximum estimate for the five-year case fatality is therefore 5% (95% CI 3% - 8%) and the minimum estimate for the five-year case fatality is 4% (95% CI 2% - 7%), assuming none of the children lost to follow-up died.

Table 32: Outcomes for the 199 children with either NETS^{2HD} form returned

	n(%)*
Death prior to five years of age	**N=199**
No	187 (94%)
Yes	12 (6%)
Cause of death	**N=12**
Direct result of the diagnosis or treatment of HD	2 (17%)
HAE	0 (0%)
Associated Anomaly	6 (50%)
Other causes	3 (25%)
Unknown	1 (8%)

5.5.5. Outcomes of the 187 surviving children with either NETS^{2HD} form returned

Of the 187 children who were known to have survived to five years of age, 25 (13%) had a stoma, nine of which (36%) were formed without the intention of later reversal (Table 33). Two (22%) of the nine permanent stomas were formed because the child had total intestinal aganglionosis, two (22%) were formed in children with developmental delay in whom the pull-through had been unsuccessful, two (22%) were formed in preference to performing a pull-through, two (22%) were formed to aid continence management, and the indication for stoma formation was unknown for one child (11%).

At five to seven years of age, 112 children (61%) were incontinent of faeces. Five (20%) of the 25 children who had a stoma had faecal incontinence despite the presence of the stoma. The severity of faecal incontinence was reported as occurring once or twice per week for 43 children (38%), every day but without social problems for 31 children (28%), and constantly and causing social problems for 26 children (23%). The severity of faecal incontinence was unknown for 12 children (11%). In the cohort of 143 children with isolated HD, i.e. those without an additional congenital anomaly or known syndrome, 88 (62%) were incontinent of faeces at five to seven years of age.

Table 33: Outcomes of the 187 surviving children with either NETS[2HD] form returned

	n (%)*
	N=187
Any stoma	
No	162 (87%)
Yes	25 (13%)
Permanent stoma	
No	177 (95%)
Yes	9 (5%)
Faecal incontinence	
No	73 (39%)
Yes	112 (61%)
At least one episode of HAE	
No	98 (52%)
Yes	89 (48%)
Urinary incontinence	
No	166 (89%)
Yes	20 (11%)
	N=162[#]
Voluntary bowel movements without enemas or rectal or colonic washouts	
Yes	130 (81%)
No	30 (19%)

*Percentage of those with complete data

[#] Described in those children without a stoma

Twenty children (11%) were not continent of urine at five to seven years of age, and 89 (48%) had experienced at least one episode of HAE between the time of diagnosis and five to seven years of age (Table 33). Seven children (4%) experienced one episode, and four children (2%) experienced two or more episodes of HAE in the 12 months prior to completion of the study questionnaire. The remaining 176 children (94%) experienced no episodes of HAE in the 12 months preceding completion of the study questionnaire.

Eighty-seven (54%) of the 162 children without a stoma at five to seven years of age maintained voluntary bowel movements without any assistance, 43 (27%) required laxatives, 13 (8%) required regular enemas, 15 (9%) required rectal irrigation, two (1%) had an Antegrade Continence Enema (ACE), and for two (1%) it was unknown whether they required assistance to open their bowels.

5.5.5.1. Outcomes of the 164 surviving children who had undergone definitive surgery and had a NETS^{2HD} clinician form returned

Unplanned reoperations are shown in Table 34. Examples of minor unplanned reoperations included examination of the anorectum under anaesthesia, incision and drainage of peri-anal abscesses, and Botox injections to the anal sphincter. Examples of intermediate unplanned reoperations included repair of incisional hernias and formation of an antegrade continence enema (ACE), and examples of major unplanned reoperations included intestinal resections and stoma formation.

Table 34: Outcomes of the 164 surviving children who had undergone definitive surgery and had a NETS^{2HD} clinician form returned

	n (% of children)
	N=164 children
Number of unplanned reoperations	
None	92 (57%)
One	27 (16%)
Two	15 (9%)
Three	7 (4%)
Four or more	23 (14%)
	n (% of unplanned reoperations)*
	N=255 operations
Type of unplanned reoperation	
Minor	156 (61%)
Intermediate	34 (13%)
Major/complex	65 (25%)

*Percentage of those with complete data

5.5.5.2. Outcomes of the 81 children with a NETS^{2HD} parent form returned

PedsQL total scale scores were calculable for 74 children (91%), and psychosocial health summary scores for 72 (89%). The mean (95% CI) total scale score was 68.3 (63.5-73.1), and the mean psychosocial health summary score was 67.8 (62.9-72.7). These were statistically significantly lower ($p<0.001$) than the mean (SD) total scale score of 78.02 (16.44), and mean (SD) psychosocial health summary score of 81.24 (15.34) derived from the reference populations described by Varni et al (154). There were 36 children (49%) whose total scale score, and 30 (42%) whose psychosocial health summary score was more than one standard deviation below the reference population means(154) (Table 35).

Fully completed PICS data were returned for 41 (59%) of the 70 children who had a NETS^{2HD} five to seven year data collection form returned and who did not have a stoma at the time of completion of the form. The median (IQR) incontinence score for these children was 19.5 (15.5 – 22.5), and the median (IQR) constipation score was 16 (11-21.5). There were 31 children (76%) who met criteria for impaired continence, and 28 (68%) who met criteria for evidence of constipation (Table 35).

Table 35: Outcomes of the 81 children with a NETS^{2HD} parent form returned

	N=81
Quality of Life	
Normal quality of life, n(%)*	38 (51%)
Reduced quality of life, n(%)*	36 (49%)
PedsQL total scale score, mean (95% CI)	68.3 (63.5-73.1)
Psychological stress	
Normal psychosocial quality of life, n(%)*	42 (58%)
Reduced psychosocial quality of life, n(%)*	30 (42%)
Psychosocial health summary score, mean (95% CI)	81.24 (15.34)
	N=70$^{\#}$
PICS	
Normal continence, n(%)*	10 (24%)
Impaired continence, n(%)*	31 (76%)
Incontinence score, median (IQR)	19.5 (15.5 – 22.5)
No constipation, n(%)*	13 (32%)
Constipation, n(%)*	28 (68%)
Constipation score, median (IQR)	16 (11-21.5)

*Percentage of those with returned data

$^{\#}$Described in those children without a stoma

PICS – Paediatric Incontinence and Constipation Score

5.5.5.3. Differences between parent and clinician reporting of faecal incontinence

For the 67 children who had a NETS^{2HD} five to seven year clinician form returned in addition to the NETS^{2HD} five to seven year parent form, there were eight (12%) where the parents did not want to say whether their child had achieved faecal continence. For the remaining children, differences between parent and clinician reporting of faecal incontinence are shown in Table 36.

5.5.5.4. Short segment versus long segment disease

There were 131 children with short-segment HD (66%) and 45 with long-segment or total colonic HD (26%) who had either NETS^{2HD} five to seven year form returned. Histological confirmation of the transition zone is only possible for children who have undergone definitive surgery, and therefore the outcomes described only relate to those children who had undergone definitive surgery.

Three children (2%) with short segment disease died after definitive surgery but prior to five years of age, one as a direct result of the diagnosis or treatment of their HD, and two as a result of other causes. No children with long-segment HD died after surgery and prior to five years of age. All other outcomes are described in Tables 37 and 38.

Table 36: Differences in clinician and parent reporting of faecal continence

	Parent reported child as continent of faeces	Parent reported child as incontinent of faeces
	N=7	**N=52**
	n(%)	**n(%)**
Clinician reported child as continent of faeces	7 (100%)	28 (54%)
Clinician reported child as incontinent of faeces	0 (0%)	24 (46%)

Table 37: Outcomes of the 173 surviving children who had a histologically confirmed transition zone and either NETS^{2HD} form returned

	Short segment	Long segment or total colonic
	N=128	**N=45**
Unplanned reoperation	**n(%)***	**n(%)***
None	74 (63%)	16 (37%)
One	18 (15%)	9 (21%)
Two	11 (9%)	4 (9%)
Three	3 (3%)	4 (9%)
Four or more	12 (10%)	10 (23%)
Stoma		
No	115 (91%)	38 (84%)
Yes	12 (9%)	7(16%)
Permanent Stoma		
No	124 (98%)	44 (98%)
Yes	3 (2%)	1(2%)
Faecal incontinence		
No	51 (40%)	14 (31%)
Yes	76 (60%)	31 (69%)
At least one episode of HAE		
No	71 (55%)	20 (44%)
Yes	57 (45%)	25 (56%)
Urinary incontinence		
No	115 (91%)	41 (91%)
Yes	12 (9%)	4 (9%)
Voluntary bowel movements without enemas or rectal or colonic washouts		
Yes	96 (84%)	27 (71%)
No	18 (16%)	11 (29%)

*Percentage of those with complete data

Described in those children without a stoma

Table 38: Outcomes of the 72 children who had a histologically confirmed transition zone and a NETS^{2HD} parent form returned

	Short segment	Long segment or total colonic
	N=51	**N=21**
Quality of Life		
Normal quality of life, n(%)*	23 (51%)	11 (55%)
Reduced quality of life, n(%)*	22 (49%)	9 (45%)
PedsQL total scale score, mean (95% CI)	69.9 (64.0-75.7)	67.5(56.0-79.0)
Psychological stress		
Normal psychosocial quality of life, n(%)*	26 (60%)	11 (55%)
Reduced psychosocial quality of life, n(%)*	17 (40%)	9 (45%)
Psychosocial health summary score, mean (95% CI)	69.9 (64.0-75.7)	66.2 (55.0-77.3)
	N=46$^{\#}$	**N=19$^{\#}$**
PICS		
Normal continence, n(%)*	8 (28%)	1 (13%)
Impaired continence, n(%)*	21 (72%)	7 (88%)
Incontinence score, median (IQR)	19.5 (15.5-23.5)	20.5 (18-22.25)
No constipation, n(%)*	10 (33%)	3 (43%)
Constipation, n(%)*	20 (67%)	4 (57%)
Constipation score, median (IQR)	16.25 (12.5-21.5)	18.5 (9-23.5)

*Percentage of those with returned data
$^{\#}$Described in those children without a stoma
PICS – Paediatric Incontinence and Constipation Score

5.5.6. Infant characteristics associated with outcome

There were 256 children in the original BAPS-CASS cohort who underwent definitive surgery and had at least one day of post-operative follow-up. Seven characteristics: sex, ethnicity, birthweight, presence of an associated anomaly, age at presentation, age at diagnosis, and anatomical location of the transition zone met criteria for assessment in the multivariable model with unplanned reoperation as the outcome. Four of these factors: sex, ethnicity, age at diagnosis, and anatomical location of the transition zone were retained in the multivariable model along with a time varying covariate for age at diagnosis. Adjusted HRs were calculated based upon a complete case analysis of the 247 children with data returned for each variable included in the final model. These children experienced 272 unplanned reoperations over 964.9 person-years of follow-up. Following adjustment for covariates retained in the final model, black or minority ethnicity, female sex, and presentation after 28 days of age were all associated with a statistically significantly reduced risk of an unplanned reoperation, HRs respectively of 0.20 (95% CI 0.09-0.41, p<0.001), 0.30 (95% CI 0.17-0.54, p<0.001) and 0.38 (95% CI 0.15-0.95, p=0.039). Total colonic aganglionosis was associated with a statistically significantly increased risk of unplanned reoperation, HR 4.93 (95% CI 2.26 10.76, p<0.001) (Table 39 and Figures 15-18).

In the sensitivity analysis investigating the association of patient factors with faecal incontinence, no statistically significant associations were identified on univariable analysis, and therefore no multivariable model was developed (Appendix 30).

Table 39: Infant characteristics associated with unplanned reoperations

	Number of re-operations	Person years	Operations per person year (95% CI)	Unadjusted Hazard ratio (95% CI)	p-value	Adjusted Hazard ratio (95% CI)	p-value
Ethnicity							
White	263	880.4	0.3 (0.26-0.34)	Ref.	Ref.	Ref.	Ref.
BME	13	101.8	0.13 (0.07-0.22)	0.40 (0.17-0.95)	0.038	0.20 (0.09-0.41)	<0.001
Gestational age at birth							
Term	256	892.4	0.29 (0.25-0.32)	Ref.	Ref.	Not retained	
Pre-term	20	102.7	0.19 (0.13-0.30)	1.08 (0.96-1.23)	0.21		
Birthweight							
2500g or more	262	880.2	0.30 (0.26-0.34)	Ref.	Ref.	Not retained	
Less than 2500g	11	97.9	0.11 (0.06-0.20)	0.38 (0.15-0.99)	0.047		
Sex							
Male	253	764.3	0.33 (0.29-0.37)	Ref.	Ref.	Ref.	Ref.
Female	23	238.0	0.10 (0.06-0.15)	0.30 (0.16-0.56)	<0.001	0.30 (0.17-0.54)	<0.001
Family history of HD							
No	249	918.9	0.27 (0.24-0.31)	Ref.	Ref.	Not retained	
Yes	14	74.4	0.19 (0.11-0.32)	0.70 (0.21-2.29)	0.552		
Associated anomaly							
Isolated HD	201	784.0	0.26 (0.22-0.29)	Ref.	0.001*	Not retained	
Syndromic	43	139.0	0.31 (0.23-0.42)	2.71 (1.09-6.71)	0.001*		
Isolated additional anomaly	31	72.9	0.42 (0.30-0.60)	1.66 (0.45-6.26)	0.001*		

*p-value for overall difference between categories
BME – Black or Minority Ethnicity

Table 39: Infant characteristics associated with unplanned reoperations - Continued

	Number re-operations	Person years	Operations per person year (95% CI)	Unadjusted Hazard ratio (95% CI)	p-value	Adjusted Hazard ratio (95% CI)	p-value
Age at presentation							
1-7 days	235	891.8	0.26 (0.23-0.30)	Ref.	0.012*	Not retained	
8-28 days	25	29.2	0.85 (0.58-1.26)	1.59 (0.67-3.77)	0.012*		
More than 28 days	16	82.0	0.20 (0.12-0.32)	0.46 (0.16-1.34)	0.012*		
Age at diagnosis							
28 days or less	247	854.3	0.29 (0.26-0.33)	Ref.	Ref.	Ref.	Ref.
More than 28 days	29	148.1	0.20 (0.14-0.28)	0.39 (0.17-0.90)	0.027	0.38 (0.15-0.95)	0.039
Pre-operative HAE							
No	229	869.1	0.26 (0.23-0.30)	Ref.	Ref.	Not retained	
Yes	47	134.0	0.35 (0.26-0.47)	1.4 (0.64-3.14)	0.396		
Transition zone (as defined at surgery)							
Rectosigmoid	166	747.1	0.22 (0.19-0.26)	Ref.	0.0124*	Ref.	Ref.
Long segment (proximal to sigmoid colon)	78	207.8	0.38 (0.30-0.47)	1.62 (0.88-2.97)	0.0124*	1.50 (0.83-2.70)	0.171
Total colonic aganglionosis	28	32.3	0.87 (0.60-1.25)	3.54 (1.46-8.57)	0.0124*	4.93 (2.26 10.76)	<0.001

*p-value for overall difference between categories

Figure 15: Kaplan-Meier graph of unplanned reoperations by ethnicity

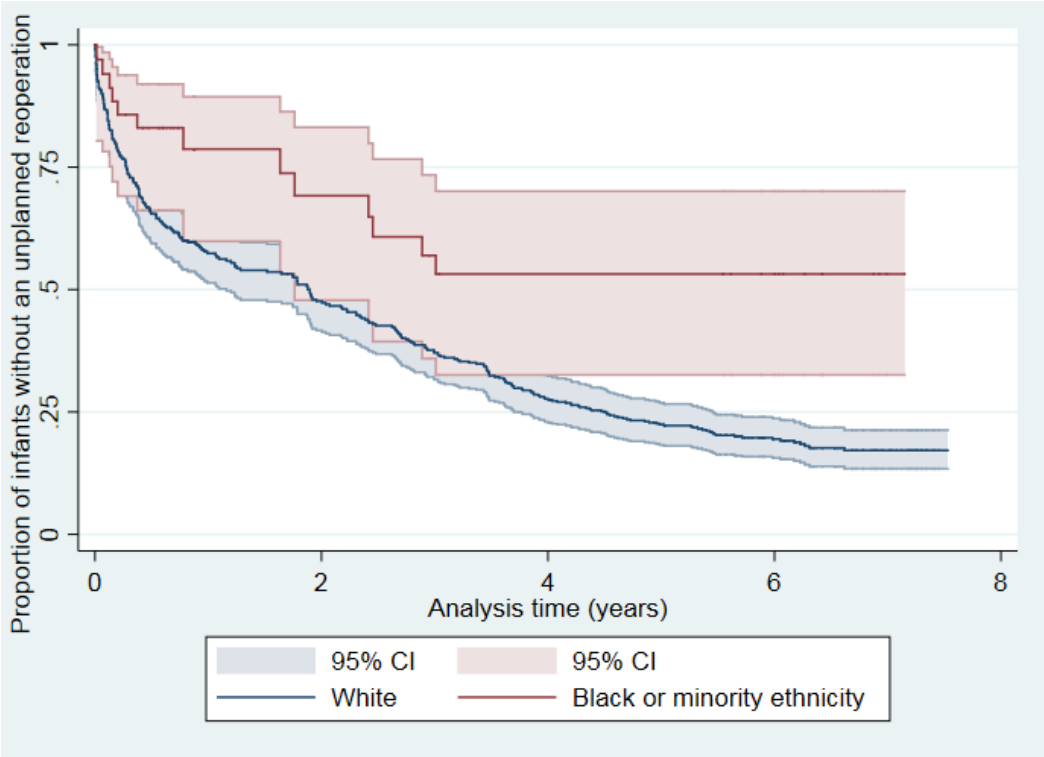


Figure 16: Kaplan-Meier graph of unplanned reoperations by sex

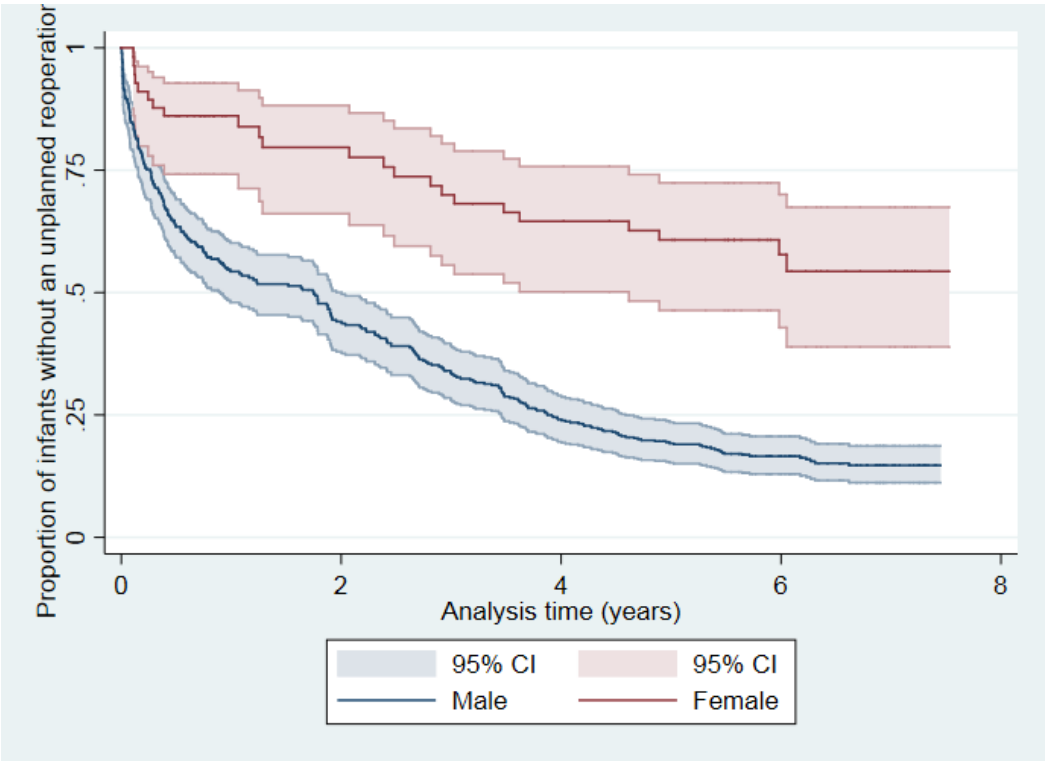


Figure 17: Kaplan-Meier graph of unplanned reoperations by age at diagnosis

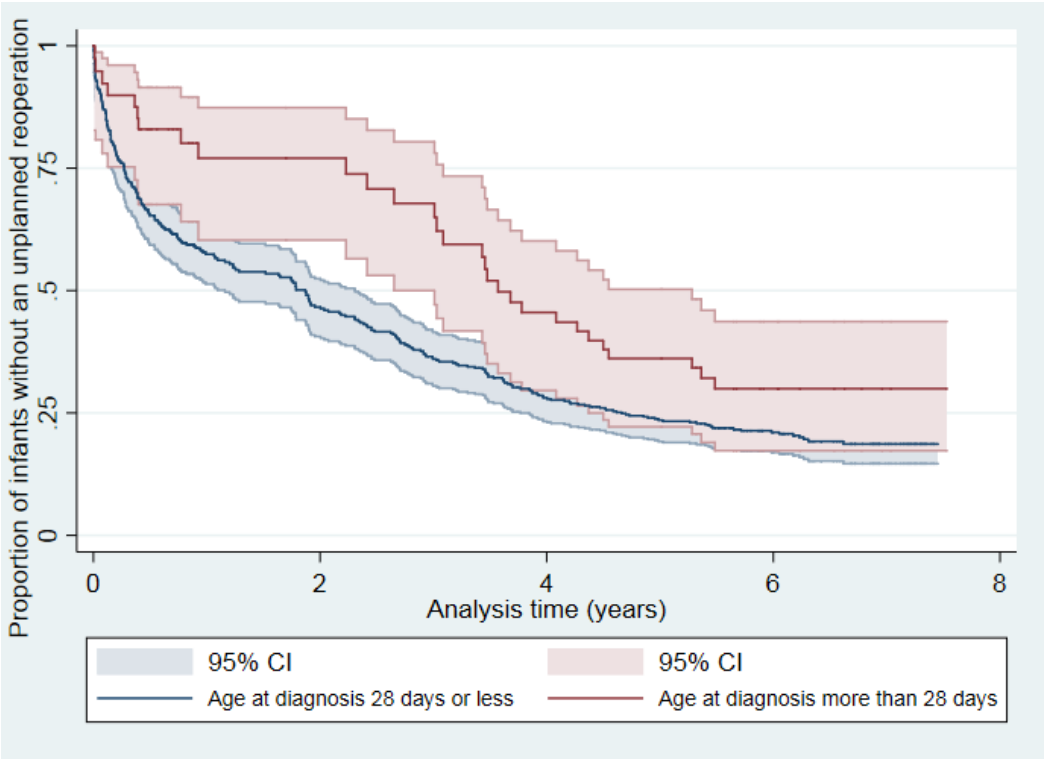
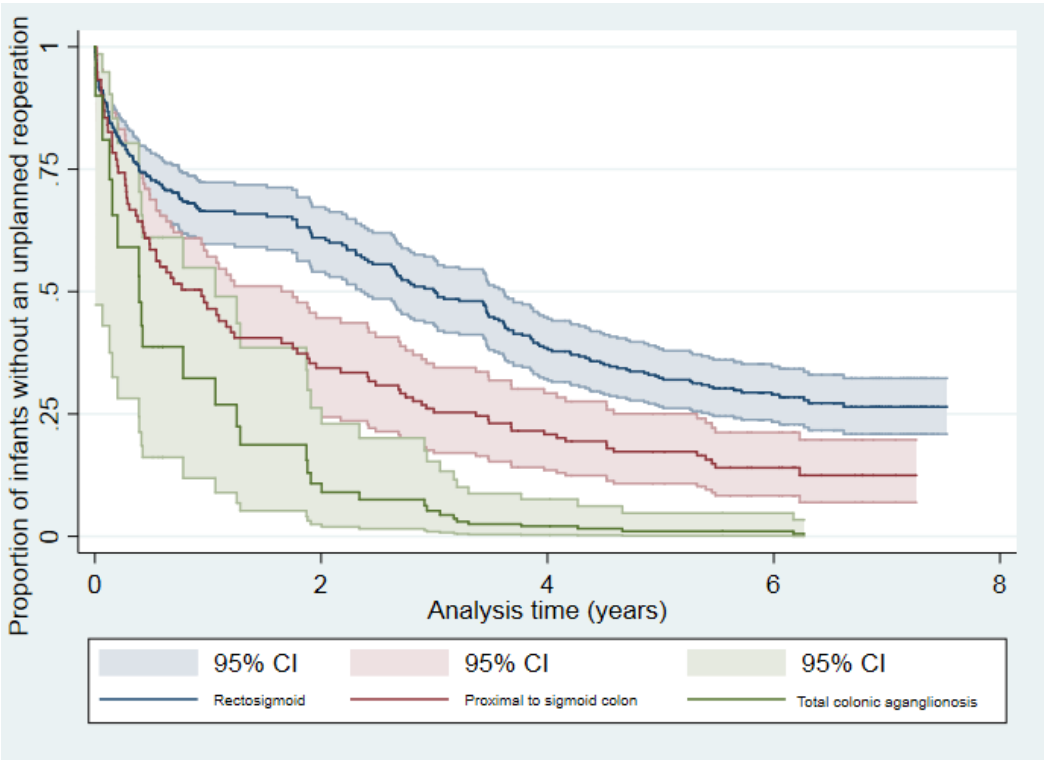


Figure 18: Kaplan-Meier graph of unplanned reoperations by anatomical location of the transition zone

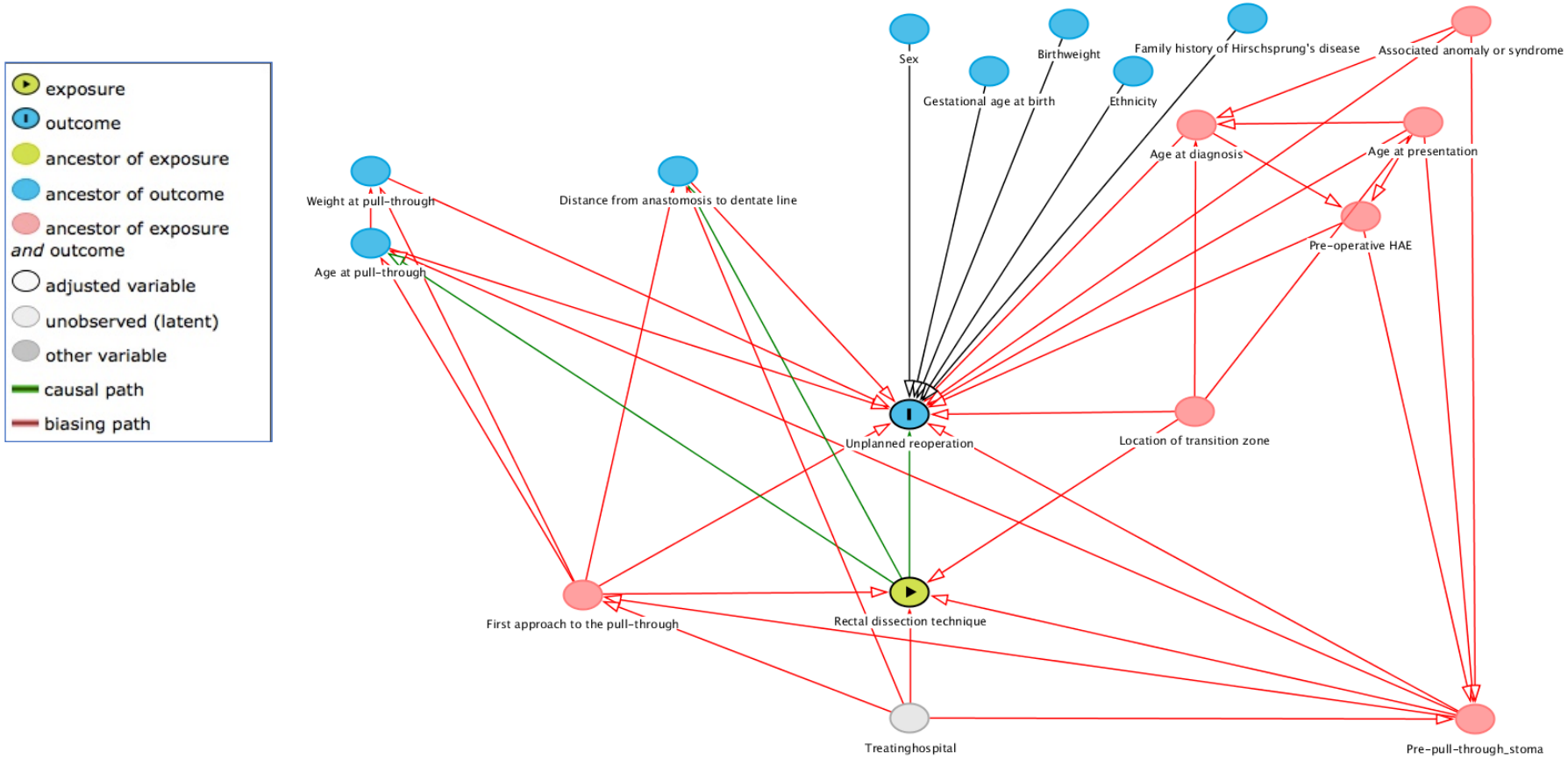


5.5.7. Confounding operative factors

5.5.7.1. Directed Acyclic Graph

Development of the DAG identified that age at pull-through, weight at pull-through, distance from the anastomosis to the Dentate line, creation of a pre-pull-through stoma, and the first approach to the pull-through lay on biasing pathways between rectal dissection technique and unplanned reoperation (Figure 19). The association of these factors with unplanned reoperation was therefore investigated using univariable, multiple-event, Cox proportional hazards models. Treating hospital also lay on a biasing pathway, however, given the small numbers of children treated in each individual centre, it was not possible to investigate the association of this factor with unplanned reoperations.

Figure 19: Directed Acyclic Graph



5.5.7.2. Model development

5.5.7.2.1. Mean centring of continuous variables

Mean (SD) weight at surgery was 5.67kg (1.72 kg), mean (SD) age at surgery was 115 days (96 days), and mean distance of the anastomosis from the Dentate line was 0.78cm (0.76 cm). Mean-centring around these values was performed prior to the Cox proportional hazards analysis.

5.5.7.2.2. Retained variables

Weight at definitive surgery, creation of a stoma prior to definitive surgery, and the first approach to the pull-through procedure met statistical criteria on univariable Cox regression analysis for assessment in the multi-variable model, and weight at surgery, and first approach to the pull-through were retained in the final model. Time varying covariates were fitted in the final model for age at diagnosis and weight at surgery. Following adjustment for ethnicity, sex, age at diagnosis, location of the transition zone and the two retained operative factors, each 250g increase in weight at surgery was associated with a 10% reduction in risk of unplanned reoperation, HR 0.90 (95% CI 0.86-0.95, $p<0.001$), and use of the combined laparoscopic and trans-anal approach to the first pull-through was associated with a 72% reduction in risk of unplanned reoperation when compared to the open approach, HR 0.28 (95% CI 0.14-0.57, $p<0.001$). There was no statistically significant difference in risk of unplanned reoperation between the other three approaches to the pull-through procedure (Table 40).

Table 40: Association of operative factors with unplanned operation

	Number of re-operations	Person years	Operations per person year (95% CI)	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Weight at pull-through					0.0944		<0.001
Per 250g increase from mean	N/A			0.94 (0.88-1.01)		0.90 (0.86-0.95)	
Age at pull-through					0.870		
Per week increase from mean	N/A			1.00 (0.98-1.02)		Not retained in multi-variable model	
Distance from anastomosis to Dentate line					0.191		
Per 0.5cm greater than mean	N/A			0.79 (0.55-1.12)		Not retained in multi-variable model	
Pre-pull-through stoma					0.062		
No	157	693.9	0.23 (0.19-0.26)	Ref.		Not retained in multi-variable model	
Yes	119	309.1	0.38 (0.32-0.46)	1.68 (0.97-2.90)		Not retained in multi-variable model	
First approach to the pull-through					0.0057		
Open	127	360.8	0.35 (0.30-0.42)	Ref.		Ref.	
Laparoscopic	80	230.1	0.35 (0.28-0.43)	1.10 (0.58-2.08)		0.93 (0.52-1.66)	0.793
Trans-anal	45	250.2	0.18 (0.13-0.24)	0.56 (0.23-1.39)		0.64 (0.26-1.57)	0.332
Combined laparoscopic and trans-anal	20	158.7	0.13 (0.08-0.20)	0.34 (0.17-0.66)		0.28 (0.14-0.57)	<0.001

HR – Hazard Ratio

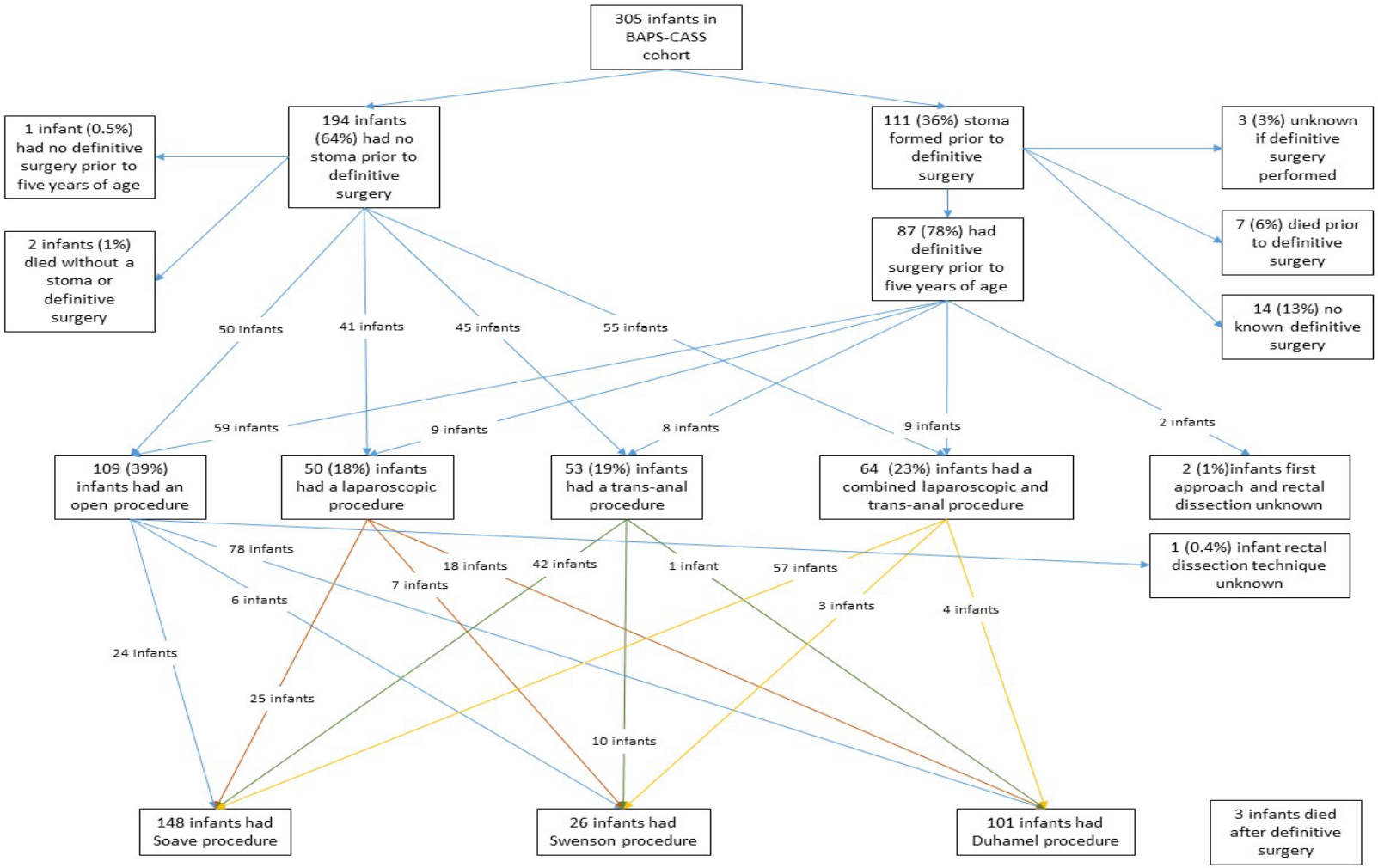
5.5.8. Comparison of rectal dissection techniques

5.5.8.1. Operative strategies utilised

Of the 305 children in the original BAPS-CASS cohort, 278 (91%) were known to have undergone definitive surgery prior to five years of age, 87 (31%) of whom had a stoma created prior to their definitive procedure. Of the 278 children who were known to have undergone definitive surgery, the first approach to this surgery was open for 109 (39%), laparoscopic for 50 (18%), purely trans-anal for 53 (19%), combined laparoscopic and trans-anal for 64 (23%), and unknown for 2 (1%). In the same group of 278 children, 148 (53%) had undergone the Soave rectal dissection procedure, 26 (9%) had undergone the Swenson rectal dissection procedure, and 101 (36%) had undergone the Duhamel rectal dissection procedure. Rectal dissection technique was unknown for three children (Figure 20).

Of the 275 children for whom the rectal dissection technique was known, 227(82%) were treated in hospitals participating in the NETS^{2HD} study, and of these, clinician five year follow-up was returned for 165 (73%), parent five year follow-up was returned for 71 (31%), both clinician and parent follow-up for 59 (26%), and either clinician or parent follow-up for 177 (78%). Of those with either form of five to seven year follow-up, 98 (55%) had undergone the Soave procedure, 17 (10%) had undergone the Swenson procedure, and 62 (35%) had undergone the Duhamel procedure. Two infants (2%) who underwent the Soave procedure, and one infant (6%) who underwent the Swenson procedure died after definitive surgery, but prior to five years of age.

Figure 20: Operative management of infants with Hirschsprung's disease



5.5.8.2. Characteristics of children undergoing each rectal dissection procedure

Characteristics of the children in each rectal dissection group are described in Table 41. Children who underwent the Duhamel procedure were more likely to have had a stoma formed pre-pull-through, have total colonic aganglionosis, and to have undergone an open procedure, and less likely to have been treated in a low-volume centre than children who had undergone the Soave procedure. The same differences existed when children who had the Duhamel procedure were compared to children who had the Swenson procedure, except in regard to stoma formation, where children who had the Swenson procedure were equally likely to have had a pre-pull-through stoma formed (Table 41).

Table 41: Characteristics of children in each rectal dissection group

	Swenson	Soave	Duhamel	
	N=16	N=96	N=62	
	n(%)	n(%)	n(%)	p-value*
Diagnosed in a low volume (< median) centre				0.034
No	3 (19%)	36 (38%)	32 (52%)	
Yes	13 (81%)	60 (63%)	30 (48%)	
Ethnicity				0.62
White	15 (94%)	86 (91%)	52 (87%)	
BME	1 (6%)	9 (9%)	8 (13%)	
Gestational age at birth				0.87
Term	14 (88%)	87 (91%)	54 (89%)	
Pre-term	2 (13%)	9 (9%)	7 (11%)	
Birthweight				0.47
2500g or more	14 (88%)	81 (87%)	56 (93%)	
Less than 2500g	2 (13%)	12 (13%)	4 (7%)	
Sex				0.79
Male	13 (81%)	71 (74%)	48 (77%)	
Female	3 (19%)	25 (26%)	14 (23%)	
Family history of HD				0.54
No	16 (100%)	89 (93%)	56 (93%)	
Yes	0 (0%)	7 (7%)	4 (7%)	
Associated anomaly				0.86
Isolated HD	13 (81%)	73 (76%)	51 (84%)	
Syndromic	2 (13%)	15 (16%)	7 (11%)	
Isolated additional anomaly	1 (6%)	8 (8%)	3 (5%)	
Age at presentation (days)				0.22
1-7 days	14 (88%)	86 (90%)	55 (89%)	
8-28 days	2 (13%)	2 (2%)	2 (3%)	
More than 28 days	0 (0%)	8 (8%)	5 (8%)	
Age at diagnosis				0.69
<31 days	14 (88%)	86 (91%)	52 (84%)	
31-60 days	0 (0%)	2 (2%)	4 (6%)	
61-90 days	1 (6%)	4 (4%)	3 (5%)	
91-120 days	0 (0%)	1 (1%)	2 (3%)	
>150 days	1 (6%)	2 (2%)	1 (2%)	
Transition zone (as defined at surgery)				0.016
Rectosigmoid	11 (69%)	77 (82%)	39 (63%)	
Long segment (proximal to sigmoid colon)	5 (31%)	16 (17%)	17 (27%)	
Total colonic aganglionosis	0 (0%)	1 (1%)	6 (10%)	

* p-value for overall difference between treatment strategies

Table 41: Characteristics of children in each rectal dissection group - Continued

	Swenson	Soave	Duhamel	
	N=16	N=96	N=62	
	n(%)	n(%)	n(%)	p-value*
Stoma created prior to pull-through				0.001
No	8 (50%)	74 (77%)	32 (52%)	
Yes	8 (50%)	22 (23%)	30 (48%)	
First attempted approach to the pull-through				<0.001
Open	5 (31%)	13 (14%)	46 (74%)	
Laparoscopic	1 (6%)	21 (22%)	14 (23%)	
Trans-anal	9 (56%)	33 (34%)	1 (2%)	
Combined laparoscopic and trans-anal	1 (6%)	29 (30%)	1 (2%)	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**p-value***
Weight at pull-through				0.57
Kilograms	5.0 (3.8-6.9)	5.3 (4.4-6.1)	5.5 (4.2-7.2)	
Age at pull-through				0.50
Days	87 (58-153)	71 (54-122)	90 (46-161)	

* p-value for overall difference between treatment strategies

5.5.8.3. Outcomes of the 177 children who had undergone definitive surgery and had either NETS^{2HD} form returned

Two infants (2%) who underwent the Soave procedure, and one infant (6%) who underwent the Swenson procedure died after definitive surgery, but prior to five years of age. No infants died following a Duhamel procedure. The child who died following a Swenson procedure died as a direct result of the diagnosis or treatment of their HD, whilst the two who died following Soave procedures died as a result of other causes.

5.5.8.4. Survival analysis based on data collected from 253 children who had at least one day of follow-up after undergoing a pull-through using the Swenson, Soave or Duhamel rectal dissection technique

In the Soave rectal dissection group there were 60 unplanned reoperations reported over a follow-up of 571.8 person-years; in the Swenson rectal dissection group there were 74 unplanned reoperations reported over a follow-up of 81.4 person-years; and in the Duhamel rectal dissection group, there were 138 unplanned reoperations reported over a person follow-up of 339.7 person-years. Unplanned reoperation rates (95% CI) were therefore 0.10 (0.08-0.14), 0.91 (0.72-1.14) and 0.41 (0.34-0.48) per person year respectively in the Soave, Swenson and Duhamel rectal dissection groups. Unadjusted Cox proportional hazards modelling suggested that when compared with the Soave rectal dissection technique, the Swenson and Duhamel rectal dissection techniques were both associated with a statistically significantly increased risk of unplanned reoperation, HRs 7.95 (95 % CI 3.01-20.98, p <0.001) and 2.47 (95% CI 1.15-5.33, p=0.021) respectively. Following adjustment for propensity score, weight at surgery and first-approach to the pull-through procedure, the

Swenson rectal dissection technique was still associated with a statistically significantly increased risk of unplanned reoperation, HR 6.97 (95% CI 2.93-16.59, p<0.001), but the Duhamel technique was no longer statistically significantly associated with an increased risk of unplanned reoperation, HR 1.36 (95% CI 0.55-3.35, p=0.502) (Figure 21 and Table 42). Rectal dissection technique and first-approach to the pull-through were identified as violating the proportional hazards assumption and therefore time-varying covariates for these two variables were included in the final Cox proportional hazards model. Categorisation of unplanned re-operations performed is described in Table 43.

Figure 21: Kaplan-Meier graph of unplanned reoperations grouped by rectal dissection technique

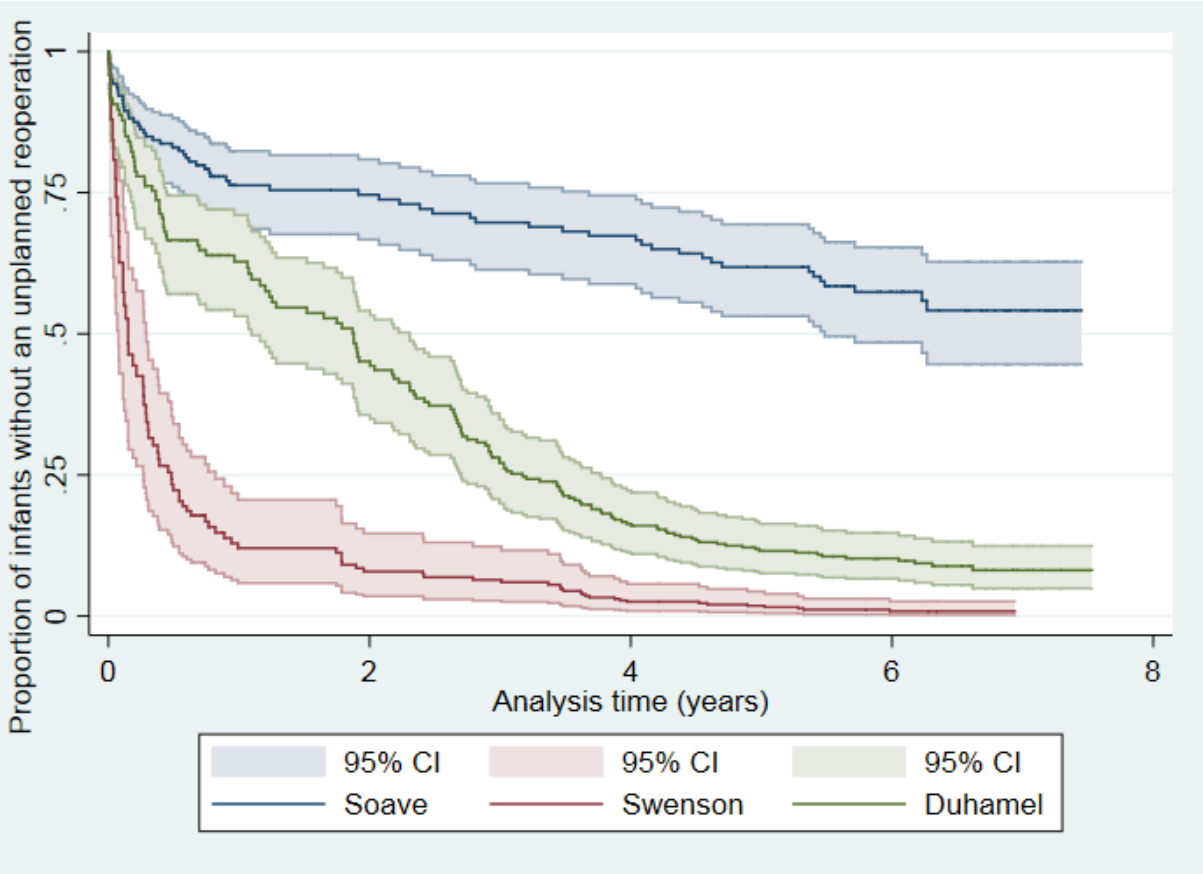


Table 42: Unplanned reoperations survival analysis comparing methods of rectal dissection

	Survival analysis based on data from all children with one or more days follow-up post pull-through							
	n (children)	**Number of re-operations**	**Person years**	**Event rate (95% CI)**	**Unadjusted Hazard ratio (95% CI)**	**p-value**	**Adjusted Hazard ratio (95% CI)**	**p-value**
Rectal dissection technique								
Soave	136	60	571.8	0.10 (0.08-0.14)	Ref.	Ref.	Ref.	Ref.
Swenson	24	74	81.4	0.91 (0.72-1.14)	7.95 (3.01-20.98)	<0.001	6.97 (2.93-16.59)	<0.001
Duhamel	93	138	339.7	0.41 (0.34-0.48)	2.47 (1.15-5.33)	0.021	1.36 (0.55-3.35)	0.502

Table 43: Categories of unplanned reoperations performed

	Swenson	Soave	Duhamel
	N=16 children	N=96 children	N=62 children
	n(%)*	n(%)*	n(%)*
Number of unplanned minor operations			
None	4 (27%)	68 (76%)	34 (59%)
One	4 (27%)	15 (17%)	9 (16%)
Two	1 (7%)	3 (3%)	5 (9%)
Three	0 (0%)	1 (1%)	2 (3%)
Four or more	6 (40%)	2 (2%)	8 (14%)
Number of unplanned intermediate operations			
None	14 (93%)	85 (96%)	43 (74%)
One	0 (0%)	3 (3%)	8 (14%)
Two	0 (0%)	1 (1%)	5 (9%)
Three	1 (7%)	0 (0%)	1 (2%)
Four or more	0 (0%)	0 (0%)	1 (2%)
Number of unplanned major operations			
None	6 (40%)	83 (93%)	43 (74%)
One	3 (20%)	4 (4%)	7 (12%)
Two	3 (20%)	1 (1%)	1 (2%)
Three	1 (7%)	1 (1%)	4 (7%)
Four or more	2 (13%)	0 (0%)	3 (5%)

* Percentage of those with complete data

5.5.8.5. Outcomes of the 174 surviving children who had undergone definitive surgery prior to five years of age and who had either NETS^{2HD} form returned

The numbers of children who had a stoma, who were continent of faeces, who were continent of urine, who maintained voluntary bowel movements without assistance, and who had experienced one or more episode of HAE are described in Table 44. Severity of faecal incontinence for those children affected is described in Table 45, the types of assistance required for children to maintain voluntary bowel movements are described in Table 46, and the number of episodes of HAE children experienced are described in Table 47.

In each of the Duhamel and Swenson groups, one permanent stoma was formed for continence management and one was formed following failure of the pull-through procedure. One infant (1%) in the Soave group, one infant (2%) in the Duhamel group, and three infants (19%) in the Swenson group had on-going faecal incontinence at five to seven years of age despite the presence of a stoma.

Table 44: Outcomes described using data collected for the 174 children who had undergone definitive surgery prior to five years of age and were alive at five years of age with either NETS^{2HD} five to seven year form returned

	Soave	Swenson^	Duhamel				
	N=96	N=16	N=62	Soave (ref.) Vs. Duhamel		Soave (ref.) Vs. Duhamel	
	n(%)*	n(%)*	n(%)*	OR (95% CI)	p-value	aOR (95% CI)	p-value
Unplanned reoperation							
None	63 (71%)	3 (20%)	25 (43%)	N/A – estimates of effect calculated using survival analysis. See Figure 21 and Table 42			
One	15 (17%)	2 (13%)	10 (17%)				
Two	5 (6%)	3 (20%)	7 (12%)				
Three	3 (3%)	1 (7%)	3 (5%)				
Four or more	3 (3%)	6 (40%)	13 (22%)				
Stoma							
No	92 (97%)	10 (63%)	52 (84%)	Insufficient events to allow comparison			
Yes	3 (3%)	6 (38%)	10 (16%)				
Permanent Stoma							
No	95 (100%)	14 (88%)	60 (97%)	Insufficient events to allow comparison			
Yes	0(0%)	2 (12%)	2 (3%)				
Faecal incontinence							
No	36 (39%)	6 (37%)	24 (39%)	Ref.	0.943	Ref.	0.367
Yes	59 (61%)	10 (63%)	38 (61%)	0.98 (0.51-1.88)		0.65 (0.25-1.66)	
Post-operative HAE							
No	57 (61%)	10 (63%)	31 (51%)	Ref.	0.15	Ref.	0.261
Yes	36 (39%)	6 (37%)	30 (49%)	1.61 (0.84-3.09)		1.69 (0.68-4.22)	
Urinary incontinence							
No	88 (93%)	15 (94%)	55 (89%)	Ref.	0.524	Ref.	0.204
Yes	7 (7%)	1 (6%)	7 (11%)	1.42 (0.49-4.12)		2.88 (0.56-14.77)	
	N=93#	**N=10#**	**N=52#**				
	n(%)*	**n(%)***	**n(%)***				
Voluntary bowel movements without need for enemas/rectal/colonic irrigation							
No	19 (21%)	2 (22%)	7 (13%)	Ref.	0.219	Ref.	0.431
Yes	73 (79%)	7 (78%)	45 (87%)	1.80 (0.71-4.58)		1.71 (0.45-6.45)	

*Percentage of those with complete data, #Described in children without a stoma, ^ no comparison made due to lack of cases
OR – Odds Ratio, aOR – adjusted odds ratio

Table 45: Severity of faecal incontinence

	Swenson	Soave	Duhamel
	N=10	N=59	N=38
Severity of faecal incontinence	**n(%)***	**n(%)***	**n(%)***
Once or twice per week	1 (10%)	26 (51%)	16 (44%)
Every day but without social problems	3 (30%)	15 (29%)	12 (33%)
Constant, with social problems	6 (60%)	10 (20%)	8 (22%)

*Percentage of those with complete data

Table 46: Maintenance of voluntary bowel movements

	Swenson	Soave	Duhamel
	N=10	N=92	N=52
Assistance required to maintain voluntary bowel movements	**n(%)***	**n(%)***	**n(%)***
None	6 (67%)	56 (61%)	24 (46%)
Laxatives	1 (11%)	17 (18%)	21 (40%)
Enemas	1 (11%)	9 (10%)	3 (6%)
Rectal washouts (including Peristeen)	1 (11%)	9 (10%)	3 (6%)
Antegrade Continence Enema	0 ()%)	1 (1%)	1 (2%)

*Percentage of those with complete data

Table 47: Number of episodes of Hirschsprung's associated enterocolitis in the past 12 months

	Swenson	Soave	Duhamel
	N=16	N=96	N=62
	n(%)*	n(%)*	n(%)*
Number of episodes of HAE in the past 12 months			
None	16 (100%)	92 (96%)	57 (92%)
One	0 (0%)	4(4%)	2 (3%)
Two or more	0(0%)	0 (0%)	3 (5%)

*Percentage of those with complete data

5.5.8.6. Outcomes of those children who underwent a Soave or Duhamel procedure and who had a NETS^{2HD} parent form returned

Sixteen children (48%) who underwent a Soave procedure, and 14 children (48%) who underwent the Duhamel procedure had PedsQL total scale scores of more than one standard deviation below the reference mean and were therefore classed as having reduced quality of life. The mean (95% CI) PedsQL total scale score for the Soave group was 70.29 (63.21-77.37), and for the Duhamel group was 67.23 (58.44-76.03). Twelve children (39%) who underwent the Soave procedure and 13 children (45%) who underwent the Duhamel procedure had psychosocial health summary scores more than one standard deviation below the reference mean and were therefore classed as having reduced psychosocial quality of life. The mean psychosocial health summary scores for the Soave and Duhamel groups respectively were 70.18 (63.25-77.11) and 67.81 (59.15-76.46) (Table 48). Quality of life data were only returned for two children who underwent the Swenson procedure, and therefore no meaningful interpretation could be made.

Fifteen children (75%) who underwent the Soave procedure and 10 children (71%) who underwent the Duhamel procedure had PICS incontinence scores below the age-specific lower 95% confidence limit and were therefore classed as having impaired continence. Eleven children (58%) who underwent the Soave procedure and 11 children (73%) who underwent the Duhamel procedure had PICS constipation scores below the lower 95% confidence limit and were therefore classified as having evidence of constipation. The median (IQR) PICS constipation score in the Soave group was 19 (10.5-23.5), and in the Duhamel group was 16 (11-21.5), and the median PICS incontinence score in the Soave group was 19.15 (17.5-22.25) and in the Duhamel group was 19.2 (17-21.75) (Table 48). PICS

data were only returned for two children who underwent the Swenson procedure, and therefore no meaningful interpretation could be made.

Table 48: Outcomes of the 71 children who had undergone a pull-through procedure using the Soave or Duhamel rectal dissection techniques and who had a NETS^{2HD} parent form returned

	Soave	**Duhamel**
	N=35	**N=33**
	n(%)*	**n(%)***
PedsQL		
Non-reduced quality of life	17 (52%)	15 (52%)
Reduced quality of life	16 (48%)	14 (48%)
PedsQL		
Non-reduced emotional quality of life	19 (61%)	16 (55%)
Reduced emotional quality of life	12 (39%)	13 (45%)
	Mean (95% CI)	**Mean (95% CI)**
PedsQL		
Total scale score	70.29 (63.2-77.4)	67.2 (58.4-76.0)
Psychosocial health summary score	70.18 (63.3-77.1)	67.8 (59.2-76.5)
	N=34	**N=27#**
PICS Continence#	**n(%)***	**n(%)***
Normal continence	5 (25%)	4 (29%)
Impaired continence	15 (75%)	10 (71%)
PICS Constipation#		
No significant constipation	8 (42%)	4 (27%)
Constipation	11 (58%)	11 (73%)
	Median (IQR)	**Median (IQR)**
PICS#		
Incontinence score	19.15 (17.5-22.3)	19.2 (17-21.8)
Constipation score	19 (10.5-23.5)	16 (11.0-21.5)

*Percentage of those with complete data

#Described in children without a stoma

PICS – Paediatric Incontinence and Constipation Score

5.6. Discussion

This description of patient-centered outcomes, collected from a contemporary cohort of children with HD has demonstrated the benefits of collecting information from parents, but also clearly highlighted some of the difficulties encountered in trying to do so using the existing paediatric surgical research infrastructure. The data that have been collected can be used to highlight where outcomes are not as good as might be hoped for, to improve counseling of parents, and, in part at least, to allow more informed decisions to be made regarding the operations that are used to treat children with HD.

5.6.1. Key findings

The key message from this study is that during their primary school years, the health and wellbeing of children with HD appeared to be significantly reduced. Approximately 45% of children had undergone at least one unplanned reoperation, 18% required enemas, or rectal or colonic washouts to maintain voluntary bowel movements, 11% were incontinent of urine, and 61% were incontinent of faeces. For 50% of those children who were incontinent of faeces, accidents were occurring on a daily basis, and in 20%, they were resulting in significant social problems. Even when children with long-segment and total colonic HD, or those with a syndrome or additional congenital anomaly were excluded, continence for the remaining children, who would be expected to be those with the best outcomes, was still not as good as would be hoped for. With mean quality of life scores statistically significantly lower than the reference population, and approximately 50% of parents reporting their child as having reduced quality of life, the overall impact of being diagnosed with and treated for HD appeared significant. However, these conclusions,

particularly those relating to quality of life, must be viewed in light of the loss to follow-up experienced in this study. Their generalisability is therefore unclear.

Whilst the lower than anticipated data return potentially limited identification of associations between patient characteristics, management factors, and outcome, this analysis nevertheless identified that girls, children who were of black or minority ethnicity, and children who presented after 28 days of age had respectively a 70%, 80% and 62% lower risk of undergoing an unplanned re-operation than children without these characteristics. It was also identified that children who had total colonic aganglionisis had a nearly five-fold increased risk of undergoing an unplanned reoperation in comparison to those with a transition zone located in the rectum or sigmoid colon.

Following adjustment for confounding operative factors and a child's propensity for allocation to a particular treatment, the type of rectal dissection used was associated with statistically significant variation in risk of unplanned reoperation. The Soave procedure was associated with the lowest risk of unplanned reoperation, followed by the Duhamel and then the Swenson, which was associated with a nearly seven-fold statistically significantly increased risk of unplanned reoperation when compared to the Soave procedure.

5.6.2. Placing the results in context

5.6.2.1. Unplanned reoperation

The NETS^{1HD} COS developed in Chapter Three defined unplanned reoperation as including any procedure that was performed as a direct result of the diagnosis or treatment of the child's HD, and any episodes of general anaesthesia that were required as a direct result of

the diagnosis or treatment of the child's HD. This definition, which was utilised in the work presented in this chapter, is much broader than those used more generally in the existing literature (73, 156-160). It is therefore very difficult to compare the figure of 43% of children undergoing one or more unplanned reoperation reported here with proportions that are reported in the wider literature.

Drawing comparisons between this study and other studies is made even harder by the fact that the number of children who have undergone an unplanned reoperation will increase with the age of the child and the duration over which they are followed up. Therefore, simply comparing proportions of children who have undergone one or more unplanned reoperation is potentially misleading. Reporting unplanned reoperations taking into account the period of follow-up, alongside raw descriptive data, as was carried out in the analysis presented here, is likely to be more informative. This method of analysis is however labour intensive, both in terms of data collection, and analysis, and does not appear to have been utilised previously for describing unplanned reoperations for children with HD.

5.6.2.2. Burden of disease

In older children or young adults with HD, the proportion of children with faecal incontinence has been reported as anything from 20% to approximately 50% (16, 17, 141, 161), urinary incontinence has infrequently been investigated, but in the instances where it has, has been reported to affect approximately 2% of children(143), and quality of life and mental health have often been suggested to be little different from people without HD(48, 162-164). Secondary outcomes for the cohort of children studied in the work presented in this chapter therefore appear to be worse than for those reported elsewhere in the existing

literature. It is unclear why this is the case, but there are four plausible explanations. Firstly, including parent reported outcomes data may have increased the proportion of adverse outcomes that are reported; secondly, outcomes may vary over time, and the age at which outcomes were reported in this work represents a point where they are at their worst; thirdly, differences in child characteristics or management strategy may exist between the cohort described in this chapter and those described elsewhere in the literature; and finally, the children for whom data have been returned in this study may have worse outcomes than those for whom data have not been returned. These possible explanations are further explored below.

5.6.2.3. Impact of including parent reported data

Data relating to a child's faecal continence status was returned by both surgeons and parents for 59 children whose outcomes were described in this chapter. Of these children, surgeons reported that 24 (41%) were incontinent of faeces, whilst parents reported that 52 (88%) were incontinent of faeces. If the 28 children who were reported by parents but not surgeons as incontinent of faeces had instead been classed as continent of faeces, as per the surgeon report, overall there would have been 84 children instead of 112 that were reported as incontinent. This would have given a proportion of children who were incontinent of faeces of 45% as opposed to 61%, an estimate that is much closer to those reported in the wider literature. Surgeon under-estimation of faecal incontinence has also been reported in previous HD studies. In 2002, Ludman et al compared outcomes for 15 adults with total colonic HD to 15 adults with recto-sigmoid HD. In this study, they described both surgeon and patient reported faecal incontinence, identifying that patients reported themselves as incontinent of faeces in 43% of cases, whilst surgeons reported them as

incontinent of faeces in only 27% of cases(165). Given that it appears that surgeons under-estimate faecal incontinence, and that in the work presented in this chapter, not all children had parent reported faecal continence data returned, there is the potential that the true rate of faecal incontinence is higher than the 61% that has been described in this study.

Discrepancies in surgeon and patient reporting of outcomes have also been described in other specialties. In 2009, Lattig et al compared surgeon and patient reported outcomes following spinal surgery. 1113 surgeons and patients were asked to assess the patients 'global outcome' following surgery using a validated five-point scale, and the correlation between their scores was assessed using Spearman's rho. Whilst moderate correlation was identified between the two scores, as evidenced by a Spearman's Rho of 0.57, the two assessments were only identical in 51.2% of cases. In approximately 25% of cases, surgeons overestimated the patient's global outcome, and in approximately 25% of cases, they underestimated the patient's global outcome(166). This work would suggest that patients and surgeons are likely to assess outcomes differently, and therefore adds further weight to the hypothesis that inclusion of parent reported data affected the outcomes described in this chapter.

5.6.2.4. Improvement in outcomes with age

Not all of the difference between the outcomes described in this chapter and outcomes described previously can be attributed to the inclusion of parent reported outcomes data. An alternative hypothesis that explains differences in outcomes such as quality of life, which can only be reported by parents or patients themselves, must be sought. One such

alternative is that outcomes vary over time, and that early to mid-childhood is a period in which they are at their worst.

In 2018, using Spline modelling based upon data from 46 children, Amin et al suggested that PedsQL physical summary scale scores for children who underwent surgery for HD improved to approximately three years of age, before a rapid decrease, a plateau and then an increase in the teenage years. Psychosocial summary scale scores similarly decreased in childhood and increased again in the early teenage years, but without the initial peak in infancy(163). Two further studies, by Hartmann et al, and Granstrom et al also support the theory that outcomes are worse in childhood than later in life (164, 167). Hartmann et al conducted a longitudinal study measuring disease specific and general health related quality of life at two time points three years apart for 152 children aged eight to eleven, and adolescents aged 12 to 16 with HD, and demonstrated that in both groups, there was an increase in disease specific functioning and psychological quality of life over time (167). Granstrom et al demonstrated that for a cohort of 48 Swedish adults with a median age of 28 years, that quality of life, as measured by the SF-36, was no different to a healthy population(164).

Such variation in outcome over time is not restricted just to quality of life. Studies that have described faecal incontinence in older teenagers and adults with HD seem generally to either report a lower proportion of affected participants than those where faecal incontinence is reported in children, or to report an improvement over time (48, 168-170) (171). Based upon the existing literature, there would therefore appear to be a reasonable body of evidence to suggest that the outcomes for the cohort of children described in this chapter is likely to improve over time.

5.6.2.5. Differences in demographics or management

Despite the evidence to suggest that at least some of the differences in outcomes between the cohort described in this chapter and the published literature are due to the age at which the cohort has been followed-up and the inclusion of parent reported data, these explanations are unlikely to represent the whole story. For example, although the work by Amin et al described quality of life for people with HD improving from childhood onwards, the mean PedsQL total scale score of 81.2 (95% CI 74.9-87.4) that they report for children aged four to eight is significantly higher than the mean score of 68.3 (95% CI 63.5 – 73.1) that is reported for the cohort described in this chapter(163). The number of children from which Amin et al have calculated this mean score is unclear, but the difference still appears stark. One explanation for this difference in reported quality of life for two cohorts of children treated in similar high-income countries is that there are differences in the underlying populations or the management strategies used. Amin et al report a slightly lower proportion of children with long-segment or total colonic HD than was identified in the work presented in this chapter, and it may therefore be that the reduced proportion of children with more severe disease led to the better PedsQL scores they present.

5.6.2.6. Selective follow-up

Outcomes reported in this work may also be worse than those published elsewhere in the literature because they are potentially not representative of outcomes for the original BAPS-CASS cohort as whole. This is a particularly important consideration for quality of life and the PICS score, as they have been derived from parent reported data, which was only returned for 27% of children. If children were randomly lost to follow-up, then data from

that 27% will still be representative of the entire cohort. However, if the likelihood of a child being followed-up was determined by their overall health and wellbeing, then the described outcomes will be biased.

Approximately 40% of parents of children whose data were used in the original BAPS-CASS study did not have the opportunity to participate in the five to seven year follow-up, as their contact details were never received by staff in the NPEU. Therefore, their non-participation could not have been affected by their opinion of their child's outcomes. However, the ability of clinicians to re-identify children and obtain permission from their parents for sharing of contact details may have been affected by the engagement of the family with hospital services. Engagement with services could reflect an on-going need for review due to complications, or it could reflect a pro-active surgical team. It is therefore difficult to predict the effect that losing these children's data will have had on the representativeness of the study's results.

It is similarly difficult to predict the effect of losing data from the 56% of parents who were contacted to participate but never returned a data collection form. The decision of these parents to participate may have been affected by their child's health and wellbeing, but similarly, could have been affected by external factors such as time-pressures and work commitments. As there were significant difficulties encountered in ensuring delivery of study packs, and in making contact with parents, it is also unclear how many parents were actually given the opportunity to participate, and therefore even more difficult to hypothecate the effect that loss to follow-up will have had on the representativeness of the study outcomes.

Overall, there were no differences between those children with parental follow-up and those without parental follow-up in regards to ethnicity, sex, age at presentation or location of transition zone; the four characteristics shown in this work to have an association with outcome. There were also no differences in the rectal dissection techniques utilised. Those children who were lost to follow-up were however less likely to have undergone a laparoscopic procedure than those who were successfully followed-up, although undergoing a laparoscopic procedure did not appear to have any association with outcome. No differences in outcomes one-year post diagnosis, as reported in the original BAPS-CASS study, were seen between children with and without parental follow-up.

Given that there were no meaningful differences in child characteristics or management between those with and without parental follow-up, and that no differences were seen between the groups in one-year outcomes reported to BAPS-CASS, it would appear that the outcomes described at five to seven years of age in this study are likely to be representative of the original cohort. However, given that it is unclear which factors will have influenced return of parent reported outcomes data, and the amount of data returned are small, there remains the possibility that the outcomes described in this work are worse than in the published literature due to selective follow-up of those children with the worst outcomes. Caution must therefore be exercised when generalising from the results, particularly those relating to quality of life and the PICS score.

5.6.2.7. Characteristics associated with variation in outcome

Many patient characteristics have previously been proposed to be associated with outcome for children with HD, and it is likely that the specific factors identified in a study will vary depending upon the outcome investigated and the age of the study participant. However, there are some characteristics, including male gender, total colonic HD and presence of Down's syndrome, which have been shown in multiple settings to be associated with poorer outcomes(165, 172-175). Given the complex, multi-factorial, genetic inheritance of HD, it is also not unreasonable to suggest that a child's underlying genotype is likely to affect their outcome.

Overall, there is an identified genetic component to approximately 12% of cases of HD. Associations have been shown with multiple syndromes, including Down's syndrome and Mowat-Wilson syndrome, as well as multiple single gene mutations, including in the RET and EDNRB genes(176-180). Ethnicity, sex and location of the transition zone, the three patient factors identified in this work as associated with variation in number of unplanned reoperations, are all at least in part, genetically determined(181, 182). These factors may therefore simply be a phenotypic reflection of an underlying genetic pre-disposition to a more severe form of HD. Children who are well enough to remain un-treated and un-hospitalised for more than 28 days are likely to do so as they have a less severe form of HD than those whose symptoms are severe enough to merit presentation to hospital prior to this point. Therefore, presentation to hospital after 28 days of age, the fourth factor shown to be associated with outcome in this work is likely to be a reflection of the underlying severity of the child's condition, as opposed to an independent determinant of outcome.

Each of the pre-operative characteristics identified in this work as associated with variation in outcome are therefore likely to be surrogate markers of other underlying factors that are determining a child's disease severity. However, identifying those underlying determinants of outcome is likely to be complex and time-consuming. Therefore, prior to their identification, the described pre-operative characteristics of ethnicity, gender, length of affected segment of bowel and age at presentation to hospital should be used for defining populations for future studies and to inform discussions relating to disease severity and potential outcome with parents.

5.6.2.8. Confounding operative factors

Work with the UKPCG identified that the question surgeons would most like investigated in relation to the treatment of children with HD, was whether the type of rectal dissection used affects a child's outcome. As with all surgical procedures, the HD pull-through is a complex intervention in which multiple factors, related to the patient, the operation, the surgeon and the post-operative care, interact to determine outcome. It will therefore never be possible in any observational study to identify the sole effect of each rectal dissection technique on outcome. However, by understanding which potential confounding factors have the greatest influence on the relationship between rectal dissection technique and outcome, it is possible to adjust for them in analyses.

Following adjustment in a multivariable Cox proportional hazards model, the work presented in this chapter identified that two out of five operative factors that lay on biasing pathways between rectal dissection technique and unplanned reoperation, were statistically significantly associated with the outcome of interest. Each 250g increase in weight at

surgery above the mean of 5.67kg was associated with an approximately 10% reduction in the risk of unplanned reoperation, whilst use of the combined laparoscopic and trans-anal procedure was associated with approximately a 60% reduction in risk of unplanned reoperations. This association between weight at surgery and outcome has not been frequently described in the existing literature. However, one retrospective review of 181 Chinese children with HD conducted by Huang et al did identify a similar relationship to that described in this chapter. In the study by Huang et al, children with low weight at the time of surgery, defined only as "*below the WHO's Child Growth Standards*" were at an approximately three-fold increased risk of post-operative enterocolitis in the first post-operative year. They did not however find any association with outcomes at later time-points.

Unlike the relationship between weight at surgery and outcome, the relationship between approach to the pull-through procedure and outcome has been investigated in many previous studies. Systematic reviews by Chen et al and Thomson et al have respectively compared the open approach to a combination of the trans-anal and laparoscopically assisted trans-anal procedures, and the purely trans-anal procedure to the laparoscopically-assisted trans-anal procedure(16, 17). Both studies experienced difficulties drawing robust conclusions due to limitations with the primary data. However, Chen et al reported that use of the trans-anal approach is associated with shorter operative times and lower rates of post-operative soiling, incontinence and enterocolitis than the open approach, whilst Thomson et al report that the only difference between the purely trans-anal procedure and the laparoscopically assisted procedure is that the purely trans-anal procedure is associated with a shorter operative time. In addition to the two systematic reviews, there have been

many small, retrospective studies, some of which were included in the systematic reviews, that have reported comparisons between the different approaches to the pull-through(157, 183-188). However, the results of these studies are generally unreliable due to the influence of chance, bias and confounding.

5.6.2.9. Comparison of rectal dissection techniques

The cohort of children who underwent the Duhamel procedure appeared to be different to the cohorts of children who underwent the Soave and Swenson procedures. Children who underwent the Duhamel were more likely to have had a pre-pull-through stoma, more likely to have total colonic HD, more likely to have undergone an open operation, and more likely to have been treated in a high volume centre. These differences are potentially explained by the fact that, for many surgeons, the Duhamel is the operation of choice for children with complex HD, even when those surgeons would primarily use a different rectal dissection technique for children with simple HD(49). Examples of children with more complex HD include those with longer segment disease, those who initially presented in extremis, and those with multiple comorbidities. Surgeons' preferred use of the Duhamel technique for treating children whom they view as having more complex disease potentially also explains why a statistically significantly higher rate of unplanned reoperations was seen in the Duhamel group than the Soave group on univariable analysis, but not once adjusted for a child's propensity score and confounding operative factors.

Multiple studies, including systematic reviews and meta-analyses have been performed describing outcomes following different types of pull-through procedure. Identifying the relative effects of each rectal dissection technique from these studies can however be

difficult, as interventions are often defined to allow comparison of entire procedures, e.g. the laparoscopic Duhamel and the trans-anal Soave, as opposed to offering a pure comparison between rectal dissection techniques. Using such procedure based intervention definitions, two recent systematic reviews have compared the open Duhamel to the 'trans-anal endo-rectal pull-through', a trans-anal operation containing aspects of both the Swenson and the Soave procedures(144, 145). Results of these reviews suggested that the Duhamel procedure was associated with longer post-operative hospital stays, a lower rate of enterocolitis, and a lower rate of post-operative stricture formation. However, the primary data upon which they were based was generally collected using methodologies that were open to the influence of chance, confounding and bias.

Where purer comparisons have been made between rectal dissection techniques, they have generally been undertaken in small, retrospective, single institution studies. In studies utilising this methodology, it has been suggested that in comparison to the Soave technique, the Swenson technique is associated with shorter operative times, reduced blood loss and lower rates of overall complications(189, 190), and the Duhamel is associated with an increased risk of enterocolitis and constipation(191, 192). Results however differ significantly between studies, with often-contradictory conclusions drawn(193, 194).

The rectal dissection groups compared in the work presented here were heterogeneous in a similar manner to much of the published literature. Within each group, multiple approaches to the pull-through were included, some infants had undergone formation of pre-pull-through stomas, and the weight at time of surgery varied. However, unlike much of the published literature, adjustment of the estimates of effect for a child's propensity score and

confounding operative factors allows a more robust assessment of the true impact of choice of rectal dissection technique on outcome. Whilst it is likely that the lower than anticipated data return rate may have led to type two errors, nevertheless, it is reasonable to conclude that the Swenson procedure is associated with an increased risk of unplanned reoperation, but that there are no differences in outcome between the Soave and Duhamel procedures. In the absence of RCT data, these are the most reliable results available to date.

5.6.3. Strengths and limitations

5.6.3.1. Reporting of core outcomes

By describing outcomes that have been identified as important to clinicians, people with HD, and parents of children with HD, one of the key strengths of the work presented here is that the results have direct relevance to clinical practice. This is in direct contrast to a large proportion of the existing literature, where the outcomes described are often hospital metrics such as length of stay, process outcomes such as operative time, or surrogate markers of success such as bowel function at an age when continence would not yet be expected(73). Reporting of these outcomes using standardised definitions, at a standardised time-point for all children in the cohort, will facilitate meta-analysis with future studies.

5.6.3.2. Non-participation of sites

Whilst one of the key strengths of the study was inclusion of parent reported outcomes data, facilitating inclusion of these data has undoubtedly also resulted in one of the key limitations of the study, the lower than anticipated data return rate. The primary reason that the overall data return rate for both clinicians and parents was lower than hoped for,

was due to non-participation of eight of the sites that contributed data to the original BAPS-CASS Study. Loss of these eight sites resulted in a nearly 20% reduction in the number of children with HD who were eligible to participate in the study.

Whilst the superficial reason for non-participation in each of these sites varied, the root cause in all except the two Irish sites was a lack of staff with the time to implement the relatively complex screening, recruitment, consent and data collection processes that had been put in place to enable de-anonymisation of the previously collected BAPS-CASS data. Without identification of staff with time to deliver the study, it was not possible to secure approvals for the study to take place in each of these non-participating sites. However, without putting in place processes to allow de-anonymisation of the data, it would not have been possible to approach parents for participation in the study. It is highly likely, that had no attempt been made to collect parent reported data, that these eight sites would have initiated the study without difficulty. Even in participating sites, the protracted approvals process resulted in the first parental questionnaire being sent out over a year after the originally planned study start date, thereby significantly reducing the time available for data collection.

However, in addition to the loss of data from these eight sites, there were also three other factors that are likely to explain the lower than hoped for data return rate. These were, difficulties in obtaining parental contact details, loss and delay of study information in the post, and difficulties contacting parents by telephone. These are discussed below.

5.6.3.3. Obtaining parental contact details

In order for staff in hospitals to be able to contact a potentially eligible child's parents, it was necessary for them to identify the child's NHS number from hospital records, use the NHS central register to identify up-to-date contact details, and then make contact with the parents by telephone. Many participating sites no longer held records of children whose data were used in the original BAPS-CASS study, and therefore instead had to re-identify children based upon matching information from local operative logs to data supplied by BAPS-CASS about a child's gender, and date of biopsy, date of stoma formation and date of definitive surgery. A combination of difficulties in identifying children from BAPS-CASS data, combined with subsequent difficulties in obtaining up to date contact details from the NHS central register, and then making contact with parents by telephone, meant that although there were no parents who declined to share their contact details with staff in the NPEU, contact details were only ever received centrally for 186 (74%) of the 240 eligible children.

5.6.3.4. Loss and delay of study information

Following receipt of contact details by study staff in the NPEU, study information packs were by default sent to parents via Royal Mail. However, follow-up telephone calls to parents highlighted that many of these packs were either delayed in being delivered or were never received at all. Significant delays were also encountered in the return of signed consent forms using Freepost envelopes. The average time from posting to receipt of the form by central research staff was approximately a month, and the longest was around three months. It is likely that these delays will have resulted in a loss of interest from some parents, and potentially explain why of the 186 packs that were sent out, consent forms were only returned for 107 (58%). If the study were repeated for other conditions, use of

stamped addressed envelopes, or fully electronic consent processes, would avoid this unforeseen problem.

5.6.3.5. Difficulties contacting parents by telephone

Difficulties in delivering study information were also compounded by difficulties in contacting parents by telephone. When the study was designed, follow-up calls to parents were planned for two and four weeks after posting of the study pack, to enable staff to ascertain whether the pack had been received, and to address any questions that parents had. However, regardless of the time of day or day of the week that phone calls were made, it was not possible to make contact with the vast majority of parents, and it is felt likely that this is due to the fact they did not want to answer an unknown number. It is therefore impossible to tell how many of the 79 parents who did not return a consent form ever actually received the study information. Slight improvements in contact rate were however seen when an amendment to the study protocol was made to enable contact using SMS messaging as well as telephone contact. In future studies, utilising this combined contact methodology throughout would therefore appear preferable to utilising telephone calls alone.

5.6.3.6. Improving data return rates

Despite the difficulties encountered in making contact with parents, it appears that the work undertaken with the NPEU parental advisory group to design the recruitment and consent process used in the study was beneficial. Based upon recommendations from this group, widespread advertising of the study in hospitals and via charities was undertaken, and parents were first contacted by telephone from their child's treating hospital, as

opposed to by post from the central research team. Of the 107 parents who consented to take part in the study, 81 (76%) returned a completed data collection form. Even when data return rate is calculated based upon the 240 children who were potentially eligible to participate in the parent arm of the study, the return rate of 34% is still nearly three times the 12% achieved in a similar study investigating long-term outcomes for children with gastroschisis conducted two years previously(195).

5.6.3.7. Impact of reduced data return on the comparison of rectal dissection techniques

The most significant impact of the low data return rate was on the ability of the study to make comparisons between rectal dissection techniques. With the available data, it was only possible to compare all three techniques based upon the primary outcome of unplanned re-operation, and this comparison was in a large part only possible due to the multiple event, Cox proportional hazards analysis used. No further comparisons were possible between the Swenson technique and other rectal dissection techniques, and it was only possible to further compare the Soave and Duhamel techniques for three of the nine secondary outcomes, faecal incontinence, urinary incontinence and HAE. Given the lower than anticipated amount of available data, there is the possibility that type II errors have occurred.

5.6.3.8. Impact of reduced data return on the representativeness of the results

Due to the non-participation of eight sites and the lack of any five to seven year data being returned for 52 (21%) of the eligible children in the 20 participating sites, it is possible that the results may not be representative either of the entire population of children treated in the participating sites, or of children treated more generally for HD in the British Isles. Non-

participating sites were more likely to be low-volume centres than participating sites, and children treated in non-participating sites were more likely to have a family history of HD, more likely to have undergone the Swenson procedure, and more likely to have undergone a combined laparoscopic and trans-anal procedure than those treated in participating sites. Children from participating sites who had neither clinician nor parent data returned between five and seven years of age were more likely to be black or minority ethnicity, more likely to be male, and less likely to have undergone the Swenson procedure than infants who had at least one questionnaire returned. There were no differences in any key outcomes at one-year post diagnosis between any of the groups of infants. However, as ethnicity and gender were both factors that were shown to be associated with outcome, there is the potential that outcomes for the group who were lost to follow-up were different to the group who were followed-up.

It is also important to note that children treated in non-participating sites were more likely to have undergone the Swenson procedure than those who were treated in participating sites, but that those children who were followed up in participating sites were more likely to have undergone the Swenson procedure than those were lost to follow-up. This pattern occurred due to the fact that the majority of Swenson procedures performed in the British Isles during the period of the original BAPS-CASS study were performed in two hospitals. One of these hospitals was a non-participating site, and one was a participating site, in which engagement was excellent, and data return rate was 100%. Where outcomes were derived based only on data collected at five to seven years of age, i.e. all outcomes other than the primary outcome, it is therefore likely that results for the Swenson procedure represent one centre, and potentially, one or two surgeons' experience, and therefore the

generalisability of these results is unknown. For the primary outcome, unplanned reoperation, where the analysis was based upon data collected at all time-points for all children whose data were used in the original study, the conclusions can be generalised with greater confidence.

5.6.3.9. Heterogeneity of age at outcome reporting

When first designed, the intention of this study was to describe core outcomes for children with HD at five years of age, as recommended in the NETS[1HD] COS. However, the delays in gaining approvals for the data collection meant that it was not possible to collect data for all children at five years of age, and therefore outcomes data were instead collected over a range of ages, from five years and six months to seven years and nine months. An alternative approach would have been to only collect data from children who were still under six years of age. However, it was anticipated that the variation in outcome between five and seven years of age would be relatively minimal, and given the already small size of the cohort, it was decided that the benefits of including data from a greater number of children outweighed the limitations that were introduced by creating a more heterogeneous cohort.

5.6.4. Implications for future work and clinical practice

The findings from this study can be used to provide parents of children with HD with a more informed picture of what to expect whilst their child is in primary school. They should be counselled to expect that prior to starting primary school, in the majority of cases, children will not be continent of faeces, that about one in ten will not be continent of urine, that approximately four in ten will have undergone at least one unplanned reoperation, and that

their disease and treatment is likely to have an impact on their overall quality of life. When describing these results however, they should be placed in context, with an explanation given that it appears likely that this is the point in a child's life when their outcomes are at their worst, and that as they move into their teenage years, current evidence suggests that their health and wellbeing will show a general trend towards improvement, with multiple studies describing no difference in overall quality of life between adults with and without HD.

Whilst there is some evidence from the work presented here that children who have undergone the Swenson procedure are more likely to undergo unplanned reoperations than those who have undergone the Soave procedure, and that therefore surgeons should be cautious in deciding to utilise this rectal dissection technique, the nature of the data collected for children who have undergone the Swenson procedure makes it difficult to draw this conclusion with certainty. What does appear likely however is that gender, ethnicity, location of transition zone and age at presentation are factors that surgeons should use for risk prognosticating, and which researchers should ensure are well described and accounted for appropriately in any future studies.

Perhaps the most striking implication for clinical practice however, is that surgeons and researchers both need to reconsider the way in which clinical data are collected. The large discrepancy in rates of faecal incontinence described by surgeons and parents can be explained in two ways. Firstly, it could be that when reviewing children in outpatients' clinic that surgeons are not reliably ascertaining whether a child is continent of faeces, or secondly, it may be that whilst surgeons are ascertaining this information correctly, it is then

not available easily in patient notes to allow accurate reporting in observational studies. Regardless of the reason, going forward, it suggests that it is essential that studies aiming to describe outcomes for children with HD include parent reported outcomes data, and if the former explanation is true, then further qualitative work must be undertaken with surgeons and parents to understand why surgeons are not ascertaining whether a child is incontinent of faeces.

Chapter Six

Discussion and conclusion

6.1. What was done in this research

The aim of this research was to investigate whether it is possible to improve outcomes in paediatric surgery through the development and implementation of COSs.

In Chapter One, the research was placed in context by summarising the factors that were known to limit delivery of high quality paediatric surgical care, and by describing the way that COSs could theoretically be utilised as the first step in overcoming these limitations. The summarised evidence was used to determine the aims, objectives and methodology utilised in the studies described in the analytical chapters three to five.

In Chapter Three, development of two COSs was described. One COS was developed to assess the overall success of treatment of infants with HD, and one was developed to assess the overall success of treatment of infants who were born with gastroschisis. In chapters four and five, two cohort studies were undertaken to assess whether there was potential for using COSs in paediatric surgical research to help improve outcomes. This potential was judged by the ability of the conducted cohort studies to develop new, clinically useful knowledge in relation to questions that were of importance to key stakeholders, including, importantly, parents and patients. Outcome selection for these cohort studies was defined by the COSs developed in Chapter Three. The first cohort study was a bi-national study investigating the patient and operative factors that affect core outcomes at 28 days of age in infants born with gastroschisis, and the second was a British Isles-wide cohort study assessing the impact of choice of surgical intervention on core outcomes at five to seven years of age in children with HD.

6.2. Why this research was undertaken

The NCEPOD review of clinical and organisational aspects of children's surgery highlighted how difficulties in decision-making were impacting outcomes for infants undergoing early surgery(1). Such decision-making, the authors argued, would only improve after the evidence-base supporting clinical practice had first been made more robust.

The IDEAL framework was developed to guide researchers through the stages of assessment of surgical interventions and to help develop the sort of evidence-base envisaged in the NCEPOD report (10). However, at the time of starting this research, very few paediatric surgical interventions were being assessed using a methodology that was appropriate after the first two stages of this five-staged framework(2). Without targeting the barriers preventing assessment of paediatric surgical interventions beyond these 'Idea' and 'Development' stages, addressing the concerns of the authors of the NCEPOD report was not possible.

Heterogeneity in the choice of outcomes reported by paediatric surgical studies was identified as the first barrier that must be removed, after which, it would be possible to successively target other limitations, and work towards building a more robust evidence-base. Development and utilisation of COSs is currently seen as the gold-standard method for reducing heterogeneity in choice of reported outcome measures. It was therefore hypothesised that if heterogeneity of outcome reporting could be reduced, that outcomes in paediatric surgery could eventually be improved.

6.3. What was known prior to this research

Prior to embarking on this research, it was known that heterogeneity in the choice of outcomes reported by studies was a key factor preventing systematic reviews from comparing the relative merits of different interventions for the treatment of both HD and gastroschisis(16-19, 75). Such heterogeneity also made it difficult to identify reporting bias and assess whether the results of conducted studies were relevant to patients, parents or clinical practice(20). As a result, wide variation existed in the treatment strategies employed by surgeons across the British Isles(4, 49), and this variation in practice was having a profoundly negative impact on the experience of parents whose children underwent early surgery(140).

COSs were increasingly recognised by key organisations, including the NIHR, the Horizon 2020 programme, the HRA and NICE, as key tools in reducing outcome reporting heterogeneity(32), and thereby improving research quality. Use of Delphi surveys combined with face-to-face consensus meetings was established as the principal method of developing COSs(20, 77)

In gastroschisis, it had been demonstrated that unless there was a clear reason not to, that individual surgeons would generally utilise the same treatment for every infant they cared for (50). However, amongst the community of surgeons as a whole, there was no clear consensus as to what that strategy should be(4). A similar picture was also seen for HD, where individual surgeons again expressed strong preferences for one particular treatment modality, but the community as whole appeared to hold equipoise between them(49).

6.4. What was not known prior to this research

At the start of this research there were key knowledge gaps in two areas. The first gaps related to which outcomes were important in HD and gastroschisis, and the second were clinical knowledge gaps, relating to the management of, and outcomes for, children born with each of these conditions.

Knowledge gaps relating to outcome importance:

1. Which outcomes key stakeholders determined important in defining the overall success of treatment of infants with HD;
2. Which outcomes key stakeholders determined important in defining the overall success of treatment of infants who were born with gastroschisis;
3. How important outcomes should be defined, and when should they be measured.

Clinical knowledge gaps

1. Which infant characteristics affect the health and wellbeing of infants treated for gastroschisis;
2. Whether the operative strategy used to treat children born with gastroschisis affects their health and wellbeing;
3. Whether the management strategies and outcomes for children treated for gastroschisis in the British Isles differ from those treated in Canada;

4. What the health and wellbeing at five to seven years of age is like for children treated for HD in the British Isles;
5. Which child characteristics are associated with variation in the health and wellbeing at five to seven years of age for children with HD; and
6. Whether the rectal dissection technique used to treat children with HD affects their health and wellbeing at five to seven years of age.

The first set of knowledge gaps was addressed in order to develop the HD and gastroschisis COSs. The second set of knowledge gaps were identified as areas that if they could be addressed through the conducted cohort studies, would demonstrate the potential for COSs to be used to improve outcomes in paediatric surgery.

6.5. What was learned during the course of this research

6.5.1. Summary

The four studies conducted as part of this research demonstrated that it was possible to develop COSs for determining the success of treatment of children with HD and gastroschisis, and to utilise these COSs to address clinically relevant questions in a secondary analysis of previously collected data as well as in a prospectively designed cohort study. Demonstrating these possibilities suggests that more widespread use of COSs in paediatric surgical research is feasible, and therefore, the realisation of their benefits, including improved clinical relevance of research, reduced risk of reporting bias, and increased ease of meta-analysis, is attainable. Although the conducted research demonstrated that developing and utilising COSs in paediatric surgical research is possible, it

also highlighted how aspects of the existing paediatric surgical research infrastructure were acting as barriers to realising the full potential of their implementation.

6.5.2. Outcomes of importance in Hirschsprung's disease and gastroschisis

The research presented in Chapter Three was the first time that a COS had been developed for a paediatric surgical condition. The four-stage process that was developed, consisting of a systematic review, a three-phase online Delphi process, a face-to-face consensus meeting, and a face-to-face measurement meeting was shown to be a practical, expeditious method for identifying the outcomes that were important to key stakeholders in defining successful treatment of paediatric surgical conditions. Engagement in this process of people with personal experience of the condition for which the COS was being developed was highlighted as both valuable and practical.

Utilising the described four-stage process, ten outcomes were identified as important to key stakeholders in determining the overall success of treatment of children with HD. These outcomes were death, faecal incontinence, urinary incontinence, unplanned reoperations, Hirschsprung's Associated Enterocolitis, an objective measure of bowel function, voluntary bowel movements without need for enemas or rectal or colonic irrigation, need for a permanent stoma, quality of life, and psychological stress for the individual with HD. Using the same methodology, eight outcomes were similarly identified by key stakeholders as important in determining successful treatment of children born with gastroschisis. These outcomes were death, sepsis, growth, number of operations, severe gastrointestinal complication, time on parenteral nutrition, liver disease and quality of life for the child.

6.5.3. How to define and when to measure core outcomes

In order to effectively operationalise the COSs, it was essential that outcomes were robustly defined, and that appropriate, standardised time-points for measuring them were identified. Reviews of the literature were undertaken to identify commonly used definitions for each of the gastroschisis and HD core outcomes. These definitions were discussed by representative samples of HD and gastroschisis stakeholders at the face-to face measurement meetings, and utilised as the basis for creating clear, specific, practical definitions for each of the identified core outcomes. These same groups of stakeholders unanimously agreed that outcomes should be reported at standardised time-points to aid comparability between studies, but that in order to accommodate different study designs, that these time-points should differ between studies where the entry point was a surgical intervention, and studies where the entry point was birth. For the former, the group determined that outcomes should be reported at 30 days, 90 days, one year, five years and ten years post intervention, and then every subsequent ten years. For the latter, the group determined that outcomes should be reported at 28 days, one year, five years and ten years of age, and then every subsequent ten years.

6.5.4. Characteristics associated with variation in the health and wellbeing of infants treated for gastroschisis

Severe gastrointestinal complication was utilised as the primary outcome for the NETS^{2G} bi-national cohort study described in Chapter Four. This outcome was defined, as per the NETS^{1G} gastroschisis COS, to include only intestinal perforation, any intestinal resection regardless of amount of bowel removed or the indication for the resection, mechanical

intestinal obstruction resulting in a repeat laparotomy, abdominal compartment syndrome, and enterocolitis. Two patient characteristics, presence of intestinal atresia, and presence of intestinal perforation, were associated with an increased incidence of severe gastrointestinal complications, and one patient characteristic, higher birthweight, was associated with a decreased incidence of severe gastrointestinal complications.

The factors identified in this work as associated with number of severe gastrointestinal complications were different to the factors previously identified by Cowan et al and Arnold et al as being associated with mortality(95, 111) (Table49). There are biologically plausible explanations why these two groups of characteristics would be different. It is therefore unclear whether the factors identified in this research as associated with unplanned reoperation can be referred to generally as factors that are associated with variation in the health and wellbeing of children with gastroschisis, or only as factors associated with variation in the number of severe gastrointestinal complications experienced by an infant born with gastroschisis.

Table 49: Factors associated with variation in outcome for infants born with gastroschsis

Arnold et al		NETS^{2G} Study		Cowan et al	
Factor	**Adjusted OR (95% CI)**	**Factor**	**Adjusted IRR (95% CI)**	**Factor**	**OR (95% CI),**
Intestinal atresia	2.01 (1.09-3.71)	**50g increase in birth weight**	0.96 (0.95-0.98)	**Intestinal necrosis**	11.47 (4.20-31.35)
Enterocolitis	3.87(1.96-7.65)	**Intestinal atresia**	2.36 (1.5-3.71)		
Rare cardiac anomalies	7.85 (2.59-23.78)	**Intestinal perforation**	3.75 (1.96-7.15)		
Lung hypoplasia	14.14 (7.31-27.35)				

6.5.5. Effect of operative strategy on outcomes for infants with gastroschisis

The comparison between operative primary fascial closure (OPFC), ward-based reduction with sutureless closure (WBR), and silo placement with staged reduction and delayed closure (SR) that was presented in Chapter Four, including 1451 infants, is larger than any similar study published in the existing literature. This comparison identified that there were differences in the effect of interventions on outcome dependent upon whether or not the infant had one or more of intestinal perforation, necrosis or matting.

In infants without necrosis, perforation or matting, the use of SR compared with OPFC was associated with a 75% decrease in the incidence of severe gastrointestinal complications, but a 40% increase in the incidence of operations, a two-fold increase in the odds of infection, and potentially an 8% increase in the number of days parenteral nutrition use. When WBR was compared to OPFC in infants without necrosis, perforation or matting, it was associated with a 20% increase in the incidence of operations in the first 28 days of life, but no other differences in outcomes.

In infants with necrosis, perforation or matting, SR was associated with a 30% greater incidence of operations than OPFC, and potentially a 6% greater number of days parenteral nutrition use, but no differences in other outcomes. No differences were identified in outcomes between OPFC and WBR in this sub-group of infants, although this may be due to the small number of infants with these characteristics who underwent WBR.

6.5.6. Gastroschisis in the British Isles compared to gastroschisis in Canada

The analysis presented in part three of Chapter Four highlighted that there were differences in the characteristics of children treated in each country, as well as differences in the management strategies used. However, as the only difference in outcome was that Canadian infants potentially received a marginally greater number of days of parenteral nutrition, the differences described in characteristics and management should not prevent further exploration of a bi-national RCT comparing OPFC and SR for the treatment of children born with gastroschisis.

6.5.7. Health and wellbeing of children with Hirschsprung's disease

Describing all ten core outcomes using parent and clinician reported outcomes data in a contemporary, multi-centre cohort of children has given a rounded assessment of the health and wellbeing of primary school aged children treated for HD in the British Isles. At five to seven years of age, over 60% of children were incontinent of faeces, 11% were incontinent of urine, 43% had undergone at least one unplanned reoperation, and 48% had experienced at least one episode of HAE. Just under 50% of children for whom data were collected, were reported to have reduced health related quality of life. This assessment suggests poorer overall outcomes than previously described in the literature.

Statistically significant differences were identified between children who were successfully followed up and those who were not. Although the clinical significance of these differences in ethnicity, sex and operative technique were uncertain, caution must be exercised when generalising results from this study, as the 199 children for whom any follow-up data was

collected represent just 65% of the 305 children in the original BAPS-CASS cohort, and the 81 children for whom parent follow-up was returned represent just 27% of the original BAPS-CASS cohort.

6.5.8. Characteristics associated with variation in the health and wellbeing of children with Hirschsprung's disease

Data from 256 children who underwent definitive surgery for their HD and who had at least one day of post-operative follow-up were used to investigate the association of key child characteristics with rates of unplanned reoperations. Following adjustment, black or minority ethnicity, female sex, and presentation after 28 days of age were respectively associated with an 80%, 70% and 62% reduction in the risk of unplanned reoperations. Total colonic aganglionosis was associated with a five-fold increase in the risk of unplanned reoperation.

In comparison to gastroschisis, there has been less large-scale research investigating the association of patient factors with outcome in children with HD. However, of the characteristics associated with unplanned reoperation found in this study, sex, ethnicity and length of affected segment of bowel have all been shown previously to have an association with other outcomes(165, 172-175). It is not therefore unreasonable to postulate that unlike in gastroschisis these factors may be associated with more general variation in health and wellbeing, as opposed to only having an association with unplanned reoperation. Based on existing evidence, it seems likely that these characteristics may be manifestations of underlying genetic variants of HD that pre-dispose to differences in outcomes.

6.5.9. Effect of rectal dissection technique on outcomes for children with Hirschsprung's disease

Multiple-event, Cox proportional hazards modeling was the most statistically efficient way to investigate the association between rectal dissection technique and the primary outcome of the NETS^{2HD} study, unplanned reoperation. This analysis demonstrated that unplanned reoperation rates in the Soave, Duhamel, and Swenson rectal dissection groups were respectively 0.10 per person year, 0.41 per person year, and 0.91 per person year. Unadjusted Cox proportional hazards modelling suggested that in comparison to the Soave technique, the Swenson and Duhamel techniques were associated with a nearly eight-fold, and a two and a half-fold increased risk of unplanned reoperation respectively. Following adjustment for propensity score, weight at surgery and first-approach to the pull-through procedure, the Swenson technique was still associated with an approximately seven fold increased risk of unplanned reoperation, but there was no longer a statistically significant difference between the Duhamel technique and the Soave technique. These results would suggest that at least part of the difference in outcome seen between the Duhamel and Soave techniques on univariable analysis was due to the fact that the Duhamel technique is being used as the intervention of choice for infants with more complex HD.

Due to the fact that less outcome data were collected than anticipated, it is difficult to draw robust conclusions regarding the relative merits of each rectal dissection technique in relation to the secondary outcomes investigated.

6.6. Strengths and limitations of this research

6.6.1. Summary of strengths and limitations of the individual studies

Both COS development studies used robust, quantitative methods to identify outcomes that were important in defining treatment success. A key strength of each of these studies was the inclusion of a large personal experience panel in identifying outcomes of importance, therefore ensuring that the COSs were relevant to the key stakeholders, not just clinicians. Both studies may however have been affected by the way in which the personal experience voice was represented. For the HD study, there were a greater proportion of participants who had experience of long-segment HD than would be expected in the general population, and for the gastroschisis study, the personal experience voice was almost entirely that of parents, not people born with the condition. These limitations may therefore have minimally affected the representativeness of the final COSs, although it is unlikely to represent a major limitation.

The major strength of the NETS^{2G} study presented in Chapter Four is the size of the population of infants with gastroschisis that was established. This cohort was the largest ever established in which it was possible to investigate the effect of treatments on outcome, and has therefore been able to provide the most robust estimates to date of the relative merits of each major reduction and closure technique. There were however two major limitations of this study. Firstly, there were significant differences in the way some outcomes were defined in the BAPS-CASS and CAPSNet studies, making data merging problematic, but highlighting the need for the consistency in data collection that future use of the COS will bring. Secondly, there was evidence of significant confounding by intention,

and whilst this was accounted for as best as possible by using propensity score adjusted analyses, it was difficult to know how much influence this had on the final results. However, in the absence of RCT data, the evidence from this study remains the most robust to date.

In contrast to the NETS^{2G} study, one of the major strengths of the NETS^{2HD} study presented in Chapter Five was that all outcomes were clearly and robustly defined according to the descriptions developed for the NETS^{1HD} COS. This allowed description of outcomes in a way that was deemed by key stakeholders to capture what they were intending when identifying outcomes as important. An additional major strength of this study was that it collected parent reported outcomes data and linked these with clinician data, thereby giving both parents and clinicians a voice, as well as improving the data accuracy. However, despite best efforts, the major limitation of this study was the response rate. This both affected the ability of the study to detect differences between treatments with statistical significance, and also meant that is was unclear how representative the results were of the originally identified cohort of children.

6.6.2. Strengths and limitations of the overall research

Prior to the start of this research, development of COSs was often a lengthy and expensive process, and appeared to many to be a purely academic exercise. Within paediatric surgery, there had not previously been any COSs developed, and there was little buy-in, either from clinical or research communities, to the idea of developing or utilising them. A major strength of this research programme is that it has started to alter that status quo. This has been achieved by developing a robust pathway through which COSs can not only be developed, but through which their utility can also be investigated, and potential benefit to

use immediately demonstrated. This pathway has involved development of collaborations between parents, patients, charities, clinicians, and two of the largest existing paediatric surgical research databases. It has also involved development of a bespoke, customisable, information technology system for delivering multiple online consensus processes at once. By seamlessly integrating the development of a COS with its subsequent utilisation in clinical research, this programme has created the ambition and facility to attempt to replicate this process in other paediatric surgical conditions.

The major limitation of this research programme however, was that despite the development of the pathway linking COS development to COS utilisation, it was not possible to address all of the desired clinical objectives. Specifically, for many core outcomes, it was not possible to make reliable comparisons between surgical interventions in the NETS^{2HD} study due to a lack of data. The large paediatric surgical databases developed by BAPS-CASS and CAPSNet, and utilised in the NETS^{2G} and NETS^{2HD} studies were specifically designed to only collect anonymous data. This approach both simplified study design and also enabled accurate calculation of disease incidences. However, due to the anonymous nature of the data collected, these frameworks did not facilitate collection of data directly from parents of affected children. Therefore, in the NETS^{2HD} study, an indirect approach to enable collection of such parent reported outcomes data was developed. This approach was designed in conjunction with parent groups and charities in order to maximise acceptability to parents, and modified in order to meet the requirements of the research ethics committee and the confidentiality advisory group. However, the end result was a complex, multi-staged process that was difficult to deliver both for local investigators and also for central research staff.

In the initial BAPS-CASS HD cohort, utilised as the sampling frame for the NETS^{2HD} study, data from 305 children were used. However, at each stage of the process of recruiting parents of these children to participate in the five to seven year follow-up study, the pool of parents from whom data could be collected shrank. Eight of the 28 paediatric surgical centres in the United Kingdom and Ireland did not participate in the study, resulting in a reduction of the pool of contactable parents from 305 to 252 (83%), and twelve of the children in participating centres had died prior to five years of age, reducing the pool further to 240 (79%). Central research staff then only received contact details from local sites for 186 children (61%). This loss of contact details was not due to refusal to share by parents, but an inability of local investigators to re-identify children, identify up to date contact details, or to make contact with parents.

By the point at which central research staff were able to make contact with parents to discuss participation in the study, the pool of parents who could be consented had already reduced to 61% of its original size. Of the 186 parents whose contact details were received, 107 (58%) consented to participate, and 81 (44%) returned completed study questionnaires. Based upon the proportion of contacted parents that returned data collection forms, if instead of only being able to contact 61% of the original cohort to discuss participation in the study, it had been possible for central research staff to contact parents of all children whose data were used in the original BAPS-CASS study, data would have been received for approximately 135 children (44%) instead of 81 (27%). Receiving the larger amount of data would have both increased the power of the study to detect statistically significant differences between treatments, and also increased the generalisabilty of the study's results.

6.7. Implications and recommendations for clinical practice

The clinical implications and recommendations from this research fall into two categories, management guidelines for infants born with gastroschisis, and information for counselling parents of children with HD. They are summarised in Table 50.

Table 50: Summary of clinical implications and recommendations

Gastroschisis

- For infants born with gastroschisis and no intestinal matting, necrosis or perforation, there are risks and benefits to treatment with operative primary fascial closure, ***and*** silo placement with staged reduction and delayed closure. However, the benefits of silo placement with staged reduction appear more significant than the benefits of operative primary fascial closure. It is therefore reasonable to cautiously recommend use of silo placement with staged reduction for treatment of infants who do not have intestinal matting, necrosis or perforation. The risks and benefits associated with each procedure should however be explained to parents and weighed alongside their personal priorities and the surgical team's experience, in order to decide which reduction and closure strategy is most appropriate for a particular infant.
- Children born with gastroschisis and intestinal perforation, necrosis or matting should be treated with operative primary fascial closure.
- As this work has demonstrated risks and benefits to both operative primary fascial closure and silo placement with staged reduction and delayed closure for children with gastroschisis and no intestinal matting, necrosis or perforation, a randomised controlled trial and economic analysis comparing the two should be undertaken. Infants with intestinal perforation, matting or necrosis should not be included in this trial.

Hirschsprung's disease

- There is some evidence to suggest that the Swenson technique is associated with a greater incidence of unplanned reoperations than the Duhamel and the Soave techniques, and therefore surgeons should be cautious when deciding to use it.
- Surgeons should counsel parents of children with Hirschsprung's disease that there is a high risk of faecal incontinence, unplanned reoperation and urinary incontinence during their child's primary school years. Work should be undertaken in conjunction with Hirschsprung's disease charities to produce reliable information sources that can help parents place this information in context.

6.7.1. Management guidelines for infants born with gastroschisis

Based upon the data presented in Chapter Four, if treated using SR as opposed to OPFC, infants with gastroschisis who are born without necrosis, perforation or matting, have a reduced risk of severe gastrointestinal complications, but an increased risk of infection and an increased duration of parenteral nutrition use. These risks and benefits should be discussed with parents, and assessed alongside their priorities and the surgical team's experience. When these results are placed in the context of the studies discussed in the background, and the implications of each outcome, there is now sufficient evidence to suggest that pending results of a high quality RCT, SR should be cautiously recommended as the intervention of choice for children with gastroschisis and no intestinal matting, perforation or necrosis. In contrast, for infants born with intestinal matting, perforation or necrosis, SR was associated with an increased risk of infection and duration of parenteral nutrition use, but no decreased risk of severe gastrointestinal complications. On the weight of this and existing evidence, OPFC should be recommended as the intervention of choice for these infants. These recommendations must however be placed in the context of the observational nature of the data from which they were derived, and the necessity for on-going research in the form of a large-scale RCT.

6.7.2. Counselling parents of children with Hirschsprung's disease

The experience of many parents whose children undergo early surgery is not optimal(140). Their experience is limited by discrepancies and contradictions in the information they receive from surgeons, and an inability of hospitals to provide them with sufficient information to understand the likely interventions they will undergo, and the outcomes they

will experience(140). Based upon data presented in Chapter Five, it is now possible to give parents of children with HD a clearer idea of the clinical implications of their child's diagnosis and its treatment. On this basis parents should be counselled that approximately six in ten children will not be fully continent of faeces when they start primary school, that approximately two in every five children will have undergone at least one unplanned reoperation by this point, and that for one in every two children, the HD will be having an impact on their quality of life. Parents should therefore be prepared for their child to need additional support at this time. However, placing these results in the context of existing literature, parents should also be counselled that it appears that from this point onwards, their child's health and wellbeing is likely to improve, and that there are studies which suggest that by adulthood, people with HD have a normal quality of life.

6.8. Future research

This thesis has highlighted six key areas where future research is needed.

6.8.1. Randomised controlled trial comparing reduction and closure strategies for gastroschisis

Whilst it is possible from the data described in Chapter Four to cautiously recommend the use of SR in children with gastroschisis and no necrosis, perforation or matting, this research has also demonstrated that there are risks and benefits to both SR, and OPFC in these infants. There were no clinical reasons demonstrated why a bi-national British Isles and Canada multi-centre RCT comparing these treatments could not be conducted, and therefore, based upon the work presented in this thesis, conducting such a trial, including

an economic evaluation of both treatments, should be a priority. Severe gastrointestinal complication would be an appropriate primary outcome for such an RCT, and utilising a survival analysis, interventions could be compared against this outcome.

A baseline hazard rate for severe gastrointestinal complications in the first month of life for infants undergoing OPFC is approximately 0.16 severe gastrointestinal complications per month. This is based upon 105 complications occurring in the 671 infants who underwent OPFC in Chapter Four, each of whom had an assumed follow-up time of one month. Again, based upon data from the study presented in Chapter Four, the minimum anticipated reduction in severe gastrointestinal complications when SR is used, would be approximately 33%. In order to detect a 33% reduction in severe gastrointestinal complications with 90% power at the 5% level of significance, from a baseline hazard rate of 0.16, when comparing SR to OPFC, an RCT would need to randomise 256 infants. In order to detect with statistical significance a more modest, but still clinically significant 20% reduction in severe gastrointestinal complications when OPFC is compared to SR, 856 infants would need to be randomised. With approximately 40% of infants with gastroschisis having no intestinal necrosis, intestinal matting or intestinal perforation at birth, there are approximately 150 infants born in the British Isles and Canada each year who would be eligible to participate in such a trial. In any RCT, the remaining gastroschisis core outcomes should be investigated as secondary outcomes alongside the primary outcome of severe gastrointestinal complication.

It is essential that a feasibility study, designed to assess and maximise recruitment is undertaken prior to any main trial. In such a study, involving other high-income, Western

countries in the trial, or targeting centres with a high incidence of gastroschisis should be explored as methods of maximising recruitment rates.

6.8.2. Teenage outcomes for children with Hirschsprung's disease

The outcomes for children with HD that were described in the NETS^{2HD} study were poorer than much of the existing literature would suggest, and it is hypothesised that part of this may be due to the age at which the outcomes were described. As previous work has suggested that outcomes improve in the teenage years, it is essential that the cohort of children from the NETS^{2HD} study are followed-up again at ten and fifteen years of age to accurately track their outcomes as they get older.

6.8.3. Comparison of rectal dissection techniques in Hirschsprung's disease

The results of the NETS^{2HD} study suggested that outcomes following the Swenson procedures might be poorer than outcomes following the Soave procedure. However, the limitations of the study prevented firm conclusions from being drawn. It is therefore essential that further large-scale observational studies are conducted in which core outcomes can be described and compared for larger groups of children who have undergone each procedure.

6.8.4. Genetic predictors of outcome in Hirschsprung's disease

It appears likely that underlying genetic variants of HD are associated with variation in outcome. Developing a deeper understanding of these genetic variants, and how they are associated with the patient characteristics that were shown in Chapter Five to be associated

with number of unplanned reoperations, would provide clinicians with a far greater ability to counsel parents regarding the likely outcomes for their child following diagnosis.

6.8.5. Further development and comparison of core outcome sets

Development of selected further COSs for paediatric surgical conditions, and comparison of these against existing COSs to identify areas of similarity and difference will be an important step in determining whether it is necessary to develop COSs for each individual condition, or whether a more generic paediatric surgical COS could be developed.

6.8.6. Development of research infrastructure

The work presented in this thesis has demonstrated that COSs can be developed for HD and gastroschisis, that they can be utilised in a secondary analysis of existing data and a prospective cohort study, and that by doing so, there is the potential to improve outcomes in paediatric surgery. However, it has also highlighted three aspects of the existing paediatric surgical research infrastructure that must be modified if the full potential of utilising COSs is to be realised. Firstly, the size of populations from which infants can be recruited must be increased; secondly, the burden on clinicians of participating in multi-centre research must be reduced; and thirdly, a simplified method of collecting parent reported outcomes data must be developed.

The major strength of the NETS^{2G} study presented in Chapter Four was the size of the study population. This was achieved in two ways, firstly, by combining population-based data from the British Isles and Canada, and secondly, in the Canadian dataset, by accruing new

cases in an on-going, continuous manner. This data collection methodology was in contrast to the NETS^{2HD} study, where data were only collected from the British Isles, and only over a two-year period. By the time children had been lost to follow-up, the already relatively small initial population had been reduced to a size at which it was difficult to make reliable comparisons between interventions. If instead of case accrual occurring over a defined two-year period for the original BAPS-CASS HD study, it had occurred in a continuous, on-going manner in a similar way to that for CAPSNet, there would now be approximately 1220 children whose data would have been collected. A dataset of this size would allow robust comparison of all interventions.

However, as was seen by the decision of six sites not to participate in the NETS^{2HD} study due to a lack of staff time, the burden of participating in large-scale multi-centre research is already not insignificant. If a model of continuous case accrual were to be moved towards, this burden would only increase, and it would become essential to find methods of identifying cases and collecting data that did not directly involve clinicians. Further work must therefore be undertaken to develop such methodology, which could involve, amongst other things, the use of routine data, structured electronic operative notes, Electronic Patient Record systems, and paid data abstractors.

In the NETS^{2HD} study, it was also demonstrated that it is currently difficult to use anonymous cohorts of children as the basis from which to collect parent reported outcomes data. However, both the gastroschisis and HD COSs included outcomes that could not be described using only data that were routinely collected in clinical practice, and it is likely that future paediatric surgical COSs will be similar. If all outcomes included in paediatric

surgical COSs are to be accurately described, it is essential that parent reported outcomes are collected as well as clinical data. Such parent reported outcomes data could be collected in two ways, firstly, by integrating data collection into existing clinical visits, and secondly, by developing the infrastructure required to consent large numbers of parents whose children undergo early surgery to participate in research similar to the NETS^{2HD} study. Further work must therefore be undertaken to investigate how these modifications to the existing research infrastructure can most cost-, and time-efficiently, be made.

6.9. Conclusion

Over the course of this research, core outcome sets for HD and gastroschisis have been developed, and then utilised in large-scale observational studies to address questions of clinical importance. By using the core outcome sets to address the questions of clinical importance, evidence has been produced which can be used to develop management guidelines for children born with gastroschisis, and to provide parents of children with HD with more relevant information about the clinical course that their child is likely to take. Whilst practical limitations to utilising core outcome sets within the existing paediatric surgical research infrastructure were identified, by demonstrating that the six identified clinical knowledge gaps could be closed, the conclusion of this thesis must be that developing and implementing the use of core outcome sets ***can*** improve outcomes in paediatric surgery.

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Appendices

Appendix 1: *Hirschsprung's Disease core outcome set development protocol and systematic review search strategies*

I.I NETS1HD Hirschsprung's disease core outcome set development protocol

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Trials

STUDY PROTOCOL Open Access

NETS[1HD]: study protocol for development of a core outcome set for use in determining the overall success of Hirschsprung's disease treatment

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Abstract

Background: Use of core outcome sets in research has been proposed as a method for countering the problems caused by heterogeneity of outcome measure reporting. Heterogeneity of outcome measure reporting occurs in Hirschsprung's disease (HD) research and is limiting the development of a robust evidence base to support clinical practice.

Methods: Candidate outcome measures have been identified through a systematic review. These outcome measures will form the starting point for a three-phase online Delphi process to be carried out in parallel by three panels of experts. Panel 1 is a neonatal panel; panel 2 is a non-neonatal panel; and panel 3 is a lay panel. In round 1, experts will be asked to score the previously identified outcome measures from 1 to 9 based on how important they think the measures are in determining the overall success of their/their child's/their patient's HD. In round 2, experts will be presented with the same list of outcome measures and graphical representations of how their panel scored that outcome in round 1. They will be asked to re-score the outcome measure, taking into account how important other members of their panel felt it to be. In round 3, experts will again be asked to re-score each outcome measure, but this time they will receive a graphical representation of the distribution of scores from all three panels, which they should take into account when re-scoring. Following round 3 of the Delphi process, 40 experts will be invited to attend a face-to-face consensus meeting. Participants will be invited in a purposive manner to obtain balance between the different panels. Results of the Delphi process will be discussed, and outcomes will be re-scored. Outcome measures where >70% of participants at the meeting scored it 7–9 and <15% scored it 1–3 will form the core outcome set.

Discussion: Development of a core outcome set will help to reduce heterogeneity of outcome measure reporting in HD. This will increase the quality of research taking place and ultimately improve care provided to infants with HD.

Keywords: Paediatric surgery, Hirschsprung's disease, Core outcome sets

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Background

Hirschsprung's disease (HD) is a condition where the nerves of the myenteric plexus do not develop correctly along the full length of the colon. It results in infants being unable to open their bowels properly, and it affects approximately 1.7 in 10,000 live births in the United Kingdom and Ireland. Treatment is usually with surgical resection of the affected sections of bowel within the first few months of life. There are currently three main approaches to conducting the definitive pull-through procedure required for treatment of HD: the open approach, the purely transanal approach [1] and the laparoscopically assisted approach [2]. There are also multiple methods used to perform colorectal/coloanal anastomosis [3–5]. To date, authors of systematic reviews have been unable to reliably determine the gold standard intervention for HD [6, 7]. One of the key factors preventing identification of a gold standard intervention is heterogeneity of outcome measure reporting in primary studies.

Heterogeneity of outcome measure reporting results in difficulties with synthesising data from individual studies, as well as resulting in studies being prone to reporting bias and a lack of patient relevance [8]. Within HD research, such heterogeneity has resulted in the conduct of studies focused on hospital-based measures or surrogate markers of success, as opposed to outcomes that are deemed important by people with HD or their families [7]. Owing to the low incidence of HD, conducted studies are frequently limited in size. In this situation, it is essential that all conducted studies be relevant to patients, report full data and be easy to synthesise with other work.

A core outcome set (COS) is a group of outcome measures that have been identified by key stakeholder groups as the most important in determining the success of treatment of a particular condition [8, 9]. Use of a COS to define the outcome measures which are the minimum it is acceptable to investigate and report in a particular field of research has been shown to be a successful method for countering heterogeneity in outcome measure reporting [10]. When development of a COS for HD is combined with increased collaboration between research institutions, the ability of HD research to answer clinically relevant questions will be increased, and generation of robust evidence-based management guidelines will be facilitated.

Methods

Ethics and registration

The Health Research Authority deemed the project to be service evaluation/service development, and therefore review by a National Health Service (NHS) Research Ethics Committee was not deemed necessary. Information on the nature of the study will be provided to participants prior to registration and again prior to completion of the first round of the survey. Potential participants are given contact details for staff within the National Perinatal Epidemiology Unit (NPEU) from whom further information can be obtained or with whom they can discuss the study further. Detailed information is also available on the study website (http://www.npeu.ox.ac.uk/nets). Consent to participate in the study is implied by completion of the registration questionnaire and data collection questionnaires. Participants can withdraw from the study at any time, either by contacting the study team or by simply not completing a data collection questionnaire. The study has been registered with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative (http://www.comet-initiative.org).

Scope of the core outcome set

The developed COS is intended to be used to assess the overall success of treatment of an infant born with HD. This will involve outcome measures identified as important from diagnosis through into adulthood. We have kept the scope of the COS broad for two reasons. First, although HD research currently covers multiple different areas of treatment, there are only a limited number of studies being conducted that use robust methodology [11]. Any intervention that is aimed at improving the overall robustness of research taking place therefore needs to be as broadly applicable as possible. Second, whilst research into the treatment of infants with HD will fall into three broad areas (management of enterocolitis, definitive surgery and re-do surgery), it is the combination of success of treatment in these three areas that matters. Developing a COS to reflect treatment success in one area whilst neglecting the importance of the other two areas would therefore likely not meet the primary aim of developing the COS.

The following are key objectives of the trial:

1. To determine which outcomes are currently reported in studies comparing surgical treatments for HD and assess the quality of reporting
2. To prioritise outcomes from patient/parent, paediatric surgical and non-surgical clinician perspectives
3. To achieve consensus between key stakeholders on a COS for assessing how successful the overall treatment of an infant with HD has been
4. To compare and contrast outcomes prioritised by patients/parents, surgeons and non-surgical clinicians

Wider aims of the trial are as follows:

1. To develop methodology for addressing difficulties likely to be encountered in development of COSs in

all paediatric surgical conditions, including the following:

a. Recruitment of parents and patients
b. Incorporation of opinions from clinicians whose priorities vary dependent on their specialty, or age they encounter the child

Design

There will be four key stages to development of the COS:

1. Systematic review to identify currently reported outcomes
2. Development of a panel of experts
3. Three-phase online Delphi process
4. Consensus meeting

Systematic review

An already conducted systematic review has been used as the basis for phase 1 of the Delphi process (Allin B, Irvine A, Patni N, Knight M. Variability of outcome reporting in Hirschsprung's disease and gastroschisis: a systematic review, unpublished). The aim of this systematic review was to identify every outcome measure investigated by studies that have been conducted since 2010 and involved more than ten participants, and in which two or more interventions for HD were compared. The systematic review included both observational and interventional studies and thereby gave a broad overview of outcomes that are currently investigated in the HD literature. The outcome domains identified by this systematic review will be used as the outcomes to be scored in phase 1 of the Delphi process. Specific time points and methods of measurement will not be incorporated into the outcomes to be scored in phase 1. These components will instead be identified through subsequent literature review; discussion at the consensus meeting; and, if necessary, a separate 'how to measure' meeting. The use of systematic reviews to inform phase 1 of a Delphi process is recommended by the COMET Initiative [12] and has previously been used in the development of other COSs, including in the Management of Otitis Media with Effusion in Cleft Palate study [13].

Panel assembly

Expert identification and recruitment

To ensure appropriate breadth of recruitment, experts will be recruited under three broad categories (disciplines, organisations and literature) and then within sub-categories, which include, amongst others, paediatric surgeons, paediatric gastroenterologists, parents, the Royal College of Paediatrics and Child Health, and the *Journal of Paediatric Surgery*. Members of the study management group (SMG) will draw up an exhaustive list of sub-categories from which at least two participants must be identified. Experts known to the SMG and fitting into one of these sub-categories will be identified first, prior to expanding recruitment using methods specific to each sub-category. Examples of expert recruitment include the following:

- Contacting all paediatric surgeons listed on the British Association of Paediatric Surgeons register of practitioners as having a specialist interest in the treatment of infants with HD
- Advertising to people with HD and their parents via mailing lists established by the Hirschsprung's & Motility Disorders Support Network
- Contacting the editors of key paediatric surgical journals and asking them to identify members of their editorial board with an interest in HD
- Advertising to paediatric gastroenterologists via mailing lists of the British Society of Paediatric Gastroenterology Hepatology and Nutrition

All identified experts will be emailed a link to an online form on which they can detail their involvement in HD and express their interest in participating in the study. Experts will also be asked to provide the names of anyone else they feel would be appropriate to invite to participate in the study. At this stage, we are seeking to clarify the suitability of experts for participation in the study and to identify further potential experts. This process will be repeated for the names provided by already-contacted experts. Expert recruitment will continue until a minimum of 50 experts, at least 2 in each category, have been recruited.

Following confirmation of their eligibility to participate in the study, experts will be sent a link to a customised online database hosted on the secure servers of the University of Oxford and developed using LimeSurvey (https://www.limesurvey.org), from which they can access phase 1 of the Delphi process.

Facilitating consensus

To be truly representative of the broad experience of those involved in HD, it is important that the COS reflect the opinions of people with HD, their parents, and a broad spectrum of clinicians, including those who treat people with HD later in life (e.g., paediatric gastroenterologists), as well as in early infancy (e.g., neonatologists). These different groups may have different priorities, which could cause difficulties in attaining consensus on a single set of important outcome measures. Thus, to facilitate achieving consensus, experts will be separated into three different panels:

1. *Neonatal panel*: Clinicians whose responsibility includes management in the neonatal period (but may also include management outside the neonatal

period). This group will include neonatologists and paediatric surgeons.
2. *Non-neonatal panel*: Researchers with expertise in HD management and clinicians responsible for management primarily outside the neonatal period. This group will include specialist nurses and paediatricians.
3. *Lay panel*: Parents (or other equivalent guardian) and adults born with HD.

Delphi process

Phase 1 data collection

To maintain anonymity and ease data collection, a customised online system will be developed to conduct a three-phase Delphi process run in parallel for the neonatal, non-neonatal and lay panels. In phase 1, participants will be presented, in alphabetical order, with outcomes identified from the systematic review. Lay equivalents will be developed for each outcome measure, and these will be used instead of scientific terms for the parent/patient panel. These terms will be developed in conjunction with the NPEU's parent advisory group.

Participants will be asked to give each outcome measure a score from 1 to 9, where 1, 2 and 3 are 'not that important'; 4, 5 and 6 are 'important'; and 7, 8 and 9 are 'really important'. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale of measurement has been chosen for use in scoring outcome measures on the basis of recommendations from the COMET Initiative [12]. After scoring all outcome measures identified by the systematic review, participants will be asked to list any additional outcome measures they feel are important in determining the success of treatment of HD, but which we have not already asked them to score. These outcomes will not be scored in phase 1.

Data will be collected over a 4-week period for each phase of the Delphi process. Participants who have not completed the survey will be sent reminders via email when they have 2 weeks, 1 week and 48 h remaining for completion of the survey. Participants who have not completed the questionnaire within 4 weeks of the phase start will be deemed not to have completed that phase. Testing has suggested that completion of the phase 1 questionnaire will take participants approximately 15 minutes.

Phase 1 analysis

The number of experts invited to participate, registering to participate and completing phase 1 of the Delphi process from each sub-category will be recorded. Outcomes will be analysed separately for each panel, with descriptive statistics calculated, including medians and inter-quartile ranges. All outcomes will be carried forward to phase 2. Additional outcomes listed by experts in phase 1 will be assessed by the SMG to determine whether they represent de novo outcomes and whether they fall within the scope of the COS. Those that are deemed to both fall within the scope of the COS and represent a de novo outcome will be taken forward to phase 2 and scored alongside the outcome measures scored in phase 1. We anticipate that there will be between 10 and 20 outcomes that meet these criteria.

Phase 2 data collection

Experts completing phase 1 will be invited to participate in phase 2 and asked to re-score each outcome on the basis of the following:

- The phase 1 score they assigned it
- Descriptive statistics from their panel

Descriptive statistics will be represented numerically and graphically.

Phase 2 analysis

Descriptive statistics will again be calculated. Bias from loss of experts between rounds will be assessed by determining if there is any difference in median round 1 scores for each outcome measure between experts who have completed both phases and experts who completed only phase 1. All outcomes will be carried forward to phase 3.

Phase 3 data collection

Experts completing phase 2 will be invited to participate in phase 3 and asked to re-score each outcome on the basis of the following:

- The phase 2 score they assigned it
- Round 2 descriptive statistics from all three panels

Phase 3 analysis

Analysis will be conducted as per phase 2.

Generation of core outcome set: consensus meeting

A roundtable consensus meeting with an independent, non-voting chair will be held at a central location in the United Kingdom to identify the final COS and determine how to measure those outcomes that form it. Participants will be invited to attend the consensus meeting in such a way as to ensure participation from all three panels that is as even as possible, with a range of experiences represented.

The final COS will comprise those outcome measures where >70% of participants at the consensus meeting score the outcome measure between 7 and 9 and less than 15% of participants at the consensus meeting score the outcome measure between 1 and 3. Every outcome measure assessed in phase 3 of the Delphi process will

be discussed and re-scored by meeting participants using the same scale as for the online portion of the study.

Prior to the meeting, participants will be given a summary of the final results of the Delphi process. During the meeting, they will be shown a graphical representation of the scores for each outcome measure (Fig. 1) and given the opportunity to explore the reasons for any differences in scores between panels. After discussion of each outcome measure, re-scoring will take place electronically and anonymously using the TurningPoint system (Turning Technologies, Youngstown, OH, USA). These scores will be used to determine whether an outcome measure is included in the COS.

Following completion of the consensus meeting, a consensus document will be drafted and put forward to participants for approval. This document will be presented at appropriate international meetings and published in peer-reviewed journals.

Data management

All data will be directly entered into a customised database by participants. Data will be stored securely on servers within the NPEU and will be managed as per standard operating protocols. Only appropriate members of the study team will have access to the data. Data analysis will be conducted by BA and MK. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklists are provided in Additional file 1.

Discussion

Development of the COS will identify outcomes that are important to people with HD, their parents and key clinical stakeholder groups. Use of such a COS in future research will help to counter many of the previously identified problems caused by heterogeneity of outcome measure reporting, including a lack of patient relevance, a high risk of reporting bias and difficulty in conducting meta-analyses.

Involvement of multiple stakeholder groups in development of the COS is one of its major strengths and will ensure that it is relevant to patients and applicable across a broad range of clinical settings. This is the first time that people with HD and their parents will have been involved in identification of key outcomes for research studies in a robust, replicable manner, and this

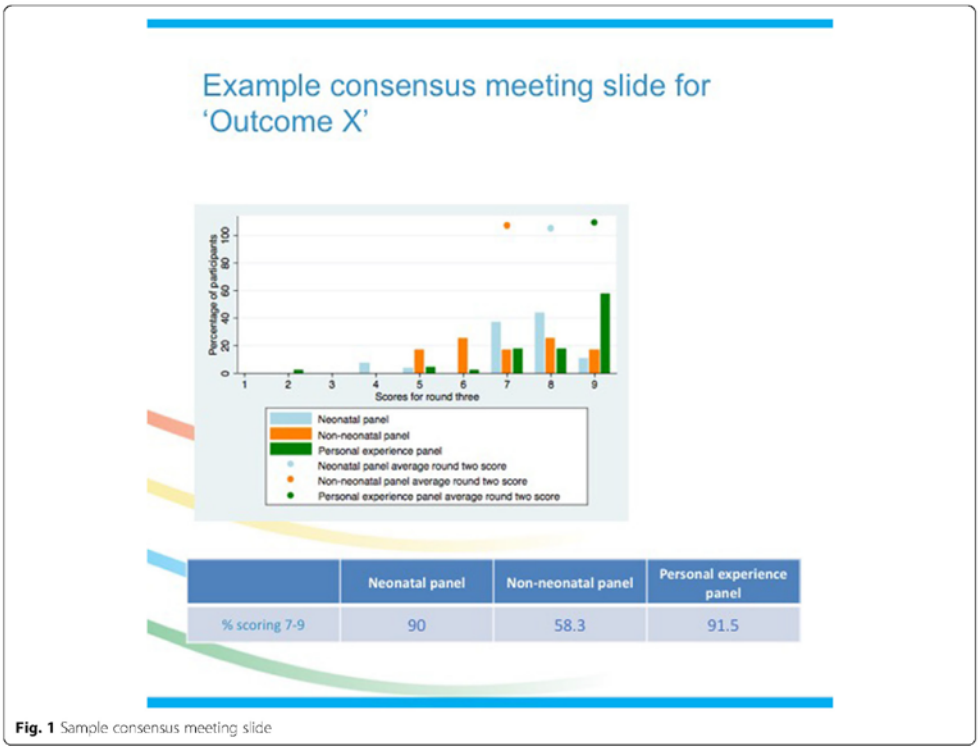

Fig. 1 Sample consensus meeting slide

effort will help to ensure that future research has a genuine patient-centred focus.

Although the COS will seek to involve participants from a range of countries involved in the management of infants with HD, none will be recruited from low- or middle-income countries. This is because it is felt likely that priorities in those countries will be very different from those in high-income countries, and therefore inclusion of participants from those settings would create too heterogeneous a study population. Given the lack of involvement of these countries and their likely difference in priorities, the most significant limitation of this COS is therefore that it is likely to be valid only for use in high-income countries.

Despite the likely limitation of its applicability to high-income countries, we believe the developed COS will have application across a wide range of HD research. One of the major challenges associated with development of the COS, however, will be ensuring that its use is taken up by other research groups. To ensure that this occurs, key paediatric surgical stakeholders, including the British Association of Paediatric Surgeons, are involved in development of the COS and will endorse the study to their memberships. Funding has also been obtained to conduct a UK-wide cohort study to investigate the identified core outcomes in infants with HD as they turn 6 years of age. Implementing the COS in a study with the power to address key clinical questions will help to demonstrate that its use is both feasible and desirable.

Use of COSs in other specialties has been shown to improve the quality of research taking place [10]. This will be the first time a COS has been developed for use in a paediatric surgical condition, and we hope it will create the infrastructure and methodology required to replicate the process in other conditions, leading to a generalised increase in the robustness of the evidence base used to support clinical practice in paediatric surgery.

Trial status

Data collection finished after submission of the manusript, but prior to publication.

Additional file

Additional file 1: SPIRIT checklist detailing where key sections of text can be identified within the protocol. (DOC 126 kb)

Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials; COS: Core outcome set; GRADE: Grading of Recommendations Assessment, Development and Evaluation; NHS: National Health Service; NIHR: National Institute for Health Research; NPEU: National Perinatal Epidemiology Unit; SMG: Study management group; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Acknowledgements

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Availability of data and materials

Not applicable.

Authors' contributions

BA is the chief investigator for the project, conceived of the study, participated in its design and coordination, and drafted the manuscript. TB participated in the study design and coordination and critically revised the manuscript for scientific content. SK participated in the study design and coordination and critically revised the manuscript for scientific content. GW participated in the study design and coordination and critically revised the manuscript for scientific content. MK participated in the study design and coordination and critically revised the manuscript for scientific content. All authors will form the study management group. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

All authors read and approved the final manuscript, and consent to its publication.

Ethics approval and consent to participate

The Health Research Authority deemed the project to be service evaluation/service development, and therefore review by an NHS research ethics committee was not deemed necessary.

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I.II Embase search strategy

1. Hirschsprung Disease.mp. or Hirschsprung disease/
2. recto-sigmoid.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. Hirschsprung*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4. Hirschsprung's Disease.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. Aganglionosis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. Colon* aganglionosis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
7. 1 or 2 or 3 or 4 or 5 or 6
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9. colon resection.mp.
10. pull through.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
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27. 7 and 26

I.III Medline search strategy

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27. 7 and 26

Appendix 2: *Gastroschisis core outcome set development protocol and systematic review search strategies*

II.I NETS1G Gastroschisis core outcome set development protocol

Allin et al. Trials (2016) 17:360
DOI 10.1186/s13063-016-1453-7

Trials

STUDY PROTOCOL Open Access

Development of a core outcome set for use in determining the overall success of gastroschisis treatment

Benjamin Allin[1,2*], Andrew Ross[2], Sean Marven[3], Nigel J Hall[4] and Marian Knight[1]

Abstract

Background: Gastroschisis research is limited in quality by the presence of significant heterogeneity in outcome measure reporting (PloS One 10(1):e0116908, 2015). Using core outcome sets in research is one proposed method for addressing this problem (Trials 13:103, 2012; Clin Rheumatol 33(9):1313-1322, 2014; Health Serv Res Policy 17(1): 1-2, 2012). Ultimately, standardising outcome measure reporting will improve research quality and translate into improvements in patient care.

Methods/design: Candidate outcome measures have been identified through systematic reviews. These outcome measures will form the starting point for an online, three-phase Delphi process that will be carried out in parallel by three panels of experts. Panel 1 is a neonatal panel, panel 2 is a non-neonatal panel and panel 3 is a lay panel.
In round 1, experts will be asked to score the previously identified outcome measures from 1–9 based on how important they think the measures are in determining the overall success of their/their child's/their patient's gastroschisis treatment.
In round 2, experts will be presented with the same list of outcome measures and with graphical representations of how their panel scored that outcome in round 1. They will be asked to re-score the outcome measure taking into account how important other members of their panel felt it to be. In round 3, experts will again be asked to re-score each outcome measure, but this time they will receive a graphical representation of the distribution of scores from all three panels which they should take into account when re-scoring.
Following round 3 of the Delphi process, 40 experts will be invited to attend a face-to-face consensus meeting. Participants will be invited in a purposive manner to obtain balance between the different panels. The results of the Delphi process will be discussed, and outcomes re-scored. Outcome measures where > 70 % of the participants at the meeting scored them as 7–9 and < 15 % scored them as 1–3 will form the core outcome set.

Discussion: Development of a core outcome set will help to reduce the heterogeneity of the outcome measure reporting in gastroschisis. This will increase the quality of research taking place and ultimately improve care provided to infants with gastroschisis.

Keywords: Paediatric surgery, Gastroschisis, Core outcome sets

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Background

Gastroschisis is an increasingly common paediatric surgical condition, which now affects approximately 1:3000 live births in the UK [1]. Mortality for infants with gastroschisis is relatively low [2]. However, the initial inpatient stay for these infants is the longest of any of the commonly encountered birth defects [3], and children are often affected by significant long-term morbidity in the form of repeat operations, need for enteral feeding assistance and parenteral nutrition use [2, 4]. The cost to the NHS of managing infants with gastroschisis is also significant, with their initial inpatient stay costing approximately £90,000, and any subsequent unplanned operations under the age of one costing approximately £25,000 [5, 6].

Multiple surgical repair strategies exist for the treatment of gastroschisis, with the two most common being operative primary fascial closure and silo placement with staged reduction and delayed closure [1]. Currently, significant heterogeneity exists in outcome measure reporting in studies comparing these two key interventions for gastroschisis (Allin BSR, Irvine A, Patni N, Knight M: Variability of outcome reporting in Hirschsprung's Disease and gastroschisis: a systematic review, unpublished). Such heterogeneity has led to studies focusing on surrogate markers of treatment success, short-term outcomes or hospital metrics, as opposed to outcomes that are of relevance to patients or that impact the long-term quality of life [7, 8]. This lack of patient relevance is one of three problems caused by heterogeneity in outcome measure reporting; the other two are a risk of reporting bias and an inability to synthesise data arising from multiple studies.

For gastroschisis, where little research is taking place and where the majority of that research is of a small sample size, reported outcomes should be relevant, accurately represent the studies' findings and be synthesisable through meta-analysis. If reported outcomes do not meet these standards, the derivation of robust, evidence-based management guidelines for infants with gastroschisis will be impossible. A lack of such guidelines may contribute to the wide variation in management and outcomes for infants with gastroschisis specifically and for infants requiring early surgery more generally [1, 2, 9–11].

The COMET (Core Outcome Measures in Effectiveness Trials) initiative was established to bring together people with an interest in the development and application of agreed upon standardized sets of outcome measures, known as core outcome sets [12, 13]. Core Outcome Sets are groups of outcome measures, commonly identified through a Delphi process and ratified by key stakeholders, as the outcomes that minimally should be reported in every study of a given condition [13]. Core outcome sets have already been developed for conditions as diverse as ankylosing spondylitis and asthma and have been shown to improve the quality of research taking place [14, 15].

Development of a core outcome set for use in gastroschisis would standardise outcome reporting, reduce reporting bias, improve patient relevance and facilitate meta-analysis. Addressing these points would significantly improve the quality of research taking place and, when combined with improved collaboration between research institutions, allow for the development of evidence-based management guidelines.

Methods/design

Ethics and registration

The Health Research Authority deemed the project to be *Service Evaluation/Service Development* and therefore review by an NHS Research Ethics Committee is not necessary. Information on the nature of the study is provided to participants prior to registration and again prior to completion of the first round of the survey. Potential participants are given contact details for staff within the National Perinatal Epidemiology Unit from whom further information can be obtained or with whom they can discuss the study further. Detailed information is also available on the study website (www.npeu.ox.ac.uk/nets). Consent to participate in the study is implied by completion of the registration questionnaire and data-collection questionnaires. Participants can withdraw from the study at any time either by contacting the study team or by simply not completing a data-collection questionnaire. The study has been registered with the COMET initiative (www.comet-initiative.org).

Scope of the core outcome set

The developed core outcome set is intended to be used to assess the overall success of treatment of an infant born with gastroschisis. This will involve outcome measures identified as important from birth into adulthood. The core outcome set is not intended to be applicable to antenatal interventions or interventions related to the mode or timing of delivery.

Key objectives

1. Determine which outcomes are currently reported in studies comparing surgical treatments for gastroschisis and assess the quality of reporting
2. Prioritise outcomes from patient/parent, paediatric surgical and non-surgical clinician perspectives
3. Achieve consensus between key stakeholders on a core outcome set for assessing how successful the overall treatment of an infant with gastroschisis has been
4. Compare and contrast outcomes prioritised by patients/parents, surgeons and non-surgical clinicians

Wider aims

1. A wider aim is to develop methodology for countering difficulties likely to be seen in the development of core outcome sets in all paediatric surgical conditions, including the following:
   a. Recruitment of parents and patients
   b. Incorporation of opinions from clinicians whose priorities vary dependent on their specialty or on the age at which they encounter the child.

Design

Four key stages occur in the development of the core outcome set:

1. Systematic review to identify currently reported outcomes
2. Development of a panel of experts
3. Three-phase online Delphi process
4. Consensus meeting

Systematic review

Two systematic reviews comparing methods of treatment for gastroschisis have been conducted. The first was a systematic review of broad scope, including both observational and experimental study designs (Allin BSR, Irvine A, Patni N, Knight M: Variability of outcome reporting in Hirschsprung's Disease and gastroschisis: a systematic review, unpublished), whilst the second focussed on randomised controlled trials and systematic reviews of randomised controlled trials [16]. Outcome measures in these reviews will be used as the starting point for the development of the core outcome set. The developed core outcome set is intended to be relevant to post-natal interventions only. Therefore, any outcome measures identified from the systematic reviews that are deemed relevant only to antenatal interventions or interventions relating to mode and timing of delivery will not be carried forward to phase 1 of the Delphi process.

Panel assembly – expert identification and recruitment

Panel assembly will be based on methods developed by Okoli et al. [17]. A knowledge resource nomination worksheet will be developed by members of the study management group. A knowledge resource nomination worksheet is used to ensure that experts are recruited across an adequate breadth of experience of gastroschisis. Initially, areas from which experts must be recruited will be identified under the headings of 'Disciplines, Organisations and Literature'. Members of the study management group will populate each of these headings with categories of experts from which participants must be recruited. Examples of categories include 'paediatric surgeons,' 'parents,' 'the Royal College of Paediatrics and Child Health,' and the '*Journal of Paediatric Surgery*'. Once the study management group has developed an exhaustive list of categories, an iterative process will be used to populate each category with names of potential experts. Initially, experts known to the study management group will be added to the knowledge resource nomination worksheet. Strategies to identify further experts in each category will then be developed. These strategies will differ from category to category, but some examples include those listed below.

Paediatric surgeons

Potential experts will include those identified as having an interest in managing infants with gastroschisis on a search of the British Association of Paediatric Surgeons register of practitioners. The clinical leads for each of the 27 paediatric surgical centres in the UK will be identified via the websites of those centres and will also be considered potential experts.

Neonatologists and paediatricians

Heads of department for all level 2 and level 3 neonatal units and their associated paediatric departments in the UK will be identified via the websites for these NHS trusts and will be considered potential experts.

Parents and patients

A parent advisory group has been established in the National Perinatal Epidemiology Unit. This group consists of parents of infants who have required early surgery, including those with gastroschisis, exomphalos, Hirschsprung's Disease and anorectal malformations. Parents of infants with gastroschisis will be identified via the mailing list for this group. Additional parents/infants will be identified through use of the *Gastroschisis, Exomphalos, and Exstrophy Parent Support* mailing lists and Facebook groups. Members of the study management group, as well as the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System steering committee, including BA, NH and SM, will be utilised to recruit infants and parents from their respective hospitals to give good representation from all regions in the UK. Parents/patients identified in each of these ways will be considered potential experts.

Journals

Editors of key paediatric and paediatric surgical journals will be considered potential experts. They will also be asked to identify any members of their editorial board who have expertise in gastroschisis.

Using similar strategies for each remaining category, the knowledge resource nomination worksheet will be populated with a master list of potential experts. Each person named on the knowledge resource nomination worksheet will be sent an information pack via email. In

these information packs, we will explain that we have identified the recipient as someone with expertise in the management of infants with gastroschisis and that we are seeking to establish whether the recipient is be suitable for and interested in participating in development of a core outcome set. The information packs will also contain a plain language summary of the COMET initiative and a lay or scientific summary of the study as appropriate. A link will be provided to an online form for experts to express their interest in participation in the study and to provide more information on their involvement in management of infants with gastroschisis. Each expert will also be asked to provide the names and contact details of anyone else they believe would be suitable for inclusion in the study. At this stage, we are seeking to clarify the suitability of experts for participation in the study and to identify further potential experts. This process will be repeated for the names provided by the previously contacted experts. Expert recruitment will continue until a minimum of 50 experts, with at least two in each category, has been recruited.

Following confirmation of their eligibility to participate in the study, experts will be sent a link to a customised online database from which they can access phase 1 of the Delphi process.

Scope of expert recruitment

An a priori decision has been made to limit recruitment of experts to those based in the UK.

Panel assembly – facilitating consensus

Clinicians who treat gastroschisis in the neonatal period, such as paediatric surgeons, may have a different set of priorities than those who primarily manage affected children later in life, such as paediatricians. This may make it difficult to attain their consensus on a single set of outcome measures. It is essential that the core outcome set represent the views of patients/parents, neonatal clinicians and non-neonatal clinicians. To ensure that this occurs, experts will be separated into the following three panels:

- Neonatal panel – clinicians whose responsibility includes management in the neonatal period (but may also include management outside of the neonatal period). This group will include neonatologists and paediatric surgeons.
- Non-neonatal panel – researchers with expertise in gastroschisis management and clinicians responsible for management primarily outside of the neonatal period. This group will include specialist nurses and paediatricians.
- Lay panel – parents, and adults who were born with gastroschisis.

Delphi process – phase 1 data collection

An online system will be used to conduct a three-phase Delphi process run in parallel for the 'neonatal', 'non-neonatal' and 'lay' panels. An online system has been chosen in order to maintain anonymity, where experts do not know the names of other experts on their panel or other experts' individual responses.

In phase 1a, participants will be presented in alphabetical order with the list of outcomes identified through the systematic reviews. The study management group will develop equivalent lay terms for each scientific outcome, and their understanding will be piloted with the National Perinatal Epidemiology Unit's parent advisory group. These lay terms will be used instead of scientific terms in the questionnaires completed by the lay panel. If there is ambiguity over the outcome or domain, either in the scientific or lay questionnaire, 'tips' will be placed alongside them to clarify meaning.

Participants will be asked to give each outcome measure a score from 1–9 where 1, 2 and 3 are 'not that important'; 4, 5 and 6 are 'important'; and 7, 8 and 9 are 'really important'.

The Grading of Recommendations Assessment, Development and Evaluation Working Group scale of measurement has been chosen for use in scoring outcome measures, based on recommendations from the COMET initiative [18].

Following completion of phase 1a, participants will be asked if there are any outcomes they consider important in determining whether treatment of their/their child's/their patient's gastroschisis has been successful, but which we have not yet identified. They will be able to list as many items as they consider necessary.

A planned period of 4 weeks will be scheduled for completion of data collection in phase 1 and for each subsequent phase. When experts have not returned their completed questionnaire within 2 weeks of the start of the phase, they will be contacted via email to remind them of the necessity to complete the phase. If they have not completed the questionnaire by the 3-week deadline, they will be contacted again via email to ascertain if they are having difficulties in completing the questionnaire or if they have decided they no longer want to participate in the study. Participants who have not completed the questionnaire within 4 weeks of the phase starting will be deemed not to have completed that phase.

Delphi process – phase 1 analysis

The number of experts invited to participate, registering to participate, and completing phase 1 of the Delphi process from each category identified in the knowledge resource nomination worksheet will be recorded.

Two reviewers will independently assess outcomes reported in phase 1b in order to determine if they represent de novo outcomes not already listed in phase 1a. De novo outcomes listed by at least one expert will be taken forward to phase 2 of the Delphi process.

Outcomes will be analysed separately for each panel with descriptive statistics, including medians and interquartile ranges, being calculated. All outcomes will be carried forward to phase 2.

Phase 2 data collection

Experts completing phase 1 will be invited to participate in phase 2 and asked to re-score each outcome based on the following:

- The phase 1 score they assigned it
- Descriptive statistics from their panel

Descriptive statistics will be represented numerically and graphically.

Phase 2 analysis

Descriptive statistics will again be calculated. Bias from loss of experts between rounds will be assessed by determining if there is any difference in median round 1 scores for each outcome measure between experts who have completed both phases and experts who only completed phase 1. All outcomes will be carried forward to phase 3.

Phase 3 data collection

Experts completing phase 2 will be invited to participate in phase 3 and will be asked to re-score each outcome based on the following:

- The phase 2 score they assigned it
- Round 2 descriptive statistics from all three panels

Phase 3 analysis

Analysis will be conducted as per phase 2.

Generation of core outcome set – consensus meeting

Experts who have completed all three phases of the Delphi process will be invited to the consensus meeting purposively with an even spread across panels and disciplines until 40 experts have confirmed their attendance. The intention of the consensus meeting is to ratify the established core outcome set, discuss outcomes where no consensus could be obtained and determine the most appropriate methods and timing for assessing the identified core outcomes. The consensus group will also discuss how identified core outcomes relate to the core areas within the OMERACT filter 2.0.

Following discussion of outcomes, each outcome will be re-scored anonymously and electronically by the meeting participants using the same scoring system as for the Delphi process. Participants will be asked to re-score outcomes based on their own scores, the results of the Delphi process and the discussions at the meeting. Outcomes reaching 'consensus in' as defined below following re-scoring at the consensus meeting will be included in the core outcome set. All others will be excluded.

Outcomes will be discussed at the consensus meeting in different groups according to the number of panels in which they have reached 'consensus in' at the end of the third phase of the Delphi process. 'Consensus in' will be defined as ≥ 70 % of participants rating the outcome 7–9, and < 15 % rating it as 1–3. Outcomes will additionally be classified as 'consensus out' if > 70 % participants rated it 1–3 and < 15 % rated it 7–9. All other outcomes will be considered as not achieving consensus in either direction. Only 'consensus in' outcomes will form part of the core outcome set.

Table 1 SPIRIT Table

	Study period						
	Enrolment	Allocation to Panel 1, 2 or 3 According to Specialty	Post-allocation				Close-out
Timepoint	*December 2015-February 2016*	February 2016	*Round 1 (Feb–March 2016)*	*Round 2 April–May 2016*	*Round 3 May–June 2016*	*Consensus meeting 221 June 2016*	*July 2016*
Enrolment:	X						
Eligibility screen	X						
Implied consent through registration	X						
(List other procedures)							
Allocation		X					
Assessments:							
(Outcome scores)			X	X	X	X	

Compliance with SPIRIT recommendations can be seen in the SPIRIT checklist (Additional file 1), and the SPIRIT Table (Table 1).

Sub-group analysis

Paediatric surgeons are broadly responsible for determining which initial treatment strategy should be undertaken for infants with gastroschisis. They are also responsible for implementing this intervention. We are interested to see whether their views on outcomes of importance are different from those of clinicians whose primary role is in the treatment of the complications of gastroschisis or in monitoring of longer-term outcomes for infants with gastroschisis. In order to do this, we will perform a sub-group analysis comparing phase 3 scores for paediatric surgeons with phase 3 scores for non-surgical clinicians.

Following completion of the consensus meeting, a consensus document will be drafted and put forward to participants for approval. This document will be presented at appropriate international meetings and published in peer-reviewed journals.

Data management

All data will be directly entered into a customised database by participants. Data will be stored securely on servers within the National Perinatal Epidemiology Unit and will be managed as per standard operating protocols. Only appropriate members of the study team will have access to the data. Data analysis will be conducted by BA and MK.

Discussion

No core outcome set currently exists for use in determining how successful the overall treatment of a child's gastroschisis has been. Development of one will standardise outcome measure reporting, thereby increasing patient relevance of research, reducing reporting bias, and increasing ease of data synthesis. Involvement of multiple key stakeholder groups in the development of the core outcome set will help ensure its validity and generalisability. Through implementation of the core outcome set, key clinical questions will be more readily answerable. Ultimately, this will aid identification of evidence-based treatments, improve outcomes for infants with gastroschisis and improve the quality of counseling of their parents.

Study status

Participant recruitment has started.

Additional file

Additional file 1: Spirit Checklist. This file contains the completed SPIRIT checklist describing where key portions of text can be identified in the protocol. (DOC 121 kb)

Abbreviations

COMET, core outcome measures in effectiveness trials; NHS, National Health Service; OMERACT, outcome measures in rheumatology

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The NIHR had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication.

Authors' contributions

BA is the chief investigator for the project, conceived the study, participated in its design and coordination and drafted the manuscript. AR participated in the study design and coordination and critically revised the manuscript for scientific content. NH participated in the study design and coordination and critically revised the manuscript for scientific content. SM participated in the study design and coordination and critically revised the manuscript for scientific content. MK participated in the study design and coordination and critically revised the manuscript for scientific content. All authors will form the study management group. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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II.II Embase search strategy

1. gastroschisis.mp. or gastroschisis/
2. birth defects.mp. or birth defect/
3. abdominal wall defects.mp. or abdominal wall defect/
4. 1 or 2 or 3
5. silo.mp. or *surgical technique/
6. (primary adj3 closure).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
7. (traditional adj3 closure).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. bianchi.mp.
9. (sutureless adj3 closure).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
10. 5 or 6 or 7 or 8 or 9
11. 4 and 10

II.III Medline search strategy

1. gastroschisis.mp. or Gastroschisis/
2. birth defects.mp. or Congenital Abnormalities/
3. abdominal wall defects.mp. or Abdominal Wall/
4. 1 or 2 or 3
5. silo.mp.
6. (primary adj3 closure).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7. (traditional adj3 closure).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. bianchi.mp. or Digestive System Surgical Procedures/
9. (sutureless adj3 closure).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10. 5 or 6 or 7 or 8 or 9
11. 4 and 10

Appendix 3: *Introductory text and instructions for the Delphi process*

III.I Phase one welcome text

The same phase one welcome text was used for both Delphi processes, and therefore only the Hirschsprung's disease example is shown.

Thank you for agreeing to take part in the NETS^{1HD} study

The NETS^{1HD} study is developing a core outcome set to use in Hirschsprung's Disease. We are doing this, because using core outcome sets makes it easier to interpret the results of research, and ultimately, determine which treatments are best.

How is a core outcome set developed?

Developing a core outcome set involves a group of experts, usually consisting of people with the condition or their parents, doctors, nurses and researchers undertaking a Delphi process. In the Delphi process, the group of experts are asked to identify which items (called outcome measures) they think are most important in determining whether a particular treatment has been successful. There are three phases to the Delphi process, and by the end of it, the experts will have come to an agreement on which outcome measures the group as a whole think are most important. These outcome measures will form the core outcome set. The following links will give you more information about core outcome sets and the Delphi process.

What to do now?

Over the following pages, you will be asked to ***score a series of outcome measures from 1-9*** based on how important you think each one is in deciding how well the overall treatment of your/your child's/yours patient's/a child's [deleted as appropriate] Hirschsprung's Disease has worked. These outcomes are what is currently investigated in Hirschsprung's Disease research. Not all of them will be relevant to everyone, so if you don't feel able to answer one of the questions, please tick 'Don't Know' instead of giving it a score. This questionnaire will form the first phase of the ***Delphi process***.

What happens after completing this survey?

Over the next few months***, in phases two and three*** of the Delphi process, you will be asked to re-score these outcomes, each time being given more information on how other groups of people have scored them. It is ***very important that you complete the questionnaires in each phase of the Delphi process***. The reliability of the results could be affected if people drop out of the study before it is completed because they feel that the rest of the group

does not share their opinions. ***If people drop out because they feel their opinions are in the minority, the final results will overestimate how much people agreed on this topic.***

After all three rounds are finished we will invite forty of the survey participants to a meeting in Leeds on the ***21st of June*** to discuss the results and to reach a final agreement about which outcomes will form the core outcome set. Funds for the meeting are limited and the 40 places will be filled on an invitation basis. This is so that we can balance the different types of experts at the meeting.

If you have any difficulties in completing the survey, please email Ben Allin

Thank you again for agreeing to take part in this study.

Ben, Marian, Tim, Simon and Gregor
(the NETS^{1HD} study team)

III.II Instructions shown in all phases – HD Delphi process

Instructions for completing the survey

It may be that the outcomes that are important ***change over time*** from being a newborn to an older child and young adult. We would like to capture ***all outcomes that are important, regardless of the age at which they are important***. Please ***bear this in mind when scoring the outcomes*** on the following pages.

You won't be able to move on from a page if you haven't answered all of the questions on it. However, you can tick ***'don't know'*** for any question you don't feel able to answer. In rounds two and three you will be able to see how important other groups of people, for example surgeons, or parents of children with Hirschsprung's Disease thought each outcome was. You can then use this information to help you choose a score for those outcome measures you previously felt unable to answer.

There are eight screens of questions to answer in this survey, and the entire survey should take about 10-15 minutes to answer. ***You can save your answers at any point and return at a later stage by clicking 'resume later'. Please do not just quit the survey though, as your answers will be lost.***

Other people taking part in the study will ***not*** be able to see how you have answered the questions. However, in order to be able to remind you of your phase one and two scores at a later date, the study team ***will*** be able to see how individuals have scored each outcome. This information ***will not affect your participation in the study, and will not be shared with anyone outside of the study team.***

III.III **Instructions shown in all phases – gastroschisis Delphi process**

Instructions for completing the survey

It may be that the outcomes that are important ***change with age.*** We would like to capture ***all outcomes that are important, regardless of the age at which they are important***. The core outcome set is not however going to be used to assess treatments administered before birth, and therefore, we are not looking to assess outcomes that are designed for investigating these interventions. Please ***bear this in mind when scoring the outcome measures*** on the following pages.

You won't be able to move on from a page if you haven't answered all of the questions on it. However, you can tick ***'don't know'*** for any question you don't feel able to answer. There are eleven screens of questions to answer in this survey, and the entire survey should take about 10-15 minutes to answer. You can save your answers at any point and return at a later stage.

Other people taking part in the study will ***not*** be able to see how you have answered the questions. However, in order to be able to remind you of your phase one and two scores at a later date, the study team ***will*** be able to see how individuals have scored each outcome. This information ***will not affect your participation in the study, and will not be shared with anyone outside of the study team.***

III.IV **Phase one instructions – HD Delphi process**

Please look at the items in the list below, and determine how important each one is in deciding whether the overall treatment of your/your child's/yours patient's/a child's [deleted as appropriate] Hirschsprung's Disease has worked well.

Please give each one a score from 1-9 where 1, 2 and 3 are 'not that important', 4,5 and 6 are 'important', and 7,8 and 9 are 'really important'. Please bear in mind that the higher the number, the more important you consider the outcome to be.

There are some outcomes which we are aware may be interpreted in several different ways. We would therefore be grateful if you could document in the comments box at the bottom of the page where you believe your interpretation of the outcome may have affected the score you assigned to it.

"Please hover your mouse over each outcome if you would like to see the medical term for that outcome." / "Please hover your mouse over each outcome to see how it has been described in the questionnaire for people with Hirschsprung's Disease and their parents" [deleted as appropriate]

III.V **Phase one instructions – gastroschisis Delphi process**

Please score items based on how important they are in determining your/your child's/your patient's/a child's [deleted as appropriate] treatment success

Please hover your mouse over each outcome if you would like to see the medical term for that outcome. / Please hover your mouse over each outcome to see how it has been described in the questionnaire for people with gastroschisis and their parents [deleted as appropriate]

III.VI Phase two welcome text – HD Delphi process

Thank you for completing phase one of the NETS[1HD] study

What to do now?

You have been allocated to ***one of three panels*** of participants, either the neonatal panel, the non-neonatal panel, or the personal experience panel. Within the ***neonatal panel***, are paediatric surgeons and neonatologists, within the ***non-neonatal panel*** are paediatricians, specialist nurses, and researchers, and in the ***personal experience panel***, are people with Hirschsprung's Disease and their parents.

Over the following pages, you will be asked to ***re-score the outcomes from phase one*** based on how important you think each one is in deciding how well the overall treatment of your/your child's/yours patient's/a child's [deleted as appropriate] Hirschsprung's Disease has worked ***in light of how other people in your panel scored it in phase one.***

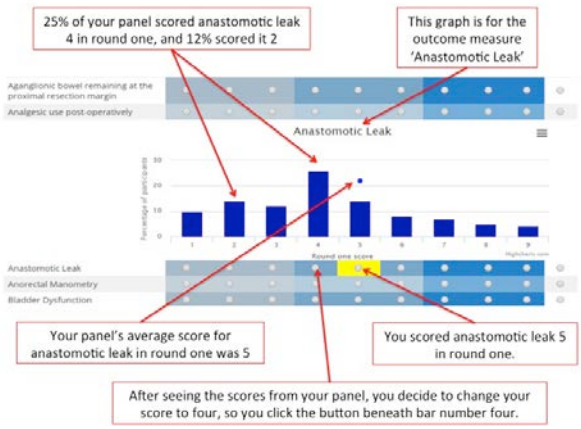
You will be shown a graph with each outcome. ***This shows how people in your panel scored that outcome in phase one***. There are three parts to each graph:

The bars show the percentage of people in your panel giving a particular score to that outcome measure in phase one. Each bar is a different score.

The blue circle represents the average score your panel gave to that outcome measure in phase one.

The yellow box shows the score you gave the outcome measure in phase one.

Below is an ***example*** graph:



If you have any difficulties in completing the survey, please email Ben Allin
Thank you again for agreeing to take part in this study.
Ben, Marian, Tim, Simon and Gregor (the NETS[1HD] study team)

III.VII Phase two welcome text – gastroschisis Delphi process

Thank you for completing phase one of the NETS[1G] study, and welcome to phase two

What happens now?

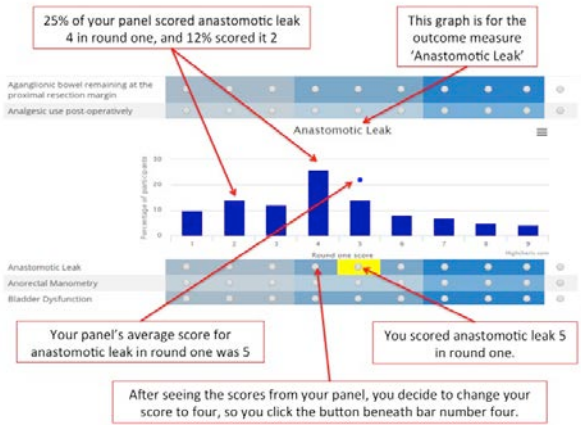
You have been allocated to ***one of three panels*** of participants, either the neonatal panel, the non-neonatal panel, or the personal experience panel. Within the ***neonatal panel,*** are paediatric surgeons, nurses, fetal medics and neonatologists, within the ***non-neonatal panel*** are paediatricians, dieticians and researchers, and in the ***personal experience panel***, are people who were born with gastroschisis and parents of children who were born with gastroschisis.

We would like you to score each outcome again, using the same 1-9 scale. However, this time we will also show you a graph that describes how other people in your panel scored that outcome in phase one. We would like you to consider whether you wish to change the score you gave each outcome in light of the information in the graphs. You do not have to change your scores if you do not wish to.

You will see one graph for each outcome, and there are three parts to each graph:

1) The bars show the percentage of people in your panel giving a particular score to that outcome in phase one. Each bar is a different score.
2) The blue circle represents the average score your panel gave to that outcome in phase one.
3) The yellow box shows the score you gave the outcome in phase one.

Below is an ***example*** graph:



If you have any questions, please email Ben Allin
Kind Regards
Ben, Marian, Andrew, Nigel and Sean (The NETS1G study team)

III.VIII **Phase two instructions – HD Delphi process**

Please look at the items in the list below, and re-score each of them based on how important ***you*** think they are in deciding whether the overall treatment of your/your child's/yours patient's/a child's [deleted as appropriate] Hirschsprung's Disease has worked well ***in light of how other people in your panel scored it in phase one***.

Please give each outcome measure a score from 1-9 where 1, 2 and 3 are 'not that important', 4,5 and 6 are 'important', and 7,8 and 9 are 'really important'. Please bear in mind that the higher the number, the more important you consider the outcome measure to be.

The scoring buttons for each outcome measure are ***below the graph for that outcome measure.*** The ***yellow box*** shows your score from phase one, and the ***blue circle*** shows the ***average*** score from your panel in phase one.

"Please hover your mouse over each outcome if you would like to see the medical term for that outcome." / "Please hover your mouse over each outcome to see how it has been described in the questionnaire for people with Hirschsprung's Disease and their parents" [deleted as appropriate]

III.IX **Phase two instructions – gastroschisis Delphi process**

We would like you to consider whether you wish to change the phase one score you gave each outcome in light of the information in the graphs below. We would still like you to score each outcome based upon how important you think it is in determining whether the overall treatment of your/your child's/your patient's gastroschisis has been successful, and you do not have to change your score if you do not wish to.

Please give each item a score from 1-9 where 1, 2 and 3 are 'not that important', 4,5 and 6 are 'important', and 7,8 and 9 are 'really important'. Please bear in mind that the higher the number, the more important you consider the outcome to be.

"Please hover your mouse over each outcome if you would like to see the medical term for that outcome." / "Please hover your mouse over each outcome to see how it has been described in the questionnaire for people with gastroschisis and their parents" [deleted as appropriate]

III.X Phase three welcome text - HD Delphi process

Thank you for completing phase two of the NETS^{1HD} study

What to do now?

You have been allocated to ***one of three panels*** of participants, either the neonatal panel, the non-neonatal panel, or the personal experience panel. Within the ***neonatal panel***, are paediatric surgeons and neonatologists, within the ***non-neonatal panel*** are paediatricians, specialist nurses, and researchers, and in the ***personal experience panel***, are people with Hirschsprung's Disease and their parents.

Over the following pages, you will be asked to ***re-score the outcomes from phase two*** based on how important you think each one is in deciding how well the overall treatment of your/your child's/yours patient's/a child's [deleted as appropriate] Hirschsprung's Disease has worked. We will also show you a graph of how ***other panels of experts have scored these outcomes.*** From the graph you will be able to see how important other people involved with the study consider a particular outcome to be and then decide if you want to change the rating you gave the outcome measure. ***There is no pressure to change your score if you do not want to.***

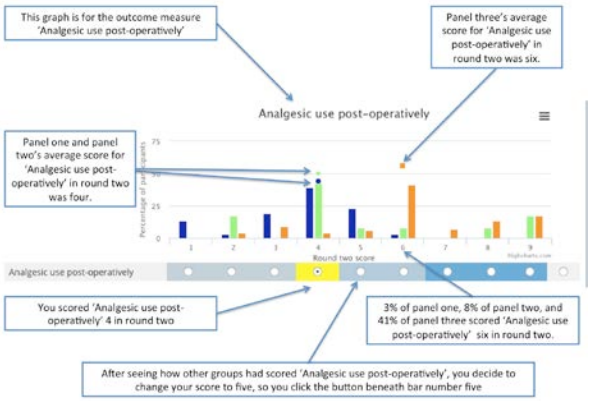
What information will I be shown?

As with phase two, you will see one graph for each outcome. There are three parts to the graph:

The different coloured bars show the percentage of people in each panel giving a particular score to that outcome measure in phase two. Each bar is a different score. The blue bars show the scores for the surgeons and neonatologists (panel 1), the green bars show the scores for the paediatricians, specialist nurses and researchers (panel 2), and the orange bars show the scores for people with Hirschsprung's disease and their parents (panel 3).

The coloured shapes show the average score from each panel for that outcome in phase two. The blue circle shows the average score for panel 1, the green diamond shows the average score for panel 2, and the orange square shows the average score for panel three.
The yellow box shows the score you gave that outcome in phase two.

Below is an ***example*** graph



If you have any difficulties in completing the survey, please email Ben Allin

Thank you again for agreeing to take part in this study.

Ben, Marian, Tim, Simon and Gregor
(the NETS^{1HD} study team

III.XI Phase three welcome text - gastroschisis Delphi process

Thank you for completing phase two of the NETS[1G] study

What to do now?

You have been allocated to ***one of three panels*** of participants, either the neonatal panel, the non-neonatal panel, or the personal experience panel. Within the ***neonatal panel***, are paediatric surgeons, nurses, fetal medics and neonatologists, within the ***non-neonatal panel*** are paediatricians, dieticians and researchers, and in the ***personal experience panel***, are people who were born with gastroschisis, and the parents of people born with gastroschisis.

Over the following pages, you will be asked to ***re-score the outcomes from phase two*** based on how important you think each one is in deciding how well the overall treatment of your/your child's/yours patient's/a child's [deleted as appropriate] gastroschisis has worked. We will also show you a graph of how ***other panels of experts have scored these outcomes.*** From the graph you will be able to see how important other people involved with the study consider a particular outcome to be and then decide if you want to change the score you gave the outcome. ***There is no pressure to change your score if you do not want to.***

What information will I be shown?

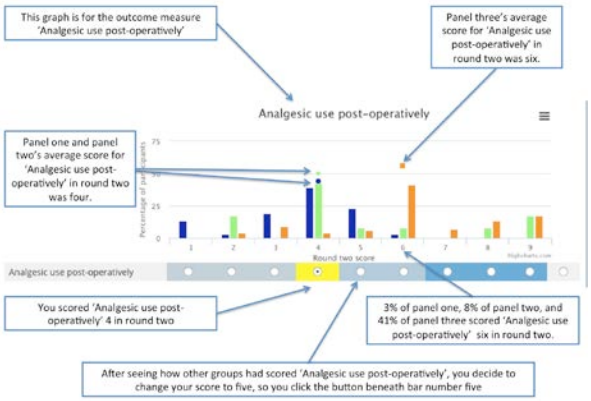
As with phase two, you will see one graph for each outcome. There are three parts to the graph:

The different coloured bars show the percentage of people in each panel giving a particular score to that outcome in phase two. Each bar is a different score. The blue bars show the scores for the neonatal panel, the green bars show the scores for the non-neonatal panel, and the orange bars show the scores for the personal experience panel.

The coloured shapes show the average score from each panel for that outcome in phase two. The blue circle shows the average score for the neonatal panel, the green diamond shows the average score for the non-neonatal panel, and the orange square shows the average score for the personal experience panel.

The yellow box shows the score you gave that outcome in phase two.

Below is an ***example*** graph



If you have any difficulties in completing the survey, please email Ben Allin
Thank you again for agreeing to take part in this study.
Ben, Andrew, Sean, Nigel and Marian
(the NETS[1G] study team)

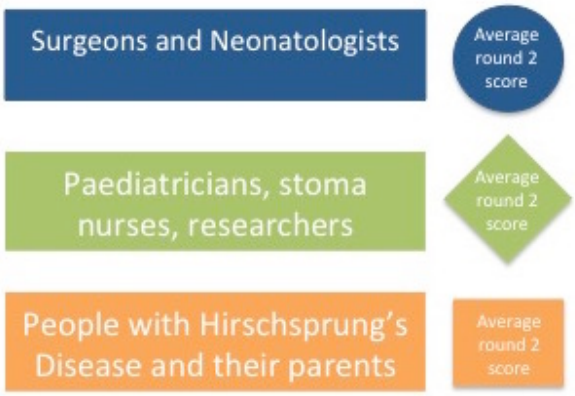
III.XII **Phase three instructions – HD Delphi process**

Please look at the items in the list below, and re-score each of them based on how important you think they are in deciding whether the overall treatment of your/your child's/yours patient's/a child's [deleted as appropriate] Hirschsprung's Disease has worked well. Please look at the graph to see how important other panels of experts think each outcome measure is. You may want to change your score based upon this information, however there is no pressure to do so if you do not wish to.

Please give each outcome measure a score from 1-9 where 1, 2 and 3 are 'not that important', 4,5 and 6 are 'important', and 7,8 and 9 are 'really important'. Please bear in mind that the higher the number, the more important you consider the outcome measure to be.

The scoring buttons for each outcome are ***below the graph for that outcome.***

Below is a key to explain what each part of the graph represents.



Please hover your mouse over each outcome if you would like to see the medical term for that outcome. / Please hover your mouse over each outcome to see how it has been described in the questionnaire for people with Hirschsprung's Disease and their parents [deleted as appropriate]

III.XIII Phase three instructions – gastroschisis Delphi process

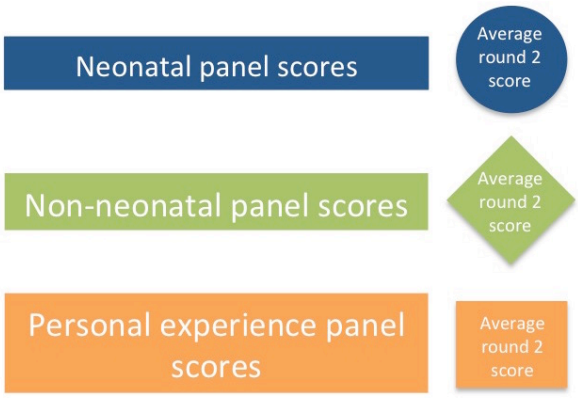
Outcomes relating to quality of life - page 1 of 2

Please look at the items in the list below, and re-score each of them based on how important you think they are in deciding whether the overall treatment of your/your child's/yours patient's/a child's gastroschisis has worked well. Please look at the graph to see how important other panels of experts think each outcome is. You may want to change your score based upon this information, however there is no pressure to do so if you do not wish to.

Please give each outcome a score from 1-9 where 1, 2 and 3 are 'not that important', 4,5 and 6 are 'important', and 7,8 and 9 are 'really important'. Please bear in mind that the higher the number, the more important you consider the outcome to be.

The scoring buttons for each outcome are *below the graph for that outcome.*

Below is a key to explain what each part of the graph represents.



Please hover your mouse over each outcome if you would like to see the medical term for that outcome. / Please hover your mouse over each outcome to see how it has been described in the questionnaire for people with gastroschisis and their parents [deleted as appropriate]

Appendix 4: *NETS^{1HD} study newsletters*

1HD NETS

Next stage in Evidence-based paediatric surgical Treatment Strategies

01

January 2016 Newsletter

Thank you all for registering to take part in the NETS[1HD] study. We are very grateful for your support

Over the period of the study we will send you four brief newsletters to update you on how the work is progressing and explain what will be happening over the next few months. If you would rather not receive these newsletters, please email *benjamin.allin@npeu.ox.ac.uk*, and we will remove you from the mailing list.

Why are we doing the NETS[1HD] study?

Hirschsprung's Disease research is mainly aimed at trying to work out whether one type of treatment is better than another. A common way of doing this is to compare children who have had one type of treatment with children who have had a different form of treatment and to then look at what happens to them, for example, how long they stay in hospital, or whether they get complications from the treatment. Each of the things that can be looked at is called an **outcome measure**. There are many different outcome measures that can be looked at, and this causes three problems in research. Firstly, there is a lot of variation in which outcome measures researchers choose to use in their studies. This means that it is **difficult to compare or combine results from different studies**. Secondly, researchers often use a certain outcome measure because it is easy to gather information about, such as how quickly children leave hospital, rather than one that is important to patients, like whether they have long-term pain. This means that the results of the research may not actually be relevant to patients with the condition. Finally, researchers will sometimes investigate many different outcome measures, but only publish the ones that support their argument. This is called reporting bias. **Each of these problems makes it harder to decide how to interpret results from a study**. At the moment, all of these problems are occurring in Hirschsprung's Disease research.

How will the NETS[1HD] study solve these problems?

The NETS[1HD] study will develop a **core outcome set for Hirschsprung's Disease**. A **core outcome set** is a list of outcome measures that should be reported as a minimum in every study looking at a particular condition. Using core outcome sets in research **addresses the problems caused by having a choice of many different outcome measures**.

Core outcome sets are developed through a **Delphi Process**. A Delphi process involves a group of experts, usually consisting of **people with the condition or their parents, doctors, nurses and researchers** being guided through a series of steps to identify the outcome measures that are **most important to the group as a whole**, and hence that should be included in the core outcome set.

By developing a core outcome set for Hirschsprung's Disease we hope to make it easier to interpret the results of research and understand which treatments are best for patients.

Registration for the NETS[1HD] study

Registration to take part in the study has gone fantastically. At present, **over 100 people have signed up to** take part, including:

- 61 Parents of children with Hirschsprung's Disease
- 10 People with Hirschsprung's Disease
- 27 Paediatric Surgeons
- 11 Other clinicians

Registration will stay open until the end of the first week in February, so if you know anyone else who is interested in taking part, please ask them to go to *www.npeu.ox.ac.uk/nets/taking-part* to sign up. We are particularly interested in hearing from more **neonatologists and paediatric gastroenterologists.**

What happens next?

In the **second week in February**, you will be emailed a link to an online questionnaire. In this questionnaire, you will be asked to **score a series of outcome measures from 1-9** based on how important you think each one is in deciding how well the overall treatment of someone's Hirschsprung's Disease has worked. This questionnaire will form the first phase of the Delphi process. **In phases two and three of the Delphi** process you will be asked to re-score these outcome measures, each time being given more information about how other groups of people have scored them.

What is the end result of the NETS[1HD] Study?

On the 21st of June, we will hold a meeting in Leeds, to which 40 people who are representative of everyone taking part in the study will be invited. The results of the Delphi process will be discussed in detail at this meeting, after which we will be able to identify a short list of outcome measures which will form the **core outcome set for Hirschsprung's Disease**. In the future, researchers will try to work out which treatments are best for children with Hirschsprung's disease by comparing them using the **NETS[1HD] core outcome set**.

Other core outcome sets - gastroschisis

In the **NETS[1G]** study, which we are just starting the registration process for, we will be developing a core outcome set for use in **gastroschisis**. Therefore, if you know anyone who might be interested in helping with that study, please pass on the information, and ask them to register at *www.npeu.ox.ac.uk/nets/taking-part*

npeu National Perinatal Epidemiology Unit

UNIVERSITY OF OXFORD

www.npeu.ox.ac.uk/nets/taking-part

Feedback from round one

Lots of useful comments were left in round one. We have used these comments to refine the outcome measures we ask about in round two, and have answered some of the common questions below.

How were the outcome measures in round one chosen?

Before starting the NETS[1HD] study, we identified ***every study published in the last five years*** that compared two treatments for Hirschsprung's Disease. The 73 outcome measures you scored in round one were the ***73 outcome measures that those studies investigated.***

A lot of these outcome measures looked at complications that can occur for people with Hirschsprung's Disease. We just want to reassure people that many of these will only ever apply to a very small proportion of people with Hirschsprung's Disease.

Why are some of the outcome measures very similar?

This is because there can be ***many different ways of looking at the same outcome measure.*** For example, some researchers will compare two different treatments for Hirschsprung's Disease by looking at how many infants develop pneumonia after the operation, how many develop a blockage in their bowel, and how many develop a collection of pus. All of these outcomes can be classed as a ***'post-operative complication'.*** Instead of comparing two treatments by looking at each of these outcome measures individually, some researchers will instead compare them by looking at how many infants develop ***any*** post-operative complication.

By asking you to score each of the individual outcome measures, and the more general collective outcome measure, we can work out if there are specific individual outcome measures you think are important, or whether the general outcome measure is as important as the individual ones.

What time period are you interested in?

We are looking to identify outcomes that you think are important in determining the ***overall success of Hirschsprung's Disease treatment.*** We are interested in outcomes regardless of the time point at which they occur. Therefore, if there are outcomes that occur ***immediately after the operation*** that you think are important in determining the overall success of Hirschsprung's Disease treatment, please tell us about them. Likewise, if there are outcomes that are more relevant later in life that you think are important, please also tell us about them. In the consensus meeting, we will discuss which outcomes are ***appropriate in different age groups***, and also discuss ***how best to measure each outcome.***

Developing a core outcome set for gastroschisis

We are still recruiting for the NETS1G study to develop a core outcome set for use in gastroschisis. We hope to start phase one of this study in July, so if you know anyone who may be interested in taking part, please ask them to register at ***www.npeu.ox.ac.uk/nets/taking-part***

1HD NETS

Next stage in Evidence-based paediatric surgical Treatment Strategies

03

May 2016 Newsletter

Round two of the NETS[1HD] study has now closed, and we would like to thank everyone for taking part

What happened in round two?

When we analysed the data from round two, there were 13 outcome measures where over 50% of people scored them 1-3,remembering that 1 is the lowest score an outcome could be rated and 9 is the highest. It is highly unlikely therefore that these 13 outcome measures would ever be scored highly enough in round three or at the consensus meeting to make it into the core outcome set. ***We have therefore taken them out of the round three questionnaire*** and you will not be required to score them again. We will list the outcomes that have been removed at the end of the questionnaire and give you the opportunity to comment should you so wish.

What happens next?

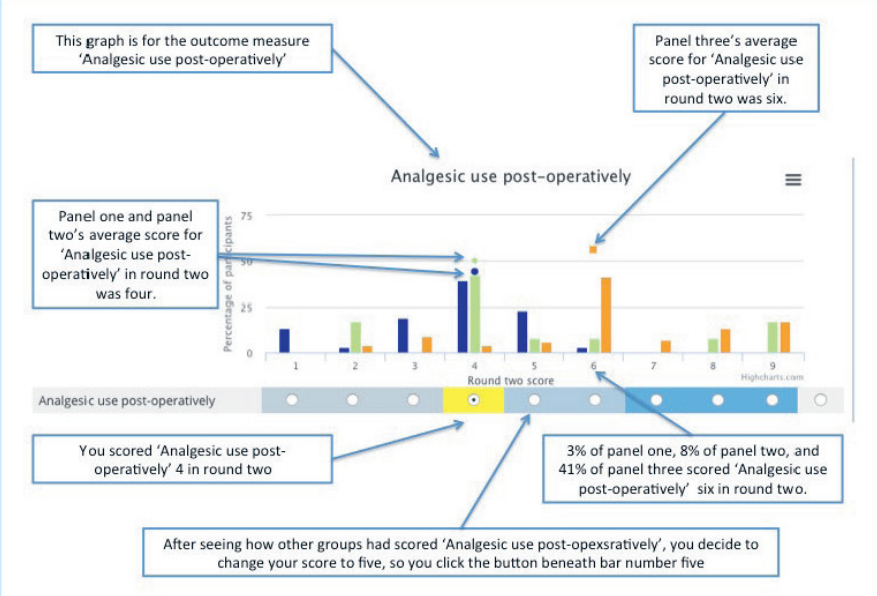
In round three, we will show you the remaining outcome measures, and ask you to score them from 1-9, again based upon how important you think they are in determining the success of someone's Hirschsprung's Disease treatment. We will also show you a graph of how ***other groups of experts have scored these outcome measures***. These experts, who as explained in previous newsletters have been divided into three panels, include people with Hirschprung's Disease, their parents, neonatologists, surgeons, paediatricians, specialist nurses and researchers. From the graph, you will be able to see how important other people involved with the study consider a particular outcome measure to be and then decide if you want to change the rating you gave the outcome measure in round two. ***There is no pressure to change your score if you do not want to.***

What information will I be shown?

As with round two, you will see one graph for each outcome measure. There are three parts to the graph:

1. The different coloured bars show the percentage of people in each panel giving a particular score to that outcome measure in round two. Each bar is a different score. The **blue bars** show the scores for the surgeons and neonatologists (panel 1), **the green bars** show the scores for the paediatricians, specialist nurses and researchers (panel 2), and the **orange bars** show the scores for people with Hirschsprung's disease and their parents (panel 3).

2. The coloured shapes show the average score from each panel for that outcome measure in round two. The blue circle shows the average score for panel 1, the green diamond shows the average score for panel 2, and the orange square shows the average score for panel three.
3. The yellow box shows the score you gave that outcome measure in round two.



Consensus Meeting

Selected people who are representative of the group as a whole will be invited to the consensus meeting ***in Leeds on the 21st of June.*** We will invite people from those who have indicated they are able to come to the meeting, in such a way as to get the most representative group possible. Breakfast and lunch will be provided on the day, along with coffee and cakes, so please let us know if you have any dietary requirements. The meeting will start at 10:00 and finish by 17:00 at the latest.

Developing a core outcome set for gastroschisis

We are still recruiting for the NETS[1G] study to develop a core outcome set for use in gastroschisis. We hope to start phase one of this study in July, so if you know anyone who may be interested in taking part, please ask them to register at ***www.npeu.ox.ac.uk/nets/taking-part***

www.npeu.ox.ac.uk/nets/taking-part

1HD NETS

Next stage in Evidence-based paediatric surgical Treatment Strategies

04

July 2016 Newsletter

Conclusion of the study?

We are now nearing the conclusion of the **NETS[1HD]** study, and would like to thank all of you for your help in developing what we believe to be a robust and exceptionally useful core outcome set for infants with Hirschsprung's Disease. Without all of your support it would not have been possible to achieve this.

From this point forward, we are working towards using the core outcome set in a large study to compare two different types of surgical treatment for infants with Hirschsprung's Disease. Use of the core outcome set in this study will help to make sure that it is truly relevant to people with Hirschsprung's Disease, their families, and clinicians. It will also help in the future to compare the results of this study with others conducted at a later date. ***We are looking for parents and patients to become members of the committee that oversees the conduct of this study. If you are interested in finding out more about this role, please contact Benjamin.allin@npeu.ox.ac.uk.***

Consensus Meeting Results

The consensus meeting for the **NETS[1HD]** study was held in Leeds on the 21st of June, and we would like to thank everyone who attended for their contributions. Following this meeting we have a shortlist of outcomes which, following refinement, will be used to form the core outcome set.

What happens now?

The next stage is for us to formalise the definitions for each outcome measure, determine the best way to measure each, and identify the most appropriate time point for measurement. We will do this through a series of steps, including reviewing the current scientific literature, and holding a further face-face meeting with a representative group of people who have participated in the study. We are aiming to have this process completed by the end of September.

When will I get to see the finalised core outcome set?

Following the final refinements of core outcome definitions, we will publish the core outcome set in a medical journal. At that point, we will email everyone a final summary of the included outcomes. Unfortunately, because of the copyright laws that apply to medical journals, we will not be able to share the core outcome set prior to publication.

Other core outcome sets

We are still recruiting people to take part in the development of a core outcome set for use in determining the success of gastroschisis treatment. If you, or anyone you know may be interested in taking part in this study, please go to ***www.npeu.ox.ac.uk/nets/taking-part***

Appendix 5: *NETS^{1G} study newsletters*

1G NETS

Next stage in Evidence-based paediatric surgical Treatment Strategies

01

April 2016 Newsletter

Thank you all for registering to take part in the NETS[1G] study. We are very grateful for your support

Over the period of the study we will send you four brief newsletters to update you on how the work is progressing and explain what will be happening over the next few months. If you would rather not receive these newsletters, please email *benjamin.allin@npeu.ox.ac.uk*, and we will remove you from the mailing list.

Why are we doing the NETS[1G] study?

Gastroschisis research is mainly aimed at trying to work out whether one type of treatment is better than another. A common way of doing this is to compare children who have had one type of treatment with children who have had a different form of treatment and to then look at what happens to them. Each of the things you could look at is called an **outcome measure,** and some examples include how long the child stays in hospital, or whether they get a complication from the treatment.

There are many different outcome measures that can be looked at, and this causes three problems in research. Firstly, there is a lot of variation in which outcome measures researchers choose to use in their studies. This means that it is **difficult to compare or combine results from different studies.** Secondly, researchers often use a certain outcome measure because it is easy to gather information about, rather than one that is important to patients. This means that the results of the research may not actually be relevant to patients with the condition. Finally, researchers will sometimes investigate many different outcome measures, but only publish the ones that support their argument. This is called reporting bias. **Each of these problems makes it harder to decide how to interpret results from a study.** At the moment, all of these problems are occurring in gastroschisis research.

How will the NETS[1G] study solve these problems?

The NETS[1G] study will develop a **core outcome set for gastroschisis.** A **core outcome set** is a list of outcome measures that should be reported as a minimum in every study looking at a particular condition. Using core outcome sets in research **addresses the problems caused by having a choice of many different outcome measures.**

Core outcome sets are developed through a Delphi Process. A **Delphi process** involves a group of experts being guided through a series of steps to identify the outcome measures that are **most important to the group as a whole.** The group of experts usually **includes people with the condition, their parents, doctors, nurses and researchers,** and the outcome measures that they decide are important will form the **core outcome set.**

By developing a core outcome set for gastroschisis we hope to make it easier to interpret the results of research and understand which treatments are best for patients.

Registration for the NETS[1G] Study

Registration for the NETS[1G] study has been going well so far. However, we plan to continue the registration process until June 2016, and begin the first phase of data collection in July 2016. This is because we are also running a study to develop a core outcome set for use in Hirschsprung's Disease, and in order to prevent participants becoming over-burdened by participating in two studies at the same time, we would like to finish the Hirschsprung's Disease study first.

What happens next?

In **July,** you will be emailed a link to an online questionnaire. In this questionnaire, you will be asked to **score a series of outcome measures from 1-9** based on how important you think each one is in deciding how well the overall treatment of someone's gastroschisis has worked. This questionnaire will form the first phase of the Delphi process. **In phases two and three of the Delphi process** you will be asked to re-score these outcome measures, each time being given more information about how other groups of people have scored them.

What is the end result of the NETS[1G] Study?

In **November 2016** we will hold a meeting, to which 40 people who are representative of everyone taking part in the study will be invited. The results of the Delphi process will be discussed in detail at this meeting, after which we will be able to identify a short list of outcome measures which will form the **core outcome set for gastroschisis.** In the future, researchers will try to work out which treatments are best for children with gastroschisis by comparing them using the NETS1G core outcome set.

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1G NETS

Next stage in Evidence-based paediatric surgical Treatment Strategies

02

November 2016 Newsletter

Phase one of the NETS[1G] study has now closed, and we would like to thank everyone for completing the questionnaire, we greatly appreciate your time.

What happens now?

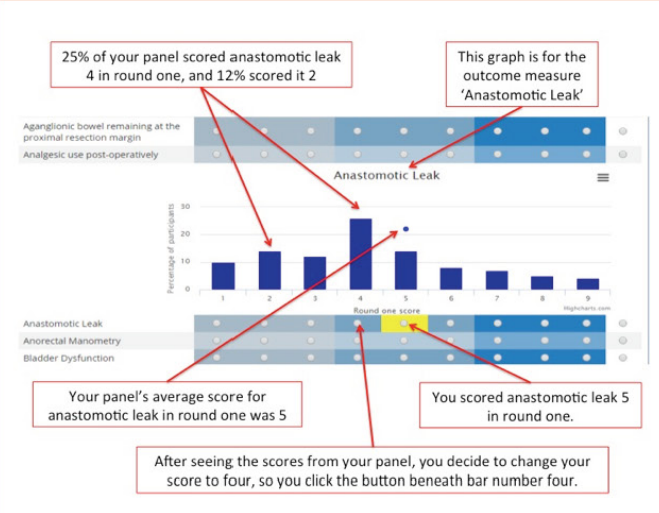
You have been allocated to ***one of three panels*** of participants, either the neonatal panel, the non-neonatal panel, or the personal experience panel. Within the ***neonatal panel,*** are paediatric surgeons, nurses, fetal medics and neonatologists, within the ***non-neonatal panel*** are paediatricians, dieticians, and researchers, and in the ***personal experience panel,*** are people who were born with gastroschisis and parents of children who were born with gastroschisis.

Next week, you will receive an email with a link to the phase two questionnaire. In this, we will ask you to score each outcome again, using the same 1-9 scale. However, this time we will also show you a graph that describes how other people in your panel scored that outcome on phase one. We would like you to consider whether you wish to change the score you gave each outcome in light of the information in the graphs. You do not have to change your scores if you do not wish to.

You will see one graph for each outcome, and there are three parts to each graph:

1. The bars show the percentage of people in your panel giving a particular score to that outcome in phase one. Each bar is a different score.
2. The blue circle represents the average score your panel gave to that outcome in phase one.
3. The yellow box shows the score you gave the outcome in phase one.

Below is an ***example*** graph:



Feedback from phase one

Lots of useful comments were left in phase one. We have used these comments to refine the outcomes we ask about in phase two, and have answered some of the common questions below.

There are some outcomes that seem irrelevant, why are you asking me to score them?

All of the outcomes that you scored in phase one are outcomes that people have recently studied when comparing two treatments for children with gastroschisis. Only some of these will be relevant or important. However, in order to identify which ones are important, we also need you to tell us which ones are not important, and therefore we have asked you to score all of them.

Why are some of the outcomes so vague? It makes it very hard to score them.

Many of the outcomes are deliberately vague, as at this stage we are simply trying to understand which broad areas are important to you. At the consensus meeting on the 8th of February, each broad outcome area that is scored as important in the Delphi process will be discussed in detail, and specific ways of measuring that outcome will be identified. For example, we have asked you to tell us how important it is to measure "Growth" as an outcome. For now, we simply want to understand whether growth in general is important as an outcome in determining the success of treatment of an infant with gastroschisis, and if you tell us that it is, then at the consensus meeting, we will work out the most appropriate way to measure growth, for example using weight, or length, or a combination of different measures.

Some of the outcomes which are complications of treatment can have a range of consequences, how do I score these?

We understand that it can be difficult to score the complications of treatments because they can have such a wide range of consequences. If you think that that complication is important regardless of the consequence it has, you should score it highly. However, if you think that the importance of the complication is determined by its outcome, then you should score the complication lower, and then score the consequence that you think is important highly. For example, the complication "Bowel resection" where a bit of bowel needs to be removed, can lead to a range of consequences. These consequences range from the need for one further operation, to the need for multiple operations, or a lifelong need for artificial feed to be given into the veins because there is not enough bowel left to absorb all of the nutrition that is needed. Each of the consequences that are described are also assessed as outcomes within the questionnaire. If therefore you thought the "Bowel resection" was only important if lifelong artificial feed needed to be given, then you should score bowel resection low, and need for lifelong artificial feed high. However, if you think that the need for bowel resection is important regardless of the consequence it has, then you should score it high, and also score highly any of the complications you think are important.

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1G NETS

Next stage in Evidence-based paediatric surgical Treatment Strategies

03

January 2017 Newsletter

Thank you for completing phase two of the NETS[1G] study. There is now just one phase left, and the questionnaire will be shorter than in phase two.

What happens now?

In phase three, we will show you all the outcomes that were highly scored in phase two, and ask you to score them from 1-9, again based upon how important you think they are in determining the success of someone's gastroschisis treatment. We will also show you a graph of how ***other groups of experts have scored these outcomes.*** This means you will now be able to see how important people born with gastroschisis, their parents, neonatologists, surgeons, paediatricians, specialist nurses, dieticians, fetal medics, and researchers think each outcome is. We are asking you to look at this information, and decide whether based upon it you would like to change your score from phase two or not. ***There is no pressure to change your score if you do not want to.***

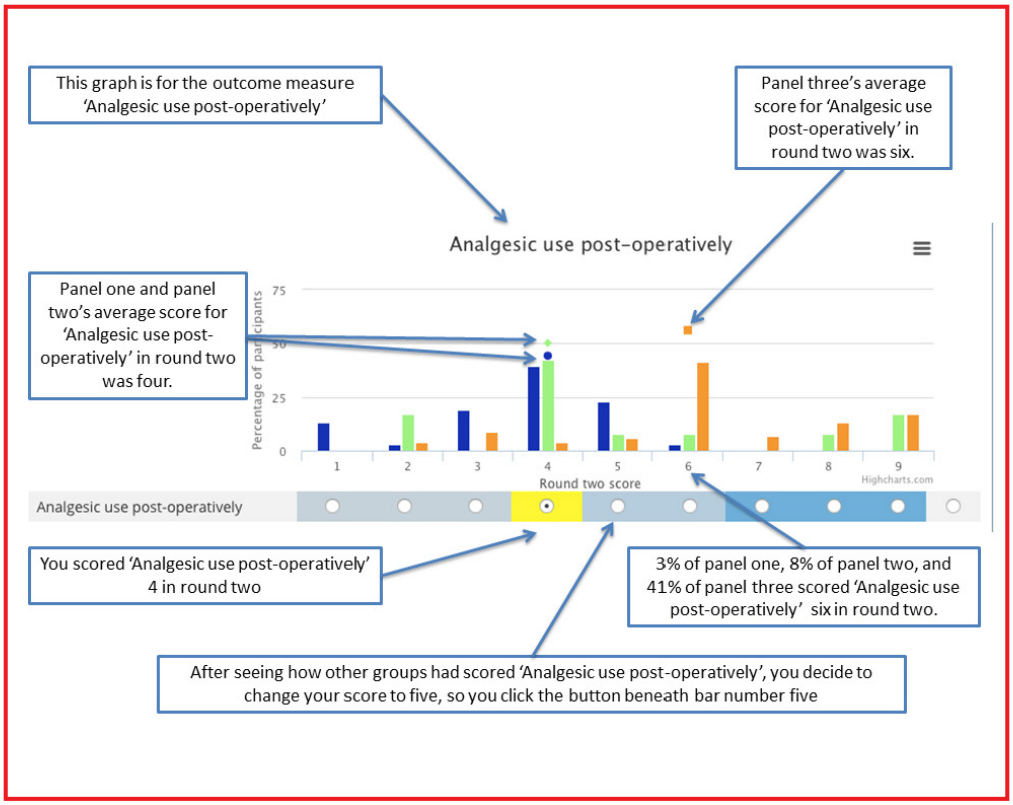
What information will I be shown?

As with phase two, you will see one graph for each outcome measure. There are three parts to the graph:

1. The different coloured bars show the percentage of people in each panel giving a particular score to that outcome in phase two. Each bar is a different score. The blue bars show the scores for the surgeons, nurses, fetal medics and neonatologists (neonatal panel), the green bars show the scores for the paediatricians, dieticians and researchers (non-neonatal panel), and the orange bars show the scores for people born with gastroschisis, and parents of children born with gastroshisis (personal experience panel).

2. The coloured shapes show the average score from each panel for that outcome in phase two. The blue circle shows the average score for the neonatal panel, the green diamond shows the average score for the non-neonatal panel, and the orange square shows the average score for the personal experience panel

3. The yellow box shows the score you gave that outcome in phase two.



What happens after the third phase?

A representative sample of the group as a whole will be invited to the consensus meeting in ***Birmingham on the 8th of February***. We will invite people from those who have indicated they are able to come to the meeting in such a way as to get the most representative group possible. Breakfast and lunch will be provided on the day, along with coffee and cakes, so please let us know if you have any dietary requirements. The meeting will start at 10:00 and finish by 17:00 at the latest.

Appendix 6: *Reasons for exclusion of Hirschsprung's Disease studies at full paper stage*

Table 51: Reasons for exclusion of Hirschsprung's Disease studies at full paper stage

Author	Title	Year	Reason for Exclusion
Ademuyiwa, AO. Et al	Swenson's pull-through in older children and adults: Peculiar peri-operative challenges of surgery	2011	No active comparison of outcomes between different surgical techniques
Akilov, K. et al	Hirschsprung's disease as a cause of chronic constipation in children	2013	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Baxter, KJ. Et al	Hirschsprung's disease in the preterm infant: Implications for diagnosis and outcome	2013	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Bradnock, TJ. Et al	Primary laparoscopic-assisted endorectal pull-through for Hirschsprung's disease: 5-year outcome data for a national cohort of 28 cases	2011	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Doodnath, R. Et al	A systematic review and meta-analysis of Hirschsprung's disease presenting after childhood	2010	No active comparison of outcomes between different surgical techniques
Downey, EC. Et al	Hirschsprung disease in the premature newborn: A population based study and 40-year single center experience	2015	No active comparison of outcomes between different surgical techniques
Ekenze, SO. Et al	Problems and outcome of Hirschsprung's disease presenting after 1 year of age in a developing country	2011	No active comparison of outcomes between different surgical techniques
Hotouras, A. Et al	Stoma related morbidity in infants operated for Hirschsprung's disease: A 17 years single centre experience	2012	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Huang, EY. Et al	Changes in hospital utilization and management of Hirschsprung disease: Analysis using the kids' inpatient database	2013	No active comparison of outcomes between different surgical techniques

Table 51: Reasons for exclusion of Hirschsprung's Disease studies at full paper stage - Continued

Author	Title	Year	Reason for Exclusion
Ismail Lotfalla, M. Et al.	Laparoscopic assisted modified duhamel technique using transanal staplers	2014	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Kapuller, V. Et al	Transanal approach for Hirschsprung's disease: Three centers experience	2010	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Kholostova, V. V. Et al	Surgical treatment of Hirschsprung's disease total form in children	2014	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Ksia, A. Et al	Soave transanal one-stage endorectal pull-through in the treatment of Hirschsprung's disease of the child above two-year-old: a report of 20 cases	2013	No active comparison of outcomes between different surgical techniques
Laughlin, D. M. Et al	Total colonic aganglionosis: A systematic review and meta-analysis of long-term clinical outcome	2012	No active comparison of outcomes between different surgical techniques
Levitt, M. A. Et al	Transanal, full-thickness, Swenson-like approach for Hirschsprung disease	2013	No active comparison of outcomes between different surgical techniques
Nouira, F. Et al	Surgical management of recto-sigmoid Hirschsprung's disease	2012	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Parsons, C. Et al	Persistent Faecal Incontinence following surgery for Hirschsprung disease	2011	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Sharma, S. Et al	Hirschsprung's disease presenting beyond infancy: Surgical options and postoperative outcome	2012	No active comparison of outcomes between different surgical techniques

Table 51: Reasons for exclusion of Hirschsprung's Disease studies at full paper stage - Continued

Author	Title	Year	Reason for Exclusion
Sowande, O. Et al	Ten-year experience with the Swenson procedure in Nigerian children with Hirschsprung's disease	2011	No active comparison of outcomes between different surgical techniques
Travassos, D. V. Et al	Is complete resection of the aganglionic bowel in extensive total aganglionosis up to the middle ileum always necessary?	2011	No active comparison of outcomes between different surgical techniques
Zhang, J. S. Et al	Transanal rectal mucosectomy and partial internal anal sphincterectomy for Hirschsprung's disease	2014	Abstract only – no evidence of active comparison of outcomes between different surgical techniques

Appendix 7: *Variability of outcome reporting in Hirschsprung's disease and gastroschisis: A systematic review (73)*

SCIENTIFIC REPORTS

OPEN

Variability of outcome reporting in Hirschsprung's Disease and gastroschisis: a systematic review

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Heterogeneity in outcome reporting limits identification of gold-standard treatments for Hirschsprung's Disease(HD) and gastroschisis. This review aimed to identify which outcomes are currently investigated in HD and gastroschisis research so as to counter this heterogeneity through informing development of a core outcome set(COS). Two systematic reviews were conducted. Studies were eligible for inclusion if they compared surgical interventions for primary treatment of HD in review one, and gastroschisis in review two. Studies available only as abstracts were excluded from analysis of reporting transparency. Thirty-five HD studies were eligible for inclusion in the review, and 74 unique outcomes were investigated. The most commonly investigated was faecal incontinence (32 studies, 91%). Seven of the 28 assessed studies (25%) met all criteria for transparent outcome reporting. Thirty gastroschisis studies were eligible for inclusion in the review, and 62 unique outcomes were investigated. The most commonly investigated was length of stay (24 studies, 80%). None of the assessed studies met all criteria for transparent outcome reporting. This review demonstrates that heterogeneity in outcome reporting and a significant risk of reporting bias exist in HD and gastroschisis research. Development of a COS could counter these problems, and the outcome lists developed from this review could be used in that process.

Systematic reviews comparing key treatments for both Hirschsprung's Disease and gastroschisis have failed to identify gold standard treatments for either condition[1–4]. This is likely to be due to a combination of reasons including the small size and retrospective nature of many of the primary studies, but also inadequate data reporting, heterogeneity in outcome definition, and use of surrogate markers of success instead of clinically relevant outcomes[1]. In a recent study reviewing 283 randomly selected Cochrane systematic reviews covering a range of conditions and interventions, Kirkham *et al.* demonstrated that over 30% of the randomised controlled trials included in these systematic reviews either did not publish at all, or did not fully publish the results for their identified primary outcomes[5]. This suggests that the potential for reporting bias is widespread within the medical literature.

Potential reporting bias and potential lack of patient relevance, combined with the fact that chance and confounding are likely to be impacting the results of many Hirschsprung's Disease and gastroschisis studies[6] limits the ability of the existing evidence base to help guide clinical management. It has been proposed that the development of core outcome sets for key conditions, combined with increased collaboration can help address these problems[1,7,8].

Core outcome sets are groups of outcomes that have been identified through a systematic review and Delphi process, and ratified by key stakeholders as the outcomes that should at a minimum be reported in every study of that condition[8]. They are a tool that has been championed by the COMET (Core Outcome Measures in Effectiveness Trials) initiative as a method for reducing reporting bias, increasing patient relevance of research, and improving meta-analysis. Their use in other conditions has been shown to significantly improve the quality of research being conducted[9], thereby enabling more evidence-based clinical practice.

Prior to developing a core outcome set it is essential to know which outcomes are currently reported in the published literature, and the quality of their reporting. The aims of this work were therefore to conduct two systematic reviews, in order to identify which outcomes are currently reported in studies comparing surgical

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interventions for Hirschsprung's Disease and gastroschisis, determine the completeness of data reporting, and make an empirical assessment of the likelihood of reporting bias in included studies.

Methods

Two systematic reviews were conducted according to pre-specified protocols that were prospectively registered on PROSPERO (CRD42015024996 and CRD42015025026). Multiple search strategies were used to identify relevant articles from Medline and EMBASE. Search terms were identified from database thesauri and free text relating to either Hirschsprung's Disease and operative interventions for Hirschsprung's Disease, or gastroschisis and interventions for gastroschisis, and combined using Boolean operators. Searches were limited to papers published in or after 2010 in order to ensure that identified outcomes were contemporaneous. Full search strategies are provided in supplementary files one and two.

Study selection and data extraction. Identified titles were assessed for inclusion by three investigators acting independently (BA and AI for Hirschsprung's Disease, and BA and NP for gastroschisis). Any conflicts were resolved by discussion, with recourse to a fourth investigator (MK) where necessary. Data from included articles were extracted independently for each review by the same two investigators, with conflicts resolved in the same manner. The following data were extracted from all studies: study design, year of study, interventions investigated, population investigated, size of study population, inclusion and exclusion criteria, outcomes reported, whether outcomes were primary or secondary, time-points at which outcomes were measured, which of the criteria for complete reporting the study met, and the ORBIT grade[5] for each investigated outcome. ORBIT grades range from A-I and are used to denote the completeness of reporting for a particular outcome.

Inclusion and exclusion criteria. All study designs except case studies and expert opinion were considered for inclusion in the review. Studies where only the abstract was available (e.g. conference proceedings) were not included in the assessment of completeness of data reporting, as this could only be analysed from the full study report. The search was limited to papers published after 2010 in order to ensure that the outcomes identified by the review remained contemporaneous. Only studies including more than 10 infants were eligible for inclusion.

Additionally, Hirschsprung's Disease studies were eligible for inclusion if they:

1. Compared two or more interventions for infants with biopsy confirmed Hirschsprung's Disease and
2. Reported outcomes following the primary definitive procedure.

Additionally, Hirschsprung's Disease studies were excluded if:

1. They only reported outcomes from one intervention without a comparator.
2. They only reported outcomes for infants undergoing a re-do procedure or
3. They only reported outcomes from the non-definitive procedure e.g. stoma formation in infants planned for a staged procedure.

Additionally, gastroschisis studies were eligible for inclusion if they compared two or more methods of visceral reduction and defect closure in infants with gastroschisis, and were excluded if they only reported outcomes from one intervention without a comparator.

Both searches were undertaken in August 2015.

Outcome description. The primary aim of this study was to generate a list of all outcomes investigated by eligible studies. The median number of outcomes reported per study was calculated as a secondary outcome measure. Similar outcomes were merged to one common term prior to analysis.

Outcome terms were then assigned to one of the five core areas from the OMERACT filter 2.0. The OMERACT filter 2.0 represents five core areas that should be covered by outcomes in order to ensure a full breadth of reporting[10]. These areas are (1) adverse events, (2) life impact, (3) resource use, (4) pathophysiological manifestations, and (5) death.

Completeness of reporting. A secondary aim of this review was to determine the completeness of outcome reporting in Hirschsprung's Disease and gastroschisis studies. Harman *et al.* proposed five core questions that could be used to assess how transparently researchers had identified and reported their choice of outcomes[11], whilst the ORBIT criteria are used to determine whether it is likely that data is missing from the studies report[5]. The percentage of studies meeting all five of Harman *et al.*'s core criteria for complete, transparent outcome reporting, and the percentage of studies reporting full data, as described by the ORBIT criteria were calculated for all outcomes investigated. Harman *et al.*'s five core criteria are:

1. Is the primary outcome clearly stated?
2. Is the primary outcome clearly defined so that another researcher would be able to reproduce its measurement?
3. Are the secondary outcomes clearly stated?
4. Are the secondary outcomes clearly defined?
5. Do the authors explain the use of the outcomes which they have selected?

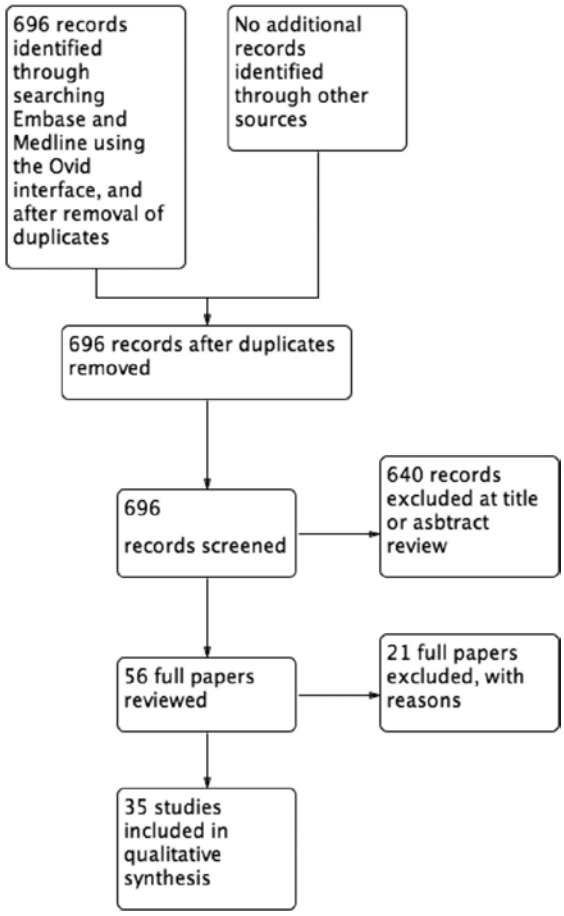

Figure 1. Hirschsprung's Disease PRISMA flow chart.

Data Synthesis. The number of outcomes reported in each eligible study and the number of times each outcome was reported were counted, and the medians and interquartile ranges calculated. The number and percentage of studies answering yes to all five core questions proposed by Harman *et al.*, and the number and percentage with full reporting according to ORBIT criteria for all investigated outcomes were also calculated.

Results

Hirschsprung's Disease included studies. The search retrieved 696 unique titles related to Hirschsprung's Disease, 640 of which were excluded following title and abstract review. Following full paper review, a further 21 papers were excluded with reasons (Supplementary File 3), leaving 35 studies as eligible for inclusion in the review (Fig. 1). Eighteen manuscripts (51%) were retrospective case series, nine (26%) were prospective cohort studies, three (9%) were case control studies, three (9%) were systematic reviews, one (3%) was a registry based study, and one (3%) was a randomised controlled trial. The median number of study participants was 62 (IQR44-156).

Outcome	Number of times reported	Outcome	Number of times reported	Outcome	Number of times reported
Development-Social	1	Medication-laxative	2	Narrowing of anastomosis or cuff	22
Sleep disturbance	1	Dilations	1	Impotence	1
Depression	1	Continence-urinary	1	Abdominal distension	3
Psychological stress	1	*Manometry*	1	Sphincter achalasia	1
Cosmetic results	2	*Bowel Movement-first post-op*	3	Feeding intolerance	1
Parenteral nutrition use	1	*Early pelvic inflammation*	1	Post-operative infection	9
Time until first feed (post-operatively)	7	*Bladder Dysfunction*	1	Fever	1
Diet tolerated	1	*Aganglionic bowel remaining*	1	Abscesses	5
Assessment of bowel function	1	***Death***	7	Anastomotic Leak	13
Bowel Function Score (BFS) questionnaire	2	Intra-operative complication	4	Pneumonia	2
Gastrointestinal Quality of Life Index (GIQLI) questionnaire	2	Intra-operative visceral injury	2	Dehiscence	7
Krickenbeck score	2	Colonic torsion	2	Enterocolitis	23
Sensation of need to defecate	2	Ischaemia	1	Granuloma	1
Voluntary bowel movements	2	Conversion	6	Colostomy morbidity	1
Frequency of bowel movements	13	Intra-operative blood loss	13	Herniation	6
Time to normal bowel habits	1	Reoperations	11	Colostomy retractions	1
Long-term bowel dysfunction	1	Excoriation	10	Late or adhesional obstruction	7
Faecal Impaction	1	Anal lacerations	1	Operation length	17
Constipation	20	Fistula	1	Time of antibiotic administration	1
Diarrhoea	3	Necrosis of and retraction of colon	1	Analgesic use post-operatively	2
Consistency of stool	3	Adhesions	1	ICU admission	1
Urgency period	3	Post-operative 'complications'	3	Hospital stay (length)	18
Requiring nappy	1	Early or persistent obstruction	8	Readmission	2
Faecal incontinence	32	Prolapse	2	Cost	2
Encopresis	1	Rectal muscularis infection	1		

Table 1. Hirschsprung's Disease outcomes and number of times reported, grouped according to OMERACT filter 2.0. Bold is life impact, *Italic is pathophysiological manifestations*, ***Bold italic is mortality***, **underlined bold is adverse events**, and underlined is resource utilisation.

Hirschsprung's Disease reported outcomes. In the 35 included studies, 95 outcomes were investigated a total of 337 times. Thirty-five outcomes were considered to be too similar to at least one other outcome to be meaningfully differentiated, and these outcomes were therefore mapped to one common term (e.g. continence/incontinence, or frequency of stool/bowel movement frequency). Following this exercise, 74 unique outcomes were identified as having been reported (Table 1).

Outcomes were mapped to the OMERACT filter 2.0. Overall, 33 'adverse event' outcomes, 28 'life impact' outcomes, seven 'resource use' outcomes, five 'pathophysiological manifestation' outcomes, and one 'death' outcome were reported. Adverse event outcomes accounted for 171 of the 338 outcomes that studies investigated (51%), whilst life impact outcomes accounted for 109 (32%).

Overall, faecal incontinence was the most commonly reported outcome and, appearing in 32 studies (91%), the only one to be investigated in more than 75% of studies. Outcomes investigated in more than 50% of studies were enterocolitis (23 studies, 66%), constipation (20 studies, 57%) and length of stay (18 studies, 51%). Thirty-three (45%) of the 74 unique outcomes were only investigated in one study. The median number of outcomes investigated per study was 11 (IQR6-13). Due to the retrospective nature of many of the included studies, and the lack of clearly defined end-points within them, it was not possible to make any meaningful assessment of the ages at which key outcomes were measured.

Hirschsprung's Disease Completeness of reporting. Of the 35 included studies, seven (20%) were available only as abstracts and were therefore excluded from assessment of overall quality and completeness of reporting. Of the remaining 28 studies, only 7 (25%) met all five of the core criteria that Harman *et al.* describe for

Study	Design	Number of infants	Number of outcomes reported	Meets *all* core criteria for complete high quality reporting	Complete data reporting
Ademuyiwa, A. O. *et al.* 2012[13]	Retrospective case series	29	7	No	No
Aworanti, O. M. *et al.*[14]	Retrospective case series	51	4	Yes	Yes
Chen, Y. *et al.*[15]	Systematic Review	131	6	No	Yes
Dahal, G. R. *et al.*[16]	Retrospective case series	11	15	Yes	No
Duncan, N. D. *et al.*[17]	Retrospective case series	45	8	No	No
Dutta, H. K. *et al.*[18]	Prospective cohort	62	13	No	No
El-Sawaf, M. *et al.*[19]	RCT	22	2	Yes	Yes
Fernandez Ibieta, M. *et al.*[20]	Case-Control	38	4	Yes	Yes
Fernandez Ibieta, M. *et al.*[21]	Retrospective case series	220	11	No	No
Gao, M. T. *et al.*[22]	Prospective cohort	70	2	No	No
Giuliani, S. *et al.*[23]	Retrospective case series	29	13	No	No
Gosemann *et al.*[24]	Systematic Review	159	4	No	Yes
Gunnarsdottir, A. *et al.*[25]	Prospective cohort	281	15	No	Yes
Jarvi, K. *et al.*[26]	Case control	101	14	Yes	No
Kim, A. C. *et al.*[27]	Retrospective case series	110	14	No	No
Li, L. Z. *et al.*[28]	Retrospective case series	14	4	No	No
Mabula, J. B. *et al.*[29]	Prospective cohort	181	13	No	No
Miyano, G. *et al.*[30]	Retrospective case series	54	10	No	No
Nah, S. A. *et al.*[31]	Retrospective case series	53	11	No	No
Nasr, A. *et al.*[32]	Case control	52	13	Yes	No
Romero, P. *et al.*[33]	Retrospective case series	11	14	No	No
Stensrud, K. J. *et al.*[34]	Prospective cohort	1555	14	No	No
Stensrud, K. J. *et al.*[35]	Prospective cohort	58	11	No	No
Sulkowski, J. P. *et al.*[36]	registry	218	12	No	No
Tang, S. *et al.*[37]	Retrospective case series	72	10	No	No
Tang, S. T. *et al.*[38]	Retrospective case series	20	11	No	No
Tang, W. *et al.*[39]	Retrospective case series	43	5	No	No
Thomson, D. *et al.*[2]	Systematic Review	50	15	Yes	Yes
Travassos, D. *et al.*[40]	Retrospective case series	90	10	No	No
Van de Ven, T. J. *et al.*[41]	Retrospective case series	153	11	No	No
Visser, R. *et al.*[42]	Retrospective case series	54	14	No	No
Vorobyov, G. I. *et al.*[43]	Retrospective case series	84	7	No	No
Wang, L. *et al.*[44]	Prospective cohort	792	6	No	No
Yang, L. *et al.*[45]	Prospective cohort	1412	10	No	No
Yang, L. *et al.*[46]	Prospective cohort	405	4	No	No

Table 2. Number of outcomes reported and completeness of outcome reporting in Hirschsprung's Disease studies.

achieving complete, high quality reporting of a study's results. When assessed against the ORBIT criteria, of the 28 full papers, only seven (25%) fully reported each of the outcomes they set out to investigate (Table 2).

Gastroschisis included Studies. The search strategy returned 234 titles related to gastroschisis, reduced to 211 after exclusion of duplicates. Following review of titles and abstracts, 167 records were excluded. A further fourteen records were then excluded with reasons following full paper analysis (Supplementary File 4), resulting in 30 studies that were deemed eligible for inclusion in the review (Fig. 2). Twenty-two papers (73%) were retrospective case series, four were prospective cohort studies (13%), two were systematic reviews (7%), one was a case-control study (3%), and one was a registry study (3%). There were no eligible randomised controlled trials. The median number of study participants was 122 (IQR 53-285).

Gastroschisis outcomes. Within the included studies, 102 outcomes were investigated a total of 247 times. Within these 102 outcomes there were 63 that were felt to be too similar to at least one other outcome to be meaningfully differentiated, and these were therefore mapped to one common term. Following this mapping process, there remained 62 unique outcomes (Table 3).

Outcomes were mapped to the OMERACT filter 2.0. Overall, 22 'adverse event' outcomes (35%), 18 'pathophysiological manifestation' outcomes (29%), 12 'life impact' outcomes (20%), nine 'resource use' outcomes (15%), and one 'death' outcome (1%) were reported. 'Adverse event' outcomes were reported 97 times (39% of all reported outcomes), whilst 'life impact' outcomes were reported 58 times (23% of all reported outcomes).

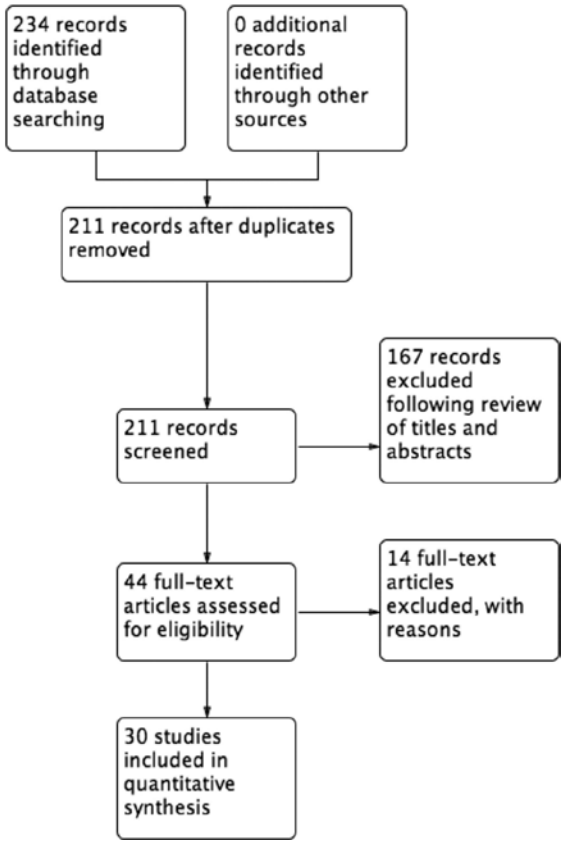

Figure 2. Gastroschisis PRISMA flow chart.

Eight of the 62 identified outcomes related to feeding (13%), and five related to mechanical ventilation (8%). These two areas therefore appear to be of interest to researchers. However, the greatest number of studies in which any individual outcome from either of these areas was investigated was 13 (43%), suggesting there is little agreement on what the most important outcome in each area is. Overall, the most commonly investigated outcome was total length of stay, appearing in 24 studies (80%). Mortality (19 studies, 63%), and development of necrotising enterocolitis (16 studies, 53%) were the only other outcomes to be reported in more than 50% of studies. The median number of times an outcome was reported was once (IQR1-2). Thirty-one outcomes (50%) were only reported in one study. The median number of outcomes reported per study was 9 (IQR5-11).

Gastroschisis completeness of reporting. Of the 30 included studies, three were only available as abstracts, and therefore excluded from analysis of completeness and quality of reporting. Of the remaining 27 studies, none met all five of the core criteria defined by Harman *et al.* for complete, high quality outcome reporting. When assessed against the ORBIT criteria, 12 studies (44%) fully reported each of the outcomes they set out to investigate (Table 4).

Discussion

This review shows substantial heterogeneity of outcome reporting in Hirschsprung's Disease and gastroschisis studies. For each condition, over 60 unique outcomes were investigated, only 5% of which were investigated in more than half of the included studies, and over 40% of which were only investigated in one study.

Outcome	Number of times reported	Outcome	Number of times reported	Outcome	Number of times reported
Time on *total* parenteral nutrition	9	*Bacteraemia*	2	**Infection, unspecified or other**	7
Time on parenteral nutrition	12	*pH, time acidotic*	1	**Infection, central line related**	6
Parenteral nutrition ever required	1	*Kidney dysfunction*	1	**Wound infection or breakdown**	12
Parenteral nutrition required post-discharge	1	*Urine output*	3	**Infection with systemic sequelae**	8
Feeding, initiation of feed in NICU	1	*Blood pressure, mean arterial*	1	**Infection free survival**	1
Feeding, full feeds at discharge from NICU	1	*Need for mesh at closure*	1	**Infection, urinary or respiratory**	3
Time to first oral feed	13	*weight <10th centile*	1	**Number of transfusions**	1
Time to full oral feeds	13	*weight gain*	1	**Silo Complication**	2
Short Bowel Syndrome	4	*Hypothyroidism*	1	**Ischaemic bowel**	2
bowel lengthening procedure required	1	Length of stay	24	**Anastomotic stricture**	2
liver transplantation	1	NICU length of stay	4	**Intestinal perforation**	3
Neurodevelopmental delay	1	Discharge, NICU to home	1	**Abdominal compartment syndrome**	7
Total time on mechanical ventilation	13	General anaesthesia, number of days, indication	1	**NEC**	16
Post closure time on mechanical ventilation	3	Central-line usage ratio (days with central line/ hospital days)	1	**Stoma complication**	2
Ventilation, peak inspiratory pressure	1	Duration of antibiotics	3	**Adhesional small bowel obstruction**	3
Ventilation, peak concentration inspired oxygen	1	Hospital charge	2	**Intestinal Failure Associated Liver Disease**	6
Post-operative ventilation required	1	Days to abdominal wall closure	1	**Unplanned reoperation**	9
Respiratory compromise	1	rehospitalisation	1	**Reoperation, need for enlargement of gastroschisis defect**	1
Neonatal Respiratory Distress Syndrome	1	***Mortality***	19	**Reoperation, need for silo replacement**	1
Cholestasis	2	**GI complication**	1	**Umbilical hernia**	3
Volume of IV fluid required	1	**Non-GI complication**	1		

Table 3. Gastroschisis outcomes and number of times reported, grouped according to OMERACT filter 2.0. Bold is life impact, *Italic is pathophysiological manifestations*, ***Bold italic is mortality***, **underlined bold is adverse events**, and underlined is resource utilisation.

Within Hirschsprung's Disease research, 32% of investigated outcomes were in the 'life impact' core area of the OMERACT filter 2.0, suggesting that there is potential for current research to be investigating outcomes of relevance to patients. The lack of meaningful information on when outcomes are measured however, meant that it was not possible to determine whether these outcomes were investigated at time points where their results would be considered valid (e.g. whether faecal continence was measured in infants who were old enough to be expected to be continent). With 64% of gastroschisis outcomes fitting into either the 'pathophysiological manifestations' or 'adverse events' core areas, it would suggest that gastroschisis research tends to have a shorter-term focus. With no gastroschisis studies, and only 25% of Hirschsprung's Disease studies meeting all of the criteria for high quality, complete outcome reporting, and only 25% of Hirschsprung's Disease and 44% of gastroschisis studies fully reporting all outcome data, there also appears to be a high risk of reporting bias within both research fields.

The search strategy and inclusion criteria for this study were designed to be sensitive whilst maintaining contemporaneity of the identified outcomes. This should provide the most robust basis for development of a core outcome set. Excluding studies conducted prior to 2010 does however introduce the potential for these reviews to miss important outcomes that were fully investigated in high quality studies prior to this point. One example of this is the only randomised controlled trial carried out to date which compares operative primary fascial closure with silo placement for treatment of gastroschisis[12]. Such exclusions have the potential to alter the data on completeness of reporting. However, we were unable to identify any plausible reasons why the study designs used, or quality of reporting should be significantly different pre and post 2010. We therefore do not believe that these exclusions will have significantly altered the conclusions of this review. By including in the current analysis outcomes investigated by systematic reviews, outcomes reported by significant primary studies prior to 2010 (including that of Pastor *et al.*) should also have been captured, and will therefore be included in the list of outcomes used for the development of the core outcome sets.

Study	Design	Number of infants	Number of outcomes reported	Meets *all* core criteria for complete high quality reporting[11]	Complete data reporting[5]
Alali *et al.*[47]	Retrospective Case Series	86	4	No	Yes
Allin *et al.*[1]	Systematic Review	804	14	No	Yes
Banyard *et al.*[48]	Retrospective Case Series	235	10	No	Yes
Barrett *et al.*[49]	Retrospective Case Series	70	4	No	No
Bradnock *et al.*[50]	Prospective Cohort Study	301	15	No	No
Charlesworth *et al.*[51]	Retrospective Case Series	156	9	No	Yes
Chesley *et al.*[52]	Retrospective Case Series	202	3	No	No
Dariel *et al.*[53]	Retrospective Case Series	64	15	No	Yes
Erdogan *et al.*[54]	Retrospective Case Series	29	12	No	No
Kandasamy *et al.*[55]	Retrospective Case Series	50	13	No	No
Kassa *et al.*[56]	Retrospective Case Series	79	3	No	No
Kunz *et al.*[3]	Systematic Review	1879	8	No	Yes
Lobo *et al.*[57]	Retrospective Case Series	37	10	No	No
Lusk *et al.*[58]	Retrospective Case Series	168	8	No	No
McNamara *et al.*[59]	Retrospective Case Series	30	3	Abstract Only	Abstract Only
Muniz *et al.*[60]	Retrospective Case Series	61	1	Abstract Only	Abstract Only
Murthy *et al.*[61]	Retrospective Case Series	442	11	No	Yes
Niramis *et al.*[62]	Retrospective Case Series	919	4	No	Yes
Orion *et al.*[63]	Retrospective Case Series	80	10	No	No
Owen *et al.*[64]	Prospective Cohort Study	393	9	No	Yes
Payne *et al.*[65]	Case Control Study	116	2	Abstract Only	Abstract Only
Safavi *et al.*[66]	Registry	402	7	No	Yes
Santos Schmidt *et al.*[67]	Retrospective Case Series	45	7	No	No
Schlueter *et al.*[68]	Retrospective Case Series	129	12	No	No
Schmidt *et al.*[69]	Prospective Cohort Study	45	8	No	No
Sirichaipornsak *et al.*[70]	Retrospective Case Series	15	9	No	No
Stanger *et al.* 2010[71]	Retrospective Case Series	679	6	No	Yes
Tsai *et al.*[72]	Retrospective Case Series	44	8	No	No
Van Manen *et al.*[73]	Prospective Cohort Study	167	12	No	Yes
Weil *et al.*[74]	Retrospective Case Series	190	10	No	No

Table 4. Number of outcomes reported and completeness of outcome reporting in gastroschisis studies.

In order to assess the quality and completeness of outcome reporting, we used tools that were initially designed for assessing randomised controlled trials and systematic reviews. However, it is not unreasonable to expect that any study making active comparison of two interventions meets all five of Harman *et al.*'s core criteria for high quality, transparent reporting, and that they fully report data for all stated a priori outcomes.

It has previously been suggested that variability in outcome definition and reporting is limiting the development of a high quality evidence in Hirschsprung's Disease and gastroschisis[1,2,4]. Our review reinforces that message, and adds to it by suggesting that there is also a high risk of reporting bias in research into both conditions, thereby further reducing the reliability of conclusions drawn from the current literature. This high risk of reporting bias echoes what was shown in a large selection of randomised controlled trials included in Cochrane systematic reviews[5].

The focus of the included studies on pathophysiological manifestations and adverse events, and lack of clarity of time-points for measurement of life impact outcomes raises the possibility that patients and their parents were not involved in determining which outcomes should be investigated by researchers and clinicians. This apparent lack of knowledge as to which outcomes are important to patients and parents in determining the success of gastroschisis and Hirschsprung's Disease treatment may account in part for the heterogeneity of outcome reporting that our reviews have demonstrated. The difficulties this heterogeneity creates for supporting clinical practice are compounded by the high risk of reporting bias that this review has also demonstrated. Both of these factors suggest that at present, caution should be exercised when using the existing literature to argue in favour of a particular treatment for either condition. There are two concrete steps that can be taken to remedy this situation, firstly, development of core outcome sets for use in gastroschisis and Hirschsprung's Disease, and secondly, enhanced national and international collaborative research studies and trials. These measures would reduce reporting bias, ease meta-analysis, increase statistical power to answer clinically relevant questions, and improve the patient relevance of research[7–9].

These systematic reviews provide the evidence that development and implementation of core outcome sets are required for Hirschsprung's Disease and gastroschisis. The outcomes identified by these reviews could be used as the starting point for a robust Delphi processes involving patients, parents and multi-disciplinary clinical groups

to develop such core outcome sets. These will be the first core outcome sets to be developed for any paediatric surgical condition, and we do not wish them to be developed simply as an academic exercise. Hirschsprung's Disease and gastroschisis were specifically chosen as the first conditions in which to develop paediatric surgical core outcome sets in order to limit the possibility of this occurring. We believe they limit this risk for two reasons. Firstly, both conditions are actively studied at present, and therefore, have a community of researchers who are anticipating the use of the developed core outcome sets. Secondly, there have been contemporaneous, UK-wide cohorts of infants established for both conditions, in whom long-term follow-up studies could be conducted utilising the developed core outcome sets. We have elected to present the results of both systematic reviews as one manuscript, as there are several common themes which lend themselves to being demonstrated best through reporting in a single article. Doing this illustrates to the paediatric surgical community the need for development and implementation of core outcome sets in both of these conditions, and potentially, in others as well.

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Author Contributions
B.A. conceived the idea for the study. B.A. and M.K. were responsible for design, analysis and interpretation of the work. B.A., A.I. and N.P. were responsible for acquisition and analysis of data for the work. B.A. was responsible for drafting the manuscript, all other authors contributed to revising it critically for intellectual content. All authors give final approval of the version to be published and give an agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. B.A. and M.K. act as guarantors for the work. The lead author affirms that he had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix 8: *Reasons for exclusion of Gastroschisis studies at full paper stage*

Table 52: Reasons for exclusion of gastroschisis studies at full paper stage

Author	Title	Year	Reason for Exclusion
Baumann, S. Et al	Gastroschisis: A retrospective single centre experience	2012	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Chandra, P. Et al.	Outcomes of surgically treated babies with gastroschisis - A 10-year experience	2010	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Emil, S. Et al	Contemporary 2-year outcomes of complex gastroschisis	2010	No active comparison of outcomes between different surgical techniques
Gupta, V. Et al	Neurodevelopment outcome at one year of age of infants with gastroschisis	2014	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Kang, R. Et al	Congenital abdominal wall defects: A six-year experience at Kosair children's hospital	2012	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Lasege, T. B. Et al	Gastroschisis treatment and outcomes at Kosair children's hospital: A ten-year review	2010	Abstract only – no evidence of active comparison of outcomes between different surgical techniques
Manson, J. Et al	Gastroschisis: A multi-centre comparison of management and outcome	2012	Abstract only – unable to determine eligibility therefore excluded
Martinez Criado, Y. Et al	Modifiable prognostic factors in the morbidity-mortality of gastroschisis	2012	No active comparison of outcomes between different surgical techniques

Table 52: Reasons for exclusion of Gastroschisis studies at full paper stage - Continued

Author	Title	Year	Reason for Exclusion
Minutillo, C. Et al	Growth and developmental outcomes of infants with gastroschisis at one year of age: A retrospective study	2013	No active comparison of outcomes between different surgical techniques
Sawicka, E. Et al	Influence of selected factors on the treatment and prognosis in newborns with gastroschisis on the basis of own experience	2013	No active comparison of outcomes between different surgical techniques
Tannuri, A. C. Et al.	Evolution of critically ill patients with gastroschisis from three tertiary centers	2011	No active comparison of outcomes between different surgical techniques
Tarca, E. Et al	Gastroschisis treatment: What are the causes of high morbidity and mortality rates?	2013	No active comparison of outcomes between different surgical techniques
Toro, M. N. H.	Management of abdominal wall defects (gastroschisis and omphalocele) at Hospital Universitario San Vicente de Paul, in Medellin, Colombia, 1998-2006	2010	Mixed gastroschisis and exomphalos cases, unable to separate
Van Manen, M. Et al.	Early childhood outcomes of infants born with gastroschisis	2013	No active comparison of outcomes between different surgical techniques

Appendix 9: *Summary of discussions at the NETS[1HD] Hirschsprung's disease consensus and measurement meetings*

IX.I Consensus meeting discussions resulting in modification of outcomes

During discussions at the consensus meeting, attendees determined that the outcomes of “Death”, “Intra-operative complication resulting in death (Clavien-Dindo grade five)”, “Post-operative complication resulting in death”, and “Intra-operative visceral injury resulting in death (Clavien-Dindo grade five)” could be represented by one outcome – “Death, with cause specified”. This was a unanimous decision, and they were therefore merged to the common outcome, which was subsequently scored. Two outcomes, “Narrowing of cuff”, and “Intra-operative complication - requires additional surgery (Clavien-Dindo grade three)” were discussed and felt to be adequately covered by the common outcome “Unplanned re-operation, with indication specified” which had already scored highly enough to meet consensus, and therefore, the decision was taken not to score them. There were three outcomes that did not meet criteria for automatic discussion at the consensus meeting, but which following discussion of other outcomes, the consensus meeting attendees felt warranted further discussion and scoring. These were “Objective score of bowel function”, “Unplanned readmission” and “Associated healthcare costs”. Following detailed discussion, meeting attendees felt that the outcomes “Associated healthcare costs”, and “Psychological stress” each represented more than one outcome, and should be scored as such. These outcomes were therefore split to “Psychological stress for the individual with Hirschsprung’s Disease”, “Psychological stress for the family of an individual with Hirschsprung’s Disease”, “Associated healthcare costs” and “Societal costs associated with the care

of an individual with Hirschsprung's Disease". These four outcomes were scored individually.

IX.II Measurement meeting discussions

IX.II.I Death with cause specified

Death was reported in seven studies included in the NETS[1HD] systematic review(16, 156, 196-200). No standard systems for classifying cause of death were identified in these studies. The group discussed whether cause of death should be provided in its full form, or classified according to pre-specified criteria. It was felt that asking for individual causes of death would not add significant useful information, would make reporting more burdensome, and cloud interpretation. The group felt that the important information to obtain from cause of death was whether it was due to the disease itself, HAE, an intervention, or unrelated.

The group determined that the core outcome should be defined as:

Death, with cause classified as due to 1) A complication of treatment (excluding HAE), 2) HAE, 3) An associated anomaly, 4) Other.

Mortality rates should be reported at the standard time-points applicable to the study design.

IX.II.II Unplanned re-operation with indication specified

Reoperation was investigated in 11 studies included in the NETS[1HD] systematic review(16, 141, 156, 157, 187, 201-206). There were no standard definitions for what should be included as a re-operation, or the timeframe over which this should be measured. As with cause of death, the group felt that asking researchers to report individual indications for reoperation would be burdensome and of little use. Multiple methods of classifying indication for reoperation were therefore discussed, and these included clinical classifications, classification according to anaesthetic required, and classification according to significance of the intervention. The group as a whole, and particularly members of the personal experience panel, felt that the most appropriate method of classification was according to the significance of the intervention, and the National Institute for Health and Care Excellence method of classification into Major or complex, intermediate, and minor should be used(207). The group felt that all reoperations related to the person's Hirschsprung's Disease should be included in this outcome, no matter how small, if they were not expected as part of the routine post-operative recovery from the person's initial surgical intervention.

The group determined that the core outcome should be defined as:

Unplanned reoperation with indication classified according to NICE criteria as minor, intermediate, or major/complex. Unplanned is defined as any procedure not considered part of routine post-intervention practice. This outcome should include any procedure that is performed as a direct result of the diagnosis or treatment of

the participants Hirschsprung's Disease, and any episodes of general anaesthesia that are required as a direct result of the diagnosis or treatment of the participant's Hirschsprung's Disease, regardless of whether or not an operative intervention is undertaken (e.g. an examination under anaesthesia, or manual evacuation). The outcome should be reported at the 'Intervention study' standard time-points.

IX.II.III Need for permanent stoma, indication specified

Need for permanent stoma was not investigated in any studies included in the NETS[1HD] systematic review.

The group discussed how to define permanency, and determined that it was the lack of intention to reverse the stoma at the time of its creation that was the important factor. The group also discussed the fact that this outcome was likely to be significantly affected by the participant's continence, and therefore should not be reported prior to the age at which continence could be expected.

The group determined that the core outcome should be defined as:

Need for permanent stoma as a direct result of the diagnosis, or treatment of the participant's Hirschsprung's Disease, including where the decision for a stoma has been made out of patient, or parental preference, or for continence management. The indication for stoma formation should be reported. A permanent stoma is defined as one which was created without the intention of later reversal. This outcome should first be reported at five years of age, or five years post-intervention,

as appropriate for the study design. It should then be reported at the appropriate study specific standard time-points.

IX.II.IV Long-term urinary incontinence

Long-term urinary incontinence was investigated in one study included in the NETS[1HD] systematic review(16).

The group discussed what volume/frequency of urinary incontinence was felt to be significant, and the age at which urinary incontinence was most likely to be pathological. It was also discussed whether it was important only to collect information on urinary incontinence that was associated with surgical complications, or also urinary incontinence that was occurring as a result of other facets of the Hirschsprung's Disease.

The group determined that the core outcome should be defined as:

Involuntary voiding of urine that is constant, associated with social problems, or requiring catheterisation. This outcome should be reported at five years of age at the earliest.

IX.II.V Long-term faecal incontinence

Faecal incontinence was investigated in 32 studies included in the NETS[1HD] systematic review.

The group discussed definitions created by other groups, including:

- "Involuntary leaking of small amounts of stool requiring a change of underwear/diaper"
- "Involuntary leaking of stool requiring change of nappy or underwear in patients over three years of age in whom constipation has been excluded by previous laxative treatment".
- The definition developed by the Paris Consensus on Childhood Constipation Terminology (PACCT) group – "Passage of stools in an inappropriate place in children with a mental age of four years or older, with no evidence of constipation based on history and/or examination".
- Martin's continence criteria – a combination of number of defecations, faecal consistency, anal inspection and digital rectal examination.
- Kelly score – a combination of continence, staining and sphincter contractility

The definition used by the PACCT group was felt to most closely represent the features of incontinence that were important to members of the group. However, importantly, the group felt that the definition should specify that the passage of stool was involuntary. The group also felt that it was impractical to assess mental age in all study participants, and instead felt that a chronological age cut off for assessment of faecal incontinence was more important. Work by Fichtner-Feigl et al (153) was discussed, which suggests that 95% of children will be continent of faeces by the age of 33 months. The group therefore decided that the first standard time-

point at which long-term faecal incontinence should be measured would be five years of age, and that this should be incorporated into the definition of the outcome.

The group also discussed the best way to assess severity of faecal incontinence, and decided that a modified version of the Krickenbeck criteria(208), which are already used in Hirschsprung's Disease and anorectal malformations, would be most appropriate.

The group determined that the core outcome should be defined as:

Involuntary passage of faecal matter in an inappropriate place by a child aged five or over. Severity of faecal incontinence should be graded as:

- Grade I – Occasionally (once or twice per week), with or without social problems
- Grade II – Every day, but without social problems
- Grade III – Constant, with social problems

IX.II.VI Long-term voluntary bowel movements without need for enemas, or rectal or colonic irrigation

There were no studies investigating this specific outcome included in the NETS1HD systematic review. However, there were 20 studies that investigated aspects of constipation, to which this outcome is closely associated (16, 17, 141, 146, 184, 187, 191, 197, 199, 204, 205, 209-216).

The group felt that the outcome as described was explicit enough to ensure robust investigation, and that it did not therefore need further elaboration.

The group determined that the core outcome should be defined as:

Long-term voluntary bowel movements without need for enemas, or rectal of colonic irrigation. This should be assessed at five years of age at the earliest.

IX.II.VII Hirschsprung's Associated Enterocolitis

HAE was investigated in 23 studies included in the NETS1HD systematic review.(16, 17, 156, 157, 184, 187, 193, 197, 199, 202-206, 209, 210, 212-215, 217, 218)

HAE is a clinical syndrome, without a definitive diagnostic test. Definition of the syndrome will vary from clinician to clinician, and diagnosis is notoriously unreliable. The group discussed some of the currently used definitions of HAE, including:

- Clinical presentation with diarrhoea, abdominal distension and fever
- Clinical syndrome of abdominal distension and explosive, foul smelling diarrhoea, with or without fever and elevated white blood cell count or C-reactive protein.
- Clinical syndrome consisting of diarrhoea, fever, colicky pan and passage of blood stained faeces
- The HAE Delphi score developed by Pastor et al(219).

The group decided that the Delphi score developed by Pastor et al was the most reproducible method of diagnosing HAE. However, they acknowledged that it may be unwieldy to use, and that one item – 'left shift of white cells on laboratory testing' was not always reported in hospitals in the British Isles. The group also discussed what would comprise a more pragmatic definition of HAE, and decided that the most robust way to standardise definition and severity was to use a definition that incorporated the need for inpatient treatment.

The group also discussed whether it was useful to know only whether an infant had ever had HAE, or if more information was needed on frequency and timing of episodes. Consensus was achieved amongst the group that it was important to know both whether an infant had ever had HAE, but also to know when and how often the episodes were occurring.

The group determined that the core outcome should be defined as:

A score of ten or more on the HAE Delphi score developed by Pastor et al.

Where it is not possible use the Hirschsprung's Associated Delphi score, for example, in hospitals where left shift of white cells is not reported, HAE should instead be defined as "Clinician decision to admit and instigate treatment for HAE".

HAE should be reported at the standard time-points appropriate for the study design used. Information should be reported on whether a participant has had any episodes

of HAE up to that time-point, but also whether they have had 0, 1, or 2 episodes of HAE in the previous 12 months, or up to the time-point of measurement, whichever is shorter.

IX.II.VIII Objective score of quality of life using appropriate age-specific measures

Quality of life was not measured in any studies included in the NETS[1HD] systematic review.

The group discussed how it was preferable to have a quality of life measure that had modules that were applicable to different age groups, that was quick and easy to complete, and that was free to use for most researchers.

Two main generic health related quality of life measures were discussed. These were the PedsQL(154), and the CHU9D(220). The PedsQL covers four areas of functioning in its core module – physical functioning, emotional functioning, social functioning, and school functioning. It also has additional disease specific modules, including for gastrointestinal symptoms, and modules looking at impact on the quality of life of the family. Other benefits to the PedsQL are that it is validated in a wide range of age groups, from two years of age upwards, and has been translated into multiple languages. The main drawback to the PedsQL is that it costs £1000 to use in funded research. It is free for use in non-funded research.

The CHU9D is shorter than the PedsQL, and only focuses on the previous 24 hours, as opposed to the previous month. It is free to use, and can also be used for assessing economic impact of interventions. The main drawbacks of the CHU9D are that it does not provide as much detail as the PedsQL, and that it can only be used in children from age 7 and up. It has also not been widely translated.

The Hirschsprung's Disease and anorectal malformations quality of life indicator was considered. It was felt that this may be an option for use in the future, but that at present it required further validation work, and more reliable translation into English prior to the group being able to recommend it. The group also discussed whether it was more appropriate to use a disease specific quality of life measure or a generic health related quality of life measure, and felt that disease specific factors would be covered in other outcomes, including bowel function score, and long-term faecal incontinence, and that the quality of life outcome should focus on more general aspects of health related quality of life.

The group felt that overall, the PedsQL provided the most appropriate measure for use in assessing health related quality of life in children with Hirschsprung's Disease. It was also felt that identifying an appropriate health related quality of life measure for use in adults was outside the scope of this exercise, and that further work would need to be done on this at a later date.

The group determined that the core outcome should be defined as:

Quality of life as measured by the age-appropriate PedsQL questionnaire.

IX.II.IX Objective score of bowel function

The group discussed how there are multiple bowel function scores in use, both within Hirschsprung's Disease research specifically, and more generally in other gastrointestinal disease research. The three most appropriate that were discussed were the Paediatric Incontinence and Constipation Score (PICS)(153), the Baylor Social Continence Score(221), and the Gastrointestinal Quality of Life Index (GIQLI)(222). The group discussed pros and cons to each.

The PICS consists of 13 questions, was developed through factor analysis in 76 normal children and 23 with anorectal functional disorders, and then validated in 122 normal infants and children. Scores are reported on two scales, possibly constipated, and possibly incontinent, with age specific scores and 95% confidence intervals for normal populations provided.

The Baylor Social Continence Score was developed in children with anorectal malformations, and covers a wide range of gastrointestinal and urinary signs and symptoms. It is longer, more complex, and more comprehensive than other scoring systems, but much of the information collected has been assessed throughout the Delphi process, and determined to be not important to participants. The benefit associated with the extra burden of reporting this additional information is therefore questionable. The Baylor score was developed on a group of 77 (34 with anorectal

malformations, 21 normal controls, and 22 children with enuresis. These children were between 5 and 20 years of age. No age normal values are produced.

The GIQLI consists of 36 questions covering a wide range of gastrointestinal symptoms, and their impact on quality of life. It has passed through a robust development and validation process, but is only appropriate for use in adults aged 18 or over. It has been used previously in multiple Hirschsprung's Disease studies.

After weighing up the pros and cons of each scoring system, the group felt that the ability to use the PICS to compare to age normal values was of great benefit in young children, whilst the breadth of the GIQLI, and its incorporation of the impact of gastrointestinal function on quality of life was of significant benefit in adults. The group therefore decided that these were the most appropriate bowel function scores to use.

The group determined that the core outcome should be defined as:

Objective score of bowel function, as measured by the PICS in children under 18 years of age, and the Gastrointestinal Quality of Life Index in adults over 18 years of age.

IX.II.X Long-term psychological stress for the individual with Hirschsprung's Disease

Psychological stress was measured in one study included in the NETS[1HD] systematic review(223).

The group discussed how psychological stress could be considered to mean either specific psychiatric conditions such as depression, or a more general assessment of the psychological impact of Hirschsprung's Disease on the person's life.

The group discussed how they felt that for children, the important aspects of psychological stress were measured by the questions asked in the PedsQL that related to feelings and interactions with others. The group considered whether the use of the strengths and difficulties questionnaire to specifically assess psychological stress in addition to the questions in the PedsQL would be of benefit, but determined that it did not cover any additional areas that were important to participants, but did add on significant reporting burden.

The group felt that the important aspects of psychological stress for adults with Hirschsprung's Disease were covered by questions in the Gastrointestinal Quality of Life Index relating to anxiety, nervousness, happiness, frustration, appearance, fatigue, personal life, sex life, and participation in leisure activities. It was felt that no additional tool was needed to measure psychological stress.

The group therefore determined that no specific instrument was required for measuring long-term psychological stress, and that this would instead be incorporate into the quality of life measure for children, and bowel function score for adults.

The group determined that the core outcome should be defined as:

Long-term psychological stress for the individual with Hirschsprung's Disease as measured by the PedsQL in children under 18, and the Gastrointestinal Quality of Life index in adults over the age of 18.

Appendix 10: NETS[1HD] study: *Development of a Hirschsprung's disease core outcome set (79)*

OPEN ACCESS

NETS[1HD] study: development of a Hirschsprung's disease core outcome set

Benjamin Saul Raywood Allin,[1] Timothy Bradnock,[2] Simon Kenny,[3] Jennifer J Kurinczuk,[1] Gregor Walker,[2] Marian Knight,[1] The NETS[1HD] Collaboration

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ABSTRACT

Objective The objective of this study was to develop a Hirschsprung's disease (HD) core outcome set (COS).

Methods Candidate outcomes were identified from a systematic review and stakeholder nomination. A three-phase Delphi process and consensus meeting were used to prioritise candidate outcomes based on scores assigned by stakeholder participants using a nine-point scale. In phases two and three, participants were shown graphical representations of their panel's scores and all panels' scores respectively for each outcome from the previous phase. After the third phase, outcomes prioritised by two or three panels were taken forward to the consensus meeting. The COS was formed from the 10 highest scoring outcomes meeting the threshold for inclusion (≥70% 7–9 and <15% 1–3).

Results Eighty-nine stakeholders (82%) completed all three phases of the Delphi process. Seventy-four outcomes were assessed in phase one of the Delphi process, the following 10 of which met criteria for inclusion in the COS: (1) death with cause specified, (2) long-term faecal incontinence, (3) long-term voluntary bowel movements without need for enemas, or rectal or colonic irrigation, (4) long-term psychological stress for the individual with Hirschsprung's disease, (5) long-term urinary incontinence, (6) objective score of quality of life, (7) objective score of bowel function, (8) unplanned reoperation, (9) >need for a permanent stoma, (10) enterocolitis.

Conclusions This HD COS is formed of 10 outcomes deemed important by key stakeholders. Use of this COS in research will reduce outcome reporting heterogeneity and increase our ability to identify gold standard treatments for HD.

What is known on this topic?

- Outcome reporting heterogeneity in published research is preventing identification of gold standard treatments for infants with Hirschsprung's disease.
- Developing and using core outcome sets in research reduces outcome reporting heterogeneity.

What this study adds?

- This study has identified 10 outcomes of importance to key stakeholders including people with Hirschsprung's disease, parents of children with Hirschsprung's disease and healthcare professionals managing children with Hirschsprung's disease.
- Use of this HD core outcome set will reduce outcome reporting heterogeneity, making it easier to identify gold standard treatments for children with Hirschsprung's disease.

BACKGROUND

Hirschsprung's disease (HD) affects 1.8 in 10 000 live-born children in the UK and Ireland and is caused by failure of complete development of the nerves of the enteric nervous system. Definitive treatment requires excision of the affected colon, with anastomosis of the remaining normal colon to the anus or rectum. Globally, there are differences in management strategies.[1] Operative strategies include open, laparoscopic and purely transanal approaches, and the Duhamel,[2] Swenson[3] and Soave[4] anastomotic techniques. Each strategy has potential advantages and disadvantages and at present it is not possible, either with primary data or through conduct of systematic reviews, to identify a gold standard approach.[5 6] The reasons for the lack of clarity are multifactorial. Specifically, most studies are small, single-centre, observational, of short duration and retrospective,[7] with significant heterogeneity of outcome reporting.[8]

Outcome reporting heterogeneity makes the evidence base difficult to interpret in three ways. First, it creates a risk that studies fail to address outcomes of relevance to patients, clinicians and commissioners of healthcare. Second, it suggests and increased risk of reporting bias within the published literature, and finally, it limits the conduct of meta-analyses.

Core outcome sets (COS) are groups of standardised outcomes that have been identified by key stakeholders as being the most important in determining success of an intervention or treatment of a particular condition.[9] Once a COS has been developed for a condition, the intention is that all future studies of that condition should report data for every outcome within the COS. Development and use of COS in this manner reduces outcome reporting heterogeneity,[10] making it easier to identify gold standard treatments. Journal editors, the National Institute for Health Research Health Technology Assessment Programme and the IDEAL collaboration have endorsed this approach (http://www.comet-initiative.org/about/COMETendorsement). The objective of this work was therefore to develop a COS that could be used in studies comparing interventions for infants with HD.

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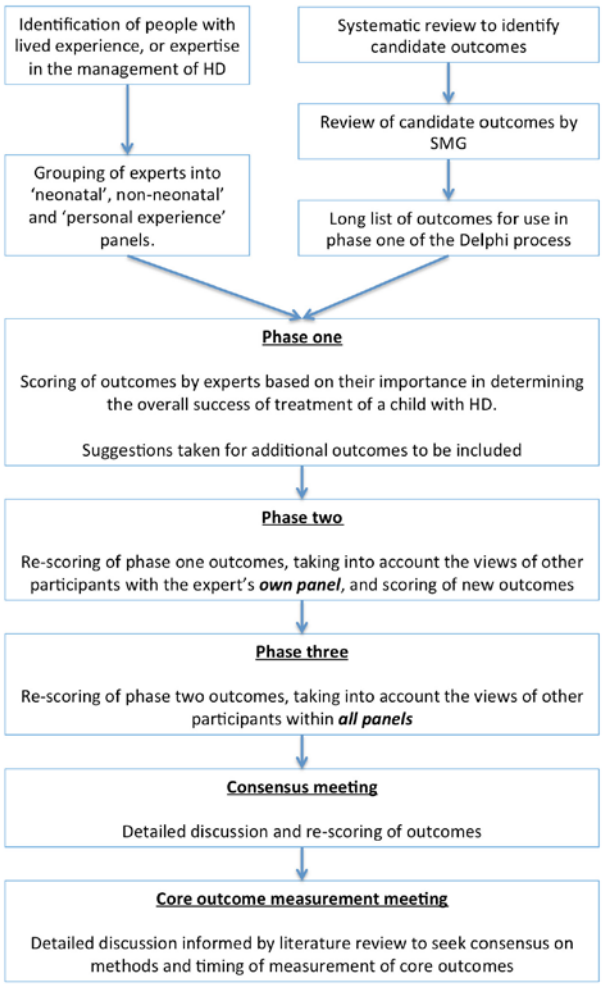

Figure 1 Study overview. HD, Hirschsprung's disease; SMG, study management group.

METHODS

The COS was developed according to a prospectively registered protocol,[11] using methodology recommended by the COMET initiative (figure 1).

Scope

The aim was to develop a COS for use in studies comparing interventions for the treatment of infants with HD in high-income countries. It may need adaptation for low-income and middle-income countries.

Participants

Participants were recruited from key stakeholder groups with either expertise in the management of infants with HD or lived experience of HD (table 1). UK and international participants were recruited.

An iterative process[12] was used to recruit participants across stakeholder groups, including among others, paediatric surgeons, gastroenterologists, people with HD and parents of children with HD. Members of all stakeholder groups had an equal role in the prioritisation of outcomes, so as to ensure that the final COS represented as best as possible, the views of those with expertise

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Table 1 Recruitment targets for key stakeholder groups

Stakeholder group	Panel	Recruitment targets
Paediatric surgeons	Neonatal panel	Surgeons registered with the British Association of Paediatric Surgeons (BAPS) as having an interest in HD surgery.
		Centre leads for the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS) nationwide HD cohort study.
		Members of the United Kingdom Paediatric Colorectal Club
		Editors of the *Journal of Paediatric Surgery* and *Paediatric Surgery International*
		Members of BAPS with a self-declared interest in the management of infants with HD
		Named experts from prominent HD treatment centres and research groups.
Neonatologists	Neonatal panel	Members of the British Association of Perinatal Medicine with a self-declared interest in the management of infants with HD
		Members of the Royal College of Paediatrics and Child Health with a self-declared interest in the management of infants with HD
Paediatric gastroenterologists	Non-neonatal panel	Members of the British Society of Paediatric Gastroenterology, Hepatology and Nutrition with a self-declared interest in the management of infants with HD
Specialist nurses	Non-neonatal panel	Members of the paediatric stoma nurses group
People with HD and parents of children with HD	Personal experience panel	Parents of children with HD who are members of the Parent Advisory Group established by the National Perinatal Epidemiology Unit
		Members of the Hirschsprung's and Motility Disorders Support Network
		Members of the CHAMPS appeal HD support group

Parents of children treated by members of the SMG and members of the BAPS-CASS Steering Committee.
HD, Hirschsprung's disease; SMG, study management group.

in managing children with HD and those with lived experience of HD. Members of the study management group (SMG) identified experts known to them, and then nominated groups from which additional experts could be recruited (table 1). Electronic media for each of the appropriate organisations were used to distribute adverts to their membership. Experts registering to participate in the study were asked to provide information relating to their experiences of HD and to nominate other potential participants. Registration details for all experts were reviewed by the SMG to ensure they had sufficient expertise to participate. Target recruitment was a minimum of 50 experts with two or more from each stakeholder group.

Participants were deemed to have withdrawn from the development process if they did not complete a phase of the Delphi process prior to the prespecified deadline, and were thus ineligible for participation in later phases or the consensus meeting. A representative sample of participants completing the Delphi process were invited to the subsequent consensus meeting and measurement meeting.

Information sources

Candidate outcomes were identified from a systematic review of surgical interventions for the primary, definitive treatment of infants with HD.[8] Additional outcomes of importance identified by the SMG but not identified in the systematic review were added to this list. At the end of phase one of the Delphi process, participants could suggest additional outcomes that were of importance to them, and if within the scope of the COS, these were added to phase two. Lay equivalent language for each outcome was developed in conjunction with parents without a medical or scientific background. Each outcome was assigned by the SMG to a core area of the OMERACT 2.0 filter (death, life impact, pathophysiological manifestation or resource use/economical impact) and identified as an adverse event if appropriate, using the guidelines described by Boers *et al*.[13]

Consensus process

A three-phase online Delphi process was conducted in parallel for the three panels and was followed by a face-to-face consensus meeting.

In phase one, participants were asked to score candidate outcomes based on their importance in deciding whether the overall treatment of a child's HD had worked well. Participants were provided with written instructions to score from 1 to 9 where 1, 2 and 3 were 'not that important', 4, 5 and 6 were 'important' and 7, 8 and 9 were 'really important'. In phase two, participants were shown graphical and numerical representations of their panel's median score and distribution of scores for each outcome from phase one and asked whether they would like to change their scores based on this information. In phase three, participants were shown graphical and numerical representations of all panels' median scores and distribution of scores for each outcome, and again asked if they would like to change their scores based on this information.

Outcome dropping and modification

Following phase two, outcomes where ≥50% of participants in any panel had scored them 1–3 and <50% of participants in all panels had scored them 7–9 were dropped. Following phase three, outcomes were deemed to meet the threshold for automatic discussion and rescoring at the consensus meeting if two or more panels deemed them to meet consensus for inclusion in the COS. Consensus for inclusion was defined as scores of ≥70% 7–9, and <15% 1–3. Other outcomes were only discussed and rescored if there was unanimous agreement among consensus meeting attendees that they warranted further review.

Consensus definition

Outcomes with scores of ≥70% 7–9 and <15% 1–3 following discussion at the consensus meeting were eligible for inclusion in the COS. However, to ensure practicality of use, it was prespecified that 10 or fewer outcomes would be included in the COS.

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If more than 10 outcomes were eligible for inclusion, then only the following 10 would be included:

- the highest scoring outcome meeting consensus for inclusion in each of the four OMERACT 2.0 filter core areas
- the highest scoring adverse event outcome meeting consensus for inclusion in the COS (if not already included as the highest scoring outcome in one of the four core areas)
- the next five highest scoring outcomes meeting consensus for inclusion in the COS, regardless of OMERACT 2.0 filter core area.

As the highest scoring adverse event outcome meeting consensus for inclusion in the COS was already included as one of the highest scoring outcomes from the core areas of the OMERACT 2.0 filter; the sixth highest scoring outcome (not already included) meeting consensus for inclusion in the COS was also included.

Highest scoring was defined as greatest percentage of participants allocating scores of 7–9. Where outcomes were tied based on this score, then the highest scoring outcome was the one with the greatest percentage of participants allocating a score of 9, then 8, then 7, continued through to 1 if necessary.

Outcome definition and measurement

A literature review was conducted to identify existing definitions and methods of measuring the outcomes included in the COS following the consensus meeting. This review informed discussion at a meeting attended by a representative sample of study participants, where outcome definition and measurement were identified by group consensus.

RESULTS

Changes from protocol

The following changes to protocol were made after registration but prior to data analysis.

No dropping of outcomes between phases of the Delphi process or between the Delphi process and the consensus meeting was originally planned. However, it was decided that outcomes should be dropped as described to allow participants to focus on discriminating between those outcomes most likely to form the COS.

No limit on the number of outcomes to be included in the COS was originally planned. However, in order to ensure practicality of use, it was determined that the COS would be limited to 10 outcomes.

Participants

One hundred and forty-five experts registered to participate in the study, 108 (74%) of whom completed phase one of the Delphi process. Ninety-six eligible participants (89%) completed phase two, and 89 eligible participants (93%) completed phase three. Seventeen participants were selected to attend the consensus meeting, and 14 attended the measurement definition meeting (tables 2 and 3).

Outcomes: initial phase one list

Seventy-four outcomes were identified by the systematic review, nine were added by the SMG, and nine were excluded as outside of the scope of the COS (online supplementary material 1).

Outcomes: addition, dropping and formation of the COS

Overall 140 individual comments were made by participants during phase one, 62 of which (44%) were made by 15 members (44%) of the neonatal panel, 73 (52%) by 35 members (57%) of the personal experience panel and 5 (4%) by 2 members (15%) of the non-neonatal panel. Based on these comments, the SMG clarified 19 outcomes (26%) and added 28 new outcomes for assessment in phase two. Six of these outcomes (21%) were proposed by the personal experience panel, 6 (21%) by other panels, and the remaining 16 (57%) by multiple panels. Overall, 102 outcomes were taken forward to phase two. Following completion of phase two, 13 outcomes (13%) were dropped, and following phase three, 44 outcomes (49%) did not meet criteria for automatic progression to the consensus meeting. Forty-five outcomes were taken to the consensus meeting, following which 15 outcomes met the criteria for inclusion in the COS, and 10 were retained (figure 2, tables 4 and 5 and online supplementary material S1). These 10 core outcomes are described in table 5.

Proposed timing and measurement of outcomes

Consensus from meeting attendees was that outcomes should be measured at standard surgical and paediatric time-points determined by study design. For studies where infants entered at the point of surgical intervention, these were defined as 30 days, 90 days, 1 year, 5 years, 10 years and every subsequent 10 years postintervention. For studies where infants entered at a set age, outcome measurement points were defined as 28 days of age, 1 year of age, 5 years of age, 10 years of age and every subsequent 10 years. It was agreed that six outcomes (table 5) should not be reported prior to 5 years of age, as early data on these outcomes are likely to be misleading.

DISCUSSION

This development process identified a COS consisting of 10 items for use in studies comparing interventions for the treatment of infants with HD. These outcomes represent factors important to stakeholders and span the breadth of the OMERACT filter 2.0. When used in appropriate studies, they will provide a rounded assessment of different interventions for HD. All studies comparing interventions for the treatment of children with HD should report data at the specified time-points for the outcomes within the COS.

Table 2 Summary of participants

	Number of participants					
	Registering for round one	Completing round one (% of those eligible)	Completing round two (% of those eligible)	Completing round three (% of those eligible)	Consensus meeting	Measurement meeting
Neonatal panel	41	34 (83)	33 (97)	31 (94)	9	7
Non-neonatal panel	15	13 (87)	12 (92)	12 (100)	2	3
Personal experience panel	89	61 (69)	51 (84)	46 (87)	6	4
Total	145	108 (74)	96 (89)	89 (93)	17	14

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Table 3 Characteristics of participants who completed the Delphi process and those who dropped out of the study

	Location* (n (%))		Age of child (years) (n (%))			Parent-reported severity of child's HD† (n (%))			Gender of participant (n (%))	
	UK	Other	≤5	6–10	11–15	≥16	Median on 1–9 scale (IQR)	Ultra-short segment	Short segment	Long segment	Male	Female
Parents of children with HD												
Completed Delphi process	29 (76)	9 (24)	19 (49)	13 (33)	1 (3)	6 (15)	7 (6–8)	1 (3)	22 (59)	14 (38)	1 (3)	38 (97)
Only completed phase one	12 (86)	2 (14)	6 (43)	5 (36)	1 (7)	2 (14)	Not collected until phase two				14	0
People with HD												
	Location (n (%))		Age (n (%))				Self-reported severity HD‡ (n (%))				Gender (n (%))	
	UK	Other	11–15years old		≥21years old		Median on 1–9 scale (IQR)	Ultra-short segment	Short segment	Long segment	Male	Female
Completed Delphi process	4 (57)	3 (43)	1 (14)		6 (86)		7 (5–8)	0 (0)	0 (0)	6 (100)	4 (57)	3 (43)
Only completed phase one	1 (100)	0 (0)	0 (0)		1 (100)		Not collected until phase two				0 (0)	1 (100)
Neonatal panel												
	Location (n (%))		Prior involvement in HD research (n (%))		Number of HD patients treated per year (n (%))		Stakeholder group (n (%))				Gender (n (%))	
	UK	Other	No	Yes	≤10	>10	Paediatric surgeons		Neonatologists		Male	Female
Completed Delphi process	29 (94)	2 (6)	11 (35)	20 (65)	21 (68)	10 (32)	27 (87)		4 (13)		23 (74)	8 (26)
Only completed phase one	2 (66)	1 (33)	0 (0)	3 (100)	0 (0)	3 (100)	3 (100)		0 (0)		3	0
Non-neonatal panel												
	Location (n (%))		Prior involvement in HD research (n (%))		Number of HD patients treated per year§ (n (%))		Stakeholder group (n (%))				Gender (n (%))	
	UK	Other	No	Yes	≤10	>10	Specialist nurses	Paediatric gastroenterologists		HD Researchers	Male	Female
Completed Delphi process	12 (100)	0 (0)	9 (75)	3 (25)	7 (58)	3 (42)	7 (58)	4 (33)		1 (8)	4 (33)	8 (66)
Only completed phase one	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)		0 (0)	1 (100)	0 (0)

*One person preferred not to say.
†One preferred not to say, one not applicable.
‡One person preferred not to score, and two did not know the length of affected bowel.
§One person did not know the length of affected bowel.
HD, Hirschsprung's disease.

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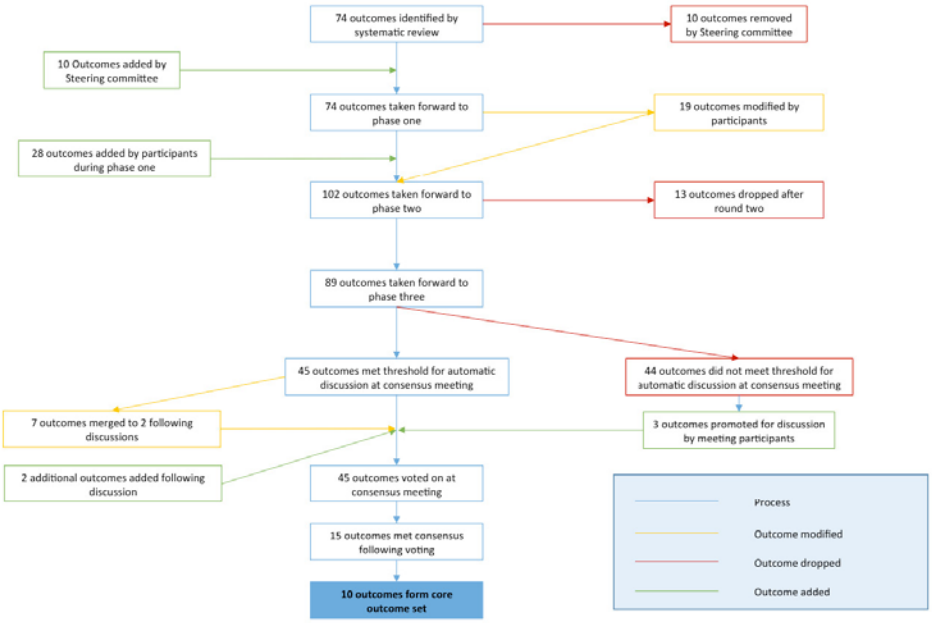

Figure 2 Outcome flow.

We believe this to be the first paediatric general surgical COS. However, paediatric COS have previously been developed, including for asthma and otitis media in children with cleft palate.[14 15] Some common themes emerge from all three, including the prevalence of factors relating to quality of life, which are likely to be common to many paediatric COS, but which are currently infrequently investigated.[8] The COIN study (http://www.comet-initiative.org/studies/details/842?result=true) will develop a COS for neonatology, and the NETS[10] study[16] is developing a COS for gastroschisis. Following completion of these, it will be important to compare and contrast the outcomes of importance in each so as to identify areas of overlap from which a unified neonatal surgical COS could potentially be developed.

This HD COS has been developed using robust methodology in accordance with recommendations from the COMET initiative. Participation rates were significantly above our target recruitment of 50 experts, with a good spread across stakeholder groups and good retention throughout the process. We therefore believe the COS to be representative of the views of the HD community as a whole. Increasingly however, there is a move towards undertaking qualitative work with key stakeholders in addition to a systematic review to inform the long-list of outcomes assessed during the Delphi process. This methodology is being promoted as there is a suspicion that outcomes identified through systematic reviews may be biased in favour of clinicians and researchers.[17]

Instead of using qualitative methods to inform the Delphi process, we opted to conduct the Delphi in an adaptive manner. All participants were asked to recommend additional outcomes of importance to them at the end of phase one and could suggest modifications to outcomes at all stages of the consensus process. The low number of additional outcomes proposed by the personal experience panel suggests that either they felt the initial list covered the majority of outcomes of importance to them or that they felt unable to propose additional outcomes. As over 50% of comments made in phase one were from members of the personal experience panel, and nearly 60% of the personal experience panel made at least one comment during phase one, we believe the former theory to be more likely. It is also reassuring that there was similarity in the number of outcomes suggested by each panel and that there was overlap in the domains from which additional outcomes were suggested by each panel.

There are three areas that may affect the representativeness of the COS. First, from the personal experience panel, there was a larger proportion of women taking part than men, meaning that the views of fathers, and men with HD, are potentially under-represented. Second, there was a slightly greater proportion of participants with long-segment and ultra-short segment HD within the study population than would be expected within the general population. This may skew the priorities of the personal experience panel more towards the extremes of the disease population. Third, the non-neonatal panel consisted of fewer participants than either the neonatal or personal experience panels. By giving equal weight to each panel as opposed to each individual participant throughout the Delphi process, individual participants within the non-neonatal panel will have had a proportionately greater influence on the scoring of outcomes throughout the Delphi process than participants in other panels. At the consensus meeting however, the meeting attendees were

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Table 4 Outcomes scored at the consensus meeting

Mortality outcomes	Resource utilisation outcomes	Life impact outcomes		Pathophysiological manifestation outcomes	Adverse event outcomes	
Death with cause specified*	**Whether home parenteral nutrition is required**	**Long-term faecal incontinence***	**Impotence**	**Aganglionic bowel remaining at the proximal resection margin**	**Intraoperative complication—life threatening (Clavien-Dindo grade four)**	**Postoperative bowel obstruction**
	Unplanned reoperation with indication specified*	Long-term voluntary bowel movements without need for enemas, or rectal or colonic irrigation*	Difficulty in conceiving a child	Hirschsprung's associated enterocolitis*	Postoperative complication—life threatening (Clavien-Dindo grade four)	Narrowing of anastomosis
	Unplanned readmission	Long-term urinary incontinence*	Attendance at school, or time spent missing lessons	Normal growth	Intraoperative visceral injury—life threatening (Clavien-Dindo grade four)	Fistula
	Associated healthcare costs	Long-term offensive odour secondary to lack of control of faeces or flatus, or inability to maintain hygiene	Long-term psychological stress-family*	Objective score of bowel function*	Anastomotic leak	Any intraoperative visceral injury
	Societal costs*	Requiring nappy or pad	Long-term bladder dysfunction		Colonic torsion	Cuff infection
		Sensation of need to defecate*	Painful defecation		Ischaemic bowel	Wound dehiscence
		Perianal excoriation with significant impact on daily life*	Difficulty with sexual relations or sexual intercourse because of the psychological or physical impact of HD or its treatment*		Faecal impaction	
		Peristomal excoriation with significant impact on daily life	Long-term difficulty in feeding			
		Need for a permanent stoma, with indication specified*	Social development			
		Need for a new stoma at any point after the pull-through procedure	Objective score of quality of life, using appropriate age specific measures*			
		Long-term psychological stress for the individual with Hirschsprung's disease*	Urgency of stool			

*Outcomes meeting consensus for inclusion in the COS.
COS, core outcome set.

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Table 5 The Hirschsprung's disease core outcome set

Core outcome	Core area	Definition	Score 7–9 (%)	Minimum age of measurement
Highest scoring outcomes in each OMERACT Filter 2.0 core area				
Death with cause specified	Death	Death, with cause classified as due to 1. A complication of treatment (excluding Hirschsprung-associated enterocolitis) 2. Hirschsprung-associated enterocolitis 3. An associated anomaly 4. Other.	100%	No minimum
Long-term faecal incontinence	Life impact	Involuntary passage of faecal matter in an inappropriate place by a child aged 5 years or over. Severity of faecal incontinence should be graded as:* 1. Occasionally (eg, once or twice per week), with or without social problems 2. Every day, but without social problems 3. Constant, with social problems.	100%	Five years of age
Objective score of bowel function	Pathophysiological manifestations	Objective score of bowel function, as measured by the Paediatric Incontinence and Constipation Score in children under 18 years of age, and the Gastrointestinal Quality of Life Index in adults over 18 years of age.	94%	No minimum
Unplanned reoperation, with indication specified	Resource use/economical impact and adverse event category	Unplanned reoperation with indication classified according to NICE criteria as minor, intermediate or major/complex. Unplanned is defined as any procedure not considered part of routine post-intervention practice. This outcome should include any procedure that is performed as a direct result of the diagnosis or treatment of the participants' HD, and any episodes of general anaesthesia that are required as a direct result of the diagnosis or treatment of the participant's HD, regardless of whether an operative intervention is undertaken (eg, an examination under anaesthesia, or manual evacuation).	89%	No minimum
Core outcome	**Definition**		**Score 7–9 (%)**	**Minimum age of measurement**
Outcomes included regardless of OMERACT core area				
Long-term voluntary bowel movements without need for enemas, or rectal of colonic irrigation	Long-term voluntary bowel movements without need for enemas, or rectal or colonic irrigation.		100%	Five years of age
Long-term psychological stress for the individual with HD	Long-term psychological stress for the individual with HD as measured by the PedsQL in children under 18 years of age, and the Gastrointestinal Quality of Life Index in adults over the 18 years of age.		100%	Five years of age
Long-term urinary incontinence	Involuntary voiding of urine that is constant, associated with social problems or requiring catheterisation.		94%	Five years of age
Objective score of quality of life using appropriate age-specific measures	Quality of life as measured by the age-appropriate PedsQL questionnaire.		94%	Five years of age
Need for a permanent stoma, with indication specified	Need for permanent stoma as a direct result of the diagnosis, or treatment of the participant's HD, including where the decision for a stoma has been made out of patient-, or parental preference, or for continence management. The indication for stoma formation should be reported. A permanent stoma is defined as one which was created without the intention of later reversal.		88%	Five years of age
Hirschsprung-associated enterocolitis	A score of 10 or more on the Hirschsprung-associated enterocolitis Delphi score developed by Pastor *et al*. Where it is not possible to use the Hirschsprung-associated Delphi score, for example, in hospitals where left shift of white cells is not reported, Hirschsprung-associated enterocolitis should instead be defined as 'Clinician decision to admit and instigate treatment for Hirschsprung's Associated Enterocolitis'. Information should be reported on whether a participant has had any episodes of Hirschsprung-associated enterocolitis up to a standard time-point, but also whether they have had 0, 1 or 2 episodes of Hirschsprung's associated enterocolitis in the previous 12 months, or up to the time-point of measurement, whichever is shorter.		88%	No minimum

*Based on a modification of the Kirchenbeck classification.[19]
†Long-term psychological stress for the individual with HD, and objective score of quality of life using appropriate age-specific measures were both identified as outcomes that should be included in the core outcome set. However, following an extensive review of the existing literature and discussion at the measurement meeting, consensus was reached that the most appropriate way to measure both outcomes would be with the PedsQL questionnaire. Therefore, both outcomes can be incorporated in the same measure in studies utilising this Hirschsprung's disease core outcome set.
HD, Hirschsprung's disease; PEDsQL, Pediatric Quality of Life Inventory.

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treated as one group, not individual panels. Within this setting, therefore, where there were less experts from the non-neonatal panel than from other panels, there is potential for the views of members of the non-neonatal panel to have been under-represented in the final COS.

This study has incorporated the views of key stakeholders to develop a COS for use in studies conducted in high-income countries comparing interventions for the treatment of infants with HD. It is important to promote the use of this COS in future large-scale observational and interventional studies but also in smaller, retrospective studies that still comprise the vast majority of paediatric surgical research.[7] Doing so will ensure studies are relevant to patients and their family, reduce the risk of reporting bias and, importantly, make meta-analysis possible. In the long run, this will improve the evidence base used to support clinical management of infants born with HD and should eventually allow translation through into improvements in patient care. It is now incumbent on funding bodies, journal editors and key decision makers in the field of paediatric surgical research to ensure that the COS is widely implemented and the benefits of its use realised.

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Contributors BSRA was responsible for design of the study, day-to-day management of the study, analysis of data and drafting of the manuscript. TB, SK, GW, JJK and MK were responsible for design of the study, management of the study and contributed to critical revisions of the manuscript. Members of NETS[1HD] contributed critically to the academic content of the study and have reviewed and critically revised the manuscript.

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Appendix 11: *Summary of discussions at the NETS[1G] measurement meeting*

XI.I **Timings**

Timings of measurement were discussed.

- It was noted that having universal time-points for all outcomes would ease reporting.
- It was discussed whether it was necessary to have two sets of time-points, those for cohort studies, and those following infants up after a specific intervention, or whether because the first intervention for most children born with gastroschisis will be at birth, the intervention time-points were redundant. It was noted that there will be very few planned secondary interventions to study in gastroschisis.
- It was discussed that there are standard time points for measuring outcomes in paediatric and surgical studies. These are:
    - 28 days of age, one year of age, five years of age, ten years of age
    - 30 days post intervention, one year post intervention, five years post intervention and ten years post-intervention
- It was discussed that many outcomes for infants with gastroschisis will occur in the period between one month and three to four months of age, and therefore, was it necessary to add an additional time-point of measurement at one of these ages. It was felt that adding multiple time-points would increase the burden of reporting too greatly.
- It was decided that all outcomes should be reported at the following time-points unless otherwise specified

Cohort studies	Intervention Studies
28 days of age	30 days post-intervention
One year of age	One year post-intervention
Five years of age	Five years post-intervention
Ten years of age	Ten years post-intervention
Every subsequent ten years	Every subsequent ten years

XI.II **Reporting**

- It was noted that a recommendation should be made in the study report that it was important to ensure adherence to reporting guidelines and standards when publishing studies using the NETS1G core outcome set. This included presentation of baseline data, accounting for missing data, and correct use of descriptive statistics.

XI.III **Death**

- It was noted that death is a rare outcome
- It was noted that from BAPS-CASS data, there appear to be few deaths between 28 days and one year of age, and therefore using the standard time-points of reporting as described would be appropriate.
- It was noted that it is hard to identify a single cause of death in infants with gastroschisis, and that many of the ultimate causes of death, e.g. sepsis, relate back to the fact that the infant has been born with gastroschisis.

- It was decided that classification of cause of death wasn't useful, and that the individual causes of death for each infant were necessary to assess interventions. It was felt that due to the rarity of the outcome that this wouldn't be overly burdensome.

The core outcome was defined as:

Death with cause specified

XI.IV **Number of operations**

- Long discussions were held around different classification systems that could be used.
- It was decided that the important operations to know about where those that were in relation to the abdomen, those in relation to central venous catheter insertion, and then others. It was also decided that it was important to know whether operations were performed under local anaesthetic of general anaesthetic.
- The table below was therefore devised for reporting the number of operations:

	General anaesthetic	**Local anaesthetic**
T**otal**		
Abdominal Operation		
Central Venous Catheter *insertion*		
Other (any)		

- It was stated the following specific reporting conditions should be noted:
    - Abdominal operation includes ***all*** episodes of silo placement, replacement, and re-application, and abdominal closure should be counted as a separate operation to silo placement. Silo 'tucks' should not be counted.
- It was discussed whether a time-point was needed between the 28/30 day time-point and the one year time-point, but was determined that sufficient detail would be collected with the existing time-points. It was determined that the outcomes should be reported at the standard time-points as appropriate for the study.

The core outcome was therefore defined as:

Total number of operations the infant has undergone, reported at standard time-points. Operations should be categorised as below, and each episode of silo placement, replacement, and re-application should be reported as a separate abdominal operation, with abdominal closure reported separately to silo placement.

XI.V **Quality of life for the child**

- It was discussed that there were many different tools for measuring quality of life, and that it was not possible to say that one was better than the others. However, it was felt that for the core outcome set to achieve its purpose, it was important for the group to recommend use of one tool, as otherwise, it would still not be possible to meta-analyse data from different studies.

- The group therefore wanted to make it clear that the tool chosen was a recommendation.
- Discussions were held amongst the group as to what the tool should measure, and this was felt to need to cover some of the areas that would be measured by assessment of neurodevelopmental outcomes, including school performance. It was also felt that it was important to collect information on GI specific quality of life, and to be able to measure the impact on the family's quality of life (as this was what was primarily affected in the initial post-operative period).
- It was felt that use of the PedsQL questionnaire would represent the best opportunity to meet the above requirements. This was due to the fact that is has validated questionnaires for use in children as young as two years of age, but also has an abdominal disease add on module, and an impact on the family module.
- It was noted that it is expensive to use the PedsQL in funded studies, but that the benefits warranted this cost.
- It was also noted that the PedsQl appears to be the most commonly used paediatric QoL tool.

The core outcome was therefore defined as:

Quality of life for the child assessed using the age appropriate PedsQL questionnaire, the PedsQL Gastrointestinal symptoms module, and if appropriate, the PedsQL family impact module.

XI.VI Time on Parenteral Nutrition

- It was noted that the outcome that should be being discussed was time on parenteral nutrition, not time on total parenteral nutrition, as described in the pre-meeting documentation. Scores from the consensus meeting were reviewed, and this was confirmed.
- It was re-affirmed that for parents, the need to use any PN is important, due to the health implications, and the implications on lifestyle as a result of having to hang bags of TPN, maintain sterility etc.
- It was discussed further how a child can go backwards and forwards in receiving PN, but that the total number of days a child is receiving PN is recorded in Badgernet.
- It was discussed how in the initial post-operative period it is the number of days that an infant received PN that matter, but that over the longer-term, it is just whether they are requiring any PN that matters. Collecting data on number of days of use, but also number requiring PN at later time-points would allow adequate counselling of parents using figures that are important to them i.e. initial time on PN, and likelihood of needing longer term PN.
- It was discussed that if a child required PN at one year, they are likely to still be requiring it at five years, and therefore there is little need to add an additional time-point for outcome reporting between these two.
- It was also discussed that in the longer term, it was most important for parents to know the likelihood of their child requiring PN at specific ages, as opposed to specific time-points post an intervention.

The core outcome was therefore defined as:

Time on parenteral nutrition

- At time-points up to one year of age, this should be reported as total number of days that the infant has received ANY parenteral nutrition
- After one year of age, it should be reported as the total number (and percentage) of infants that are receiving ANY parenteral nutrition at each of the appropriate time-points.
- This outcome should only be reported using the age time-points, not the intervention study time-points, as these were felt to be more meaningful.

XI.VII Liver Disease

- The point at which it becomes important to detect liver disease was discussed, focussing around whether it was only important if it impacted treatment.
- It was discussed that there are multiple things in the treatment of a child with gastroschisis that can result in liver dysfunction, including use of an UVC, surgery, sepsis and parenteral nutrition.
- It was noted that liver disease is normally detected through identification of abnormal liver function tests, not through clinical signs and symptoms.
- It was noted that the previously specified three levels of IFALD can be used more broadly for classifying all liver disease, and that type I normally gets better whereas type II is normally progressive, with type III representing end

stage liver disease. It was recognised that interventions should occur at all three stages.

- It was decided that a more simple definition of liver disease should be used as opposed to the BSPGHAN IFALD definition, and that for most clinicians, the important measure was disruption to bilirubin.
- It was discussed that it was important however to only report meaningful changes in bilirubin, as opposed to transient, or minor disruption.
- It was noted that the outcome should be used as a measure of liver disease, not IFALD, or liver failure, or need for transplant etc.

The core outcome was therefore defined as:

Persistent conjugated hyperbilirubinaemia (>50 μmol/L) for ≥ two weeks, with no known other underlying liver disease

XI.VIII **Growth**

- It was discussed whether it was important to know if growth was occurring, or what growth was like in relation to a normal population.
- Growth was reported as a significant concern to parents
- It was discussed that if a measure of adequate nutrition is desired, then it is vital to measure length and head circumference as well as weight.
- It was discussed which measures of growth should be used, and it was felt that z-scores were the most appropriate, as they allow:
    - Groups within the study to be compared to one another
    - Infants in the study to be compared to a reference population
    - Easy meta-analysis to be performed
- It was discussed that it is important to select the correct reference population for calculating z-scores and that this should be the UK-WHO population published in 2006.
- Use of an 'Optimal' population as the reference will allow studies to identify where children with gastroschisis are different to optimally nourished infants, not to other infants with gastroschisis. However, the use of means and SD as summary measures for z-scores will also allow comparison of infants within the studied population.
- It was noted that software can be downloaded for free to calculate z-scores from height, weight, length and age.

The core outcome was therefore defined as:

Growth, reported as:

- Mean (SD) z-score for weight, head circumference and length in each study group up to one year of age.
- Mean (SD) z-score for weight and height in each study group from age five onwards.

XI.IX **Sepsis**

- Long discussions were held around sepsis definitions, and the group acknowledged that it was not going to be possible to identify a perfect definition for neonatal and paediatric sepsis. They have instead attempted to achieve a compromise that best captures what is felt important within the outcome, but also what is important in existing definitions of sepsis.
- The group also acknowledged that work had been on going to create new definitions for paediatric sepsis, but that these had been postponed at present. If this work restarts, it should be used to inform a review of the definition used in the core outcome set.
- The existing definition of sepsis as SIRS plus a presumed or confirmed infective source was not felt to be helpful by the group, as the definitions used for SIRS were not thought to be reliable in infants with the abnormal physiology that is associated with gastroschisis.
- It was also discussed how there are many infants that neonatologists in particular would define as having sepsis who would not meet the SIRS criteria.

- It was felt that the SIRS definition may be useful later in life, but certainly not in the neonatal period. The group expressed a desire to find a unified definition that worked for all age groups.
- It was also discussed how the European Medicines Agency had summarised the various measures that are currently used for identifying sepsis, but there was not a workable definition proposed.
- It was proposed that parents are less interested in whether an infection is confirmed or suspected, than they are in whether something happens to their child i.e. given antibiotics, or feeding withheld. However, for the purposes of comparing treatments, it is also important to have information on a reliable marker of clinical importance.
- Long discussions were held around the importance of finding a reliable/confirmed group of infants with sepsis. It was felt that the best way to do this was using positive blood or CSF cultures, acknowledging that this would miss a reasonable proportion of infants who were septic, but who did not have positive cultures.
- The group therefore felt that it was important to also seek reporting of infants who had a suspicion of sepsis, but in whom it was not confirmed, i.e. those who did not have a positive culture.
- It was discussed how it was important to capture the systemic impact of sepsis in the definition, as it was specifically sepsis, and not just bacteraemia or an infection that was deemed important at the consensus meeting.
- It was discussed how it was important to not capture infants where sepsis was recorded as a list of differentials, but quickly ruled out, or thought to be

unlikely. It was decided therefore to include a measure of treatment given in the definition, but to leave the definition of 'treatment' to the individual researcher, as 'a course of treatment' was likely to vary dependent on condition, and the group could not agree on a unifying definition.

- It was discussed how sepsis should be reported as an outcome even in older children, as they are at risk of line infections etc.
- Discussed whether this should be a binary yes/no outcome, or if it was important to collect information on the number of episodes of sepsis that had occurred. It was decided that it was the total number of episodes per infant that was important.

The core outcome was therefore defined as:

The number of times treatment was given for proven or presumed sepsis prior to the time-point of measurement.

- The number of episodes where sepsis was proven by a positive blood or CSF culture should be reported separately from the number of episodes where treatment was given for sepsis, but the blood or CSF culture was negative.
- This outcome should be reported as the median (IQR and range) number of episodes of proven or presumed sepsis per infant in each treatment group as appropriate for the study. It should not be categorised.
- The outcome should be reported at the standard time-points.

XI.X Severe gastrointestinal complication including abdominal compartment syndrome, intestinal obstruction, intestinal resection, intestinal perforation and necrotising enterocolitis

- It was discussed that this outcome was looking for ***complications*** and therefore all definitions within it are only applicable at time-points after the initial surgical intervention for the treatment of the infant's gastroschisis.
- It was discussed that all resections should be included in the outcome, regardless of cause, as it was impossible to reliably separate those required as a result of a congenital atresia from those required as a result of ischaemia, stricture etc.
- Resection was therefore defined as:
    - Removal of any amount of bowel regardless of the cause.
- Perforation was defined as
    - Identification of a hole in the bowel wall
- Abdominal compartment syndrome was discussed at length.
- Discussions included the fact that is was hard to accurately measure intra-abdominal pressure in children and neonates, and that in any case it was very rarely done clinically. It was also not possible to put a threshold on the pressure that correlated to ACS, and clinicians reported that their management of a child would not be most strongly guided by an IAP reading, although this could be used as an adjunct where there was clinical doubt as to a diagnosis of ACS.

- It was discussed how ACS needed in its definition a measure of either IAP, or whether an intervention was conducted to relieve raised pressure.
- It was noted that there will be some children with ACS who should have undergone a surgical intervention who didn't, because ACS was not identified, and therefore will not necessarily be captured by a definition incorporating delivery of a surgical intervention.
- Existing clinical definitions for ACS have been created which list clinical signs suggesting raised IAP as oliguria, anuria, respiratory de-compensation, hypotension, shock and metabolic acidosis.
- ACS was defined as:
    - Suspected raised intra-abdominal pressure with at least two of oliguria or anuria, respiratory de-compensation, hypotension /shock, or metabolic acidosis.
- It was discussed how obstruction can be functional or mechanical, but that functional is usually due to gut dysmotility, and is not therefore likely to represent a complication of treatment.
- Obstruction was therefore defined as:
    - Mechanical intestinal obstruction resulting in a repeat laparotomy
    - Gut dysmotility should not be included in this outcome even if it results in another laparotomy. The need for another operation will be captured in number of operations.
- It was discussed how NEC is likely to represent end organ dysfunction as opposed to one specific diagnosis.

- It was discussed how lots of infants with gastroschisis develop query NEC, but very few have it confirmed.
- It was discussed how NEC in infants with gastroschisis is different from that in pre-term neonates, and should therefore probably more correctly be termed enterocolitis rather than NEC.
- It was discussed at this point whether all of the complications we were defining were those where a repeat operation was required, and therefore whether this outcome was a subset of the number of operations outcome. However, it was felt that it was important to collect details on infants with enterocolitis even if they didn't undergo an operation, as the vast majority will be managed with antibiotics and feeding cessation, and therefore this outcome needed to be separate from number of operations.
- It was discussed how there are multiple definitions for NEC, but that none work particularly well and many will capture other conditions
- The Vermont-Oxford definition, as used by BAPS-CASS was settled on after long discussions of the pros and cons of each.
- Enterocolitis was therefore defined as:
    - Suspected enterocolitis with at least one of:
        - Bilious aspirates or emesis
        - Abdominal distension
        - Occult or gross blood in stool (no fissure)
    - And at least one of:
        - Pneumatosis intestinalis
        - Hepatobiliary gas

        - Pneumoperitoneum
- It should be noted that Battersby et al have recently also published a gestational age specific scoring system for diagnosing NEC which once established could be refined for use in this COS.

The core outcome was therefore defined as

Total number of severe gastrointestinal complications occurring after the initial surgical intervention, and prior to the point of measurement. Severe gastrointestinal complication should include the following:

- Any intestinal resection, regardless of amount of bowel removed of the indication for the resection
- Intestinal perforation
- Mechanical intestinal obstruction resulting in a repeat laparotomy
- Abdominal compartment syndrome, defined as 'suspected raised intra-abdominal pressure with at least two of oliguria or anuria, respiratory de-compensation, hypotension/shock, or metabolic acidosis, that leads to intervention.
- Enterocolitis, defined as:
    - Suspected enterocolitis with at least one of:
        - Bilious aspirates or emesis
        - Abdominal distension
        - Occult or gross blood in stool (no fissure)
    - And at least one of:

    - Pneumatosis intestinalis
    - Hepatobiliary gas
    - Pneumoperitoneum
- This outcome should be reported at the standard time-points appropriate for the study design.

Appendix 12: *Development of a gastroschisis core outcome set (80)*

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Development of a gastroschisis core outcome set

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ABSTRACT

Objective Outcome reporting heterogeneity impedes identification of gold standard treatments for children born with gastroschisis. Use of core outcome sets (COSs) in research reduces outcome reporting heterogeneity and ensures that studies are relevant to patients. The aim of this study was to develop a gastroschisis COS.

Design and setting Systematic reviews and stakeholder nomination were used to identify candidate outcomes that were subsequently prioritised by key stakeholders in a three-phase online Delphi process and face-to-face consensus meeting using a 9-point Likert scale. In phases two and three of the Delphi process, participants were shown graphical and numerical representations of their own, and all panels scores for each outcome respectively and asked to review their previous score in light of this information. Outcomes were carried forward to the consensus meeting if prioritised by two or three stakeholder panels in the third phase of the Delphi process. The COS was formed from outcomes where ≥70% of consensus meeting participants scored the outcome 7–9 and <15% of participants scored it 1–3.

Results 71 participants (84%) completed all phases of the Delphi process, during which 87 outcomes were assessed. Eight outcomes, mortality, sepsis, growth, number of operations, severe gastrointestinal complication, time on parenteral nutrition, liver disease and quality of life for the child, met criteria for inclusion in the COS.

Conclusions Eight outcomes have been included in the gastroschisis COS as a result of their importance to key stakeholders. Implementing use of the COS will increase the potential for identification of gold standard treatments for the management of children born with gastroschisis.

What is already known on this topic?

- It is not currently possible to identify gold standard treatments for children with gastroschisis, partly because of outcome reporting heterogeneity.
- Many gastroschisis studies investigate outcomes that are not relevant to patients or clinical practice.
- The use of core outcome sets in research reduces outcome reporting heterogeneity and helps improve the clinical relevance of research.

What this study adds?

- This study has developed a gastroschisis core outcome set consisting of eight outcomes that are important to parents, people born with gastroschisis and clinicians.
- The eight outcomes are death, sepsis, growth, number of operations, time on parenteral nutrition, liver disease, number of severe gastrointestinal complications and quality of life.
- The core outcome set can be used in future observational and interventional studies and will reduce outcome reporting heterogeneity and increase clinical relevance of studies.

INTRODUCTION

Gastroschisis is increasing in incidence and is estimated to affect between 3.6 and 4.4 per 10 000 live births in the UK.[1 2] As with many neonatal surgical conditions, there are a number of treatment options in everyday use, and for gastroschisis, the two most common are operative primary fascial closure and silo placement, followed by staged reduction and delayed closure. Strategies for immediate postoperative management, introduction of enteral feeding and parenteral nutritional support also vary widely. There is therefore robust debate among the paediatric surgical and neonatal communities as to which intervention or combination of interventions produces the best outcomes, and due to limitations with the primary evidence base, it is not currently possible for systematic reviews to reliably inform this debate. Limitations of the primary evidence base include the small sample size and retrospective nature of many of the studies and the existence of significant outcome reporting heterogeneity.[3 4] Outcome reporting heterogeneity suggests there is a lack of consensus among researchers as to which outcomes should be used to define success of treatment in a particular condition and indicates that studies are at risk of lacking relevance to patients, of being affected by reporting bias and being difficult to meta-analyse.

A core outcome set (COS) is a group of outcomes that have been identified by key stakeholders as being the most important in determining success of treatment of a particular condition. Once a COS has been developed for a particular condition, all future studies conducted within the scope of the COS should investigate and report as a minimum all outcomes included within the COS.[5] Additional outcomes can also be investigated and reported if appropriate for the study, but the reporting at a minimum of all core outcomes ensures that a study will be relevant to patients and clinical practice, at a low risk of reporting bias and meta-analysable with other studies investigating the same clinical question.[5] The aim of this study was therefore to

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develop a COS that could be used in studies comparing the overall success of postnatal treatments for children born with gastroschisis.

METHODS

Protocol registration

The protocol was prospectively registered in October 2014 on the Core Outcome Measures in Effectiveness Trials (COMET) initiative website (http://www.comet-initiative.org/studies/searchresults?guid=d1e190c8-a2eb-4d49-a341-7d3ec79be12c) and published in a peer-reviewed journal.[6]

Scope

The COS is intended for use in studies comparing postnatal interventions for the treatment of children born with gastroschisis in high-income countries. It is likely that outcomes of importance in low-income and middle-income countries will be different to those that are important in high-income settings, and therefore, the relevance of the COS to studies conducted in these settings should be considered prior to it being used. The COS is also not intended to be applicable to studies investigating antenatal interventions or factors related to the mode or timing of delivery of babies with a prenatal diagnosis of gastroschisis.

Process

Three panels of stakeholders completed a three-phase online Delphi process in order to prioritise outcomes identified from a systematic review and stakeholder nomination. Prioritised outcomes were discussed and rescored at a face-to-face consensus meeting, and those that met a prespecified threshold were included in the final COS. A separate face-to-face meeting was held to identify measurement definitions for each outcome included in the COS (figure 1).

Participants

So as to represent the full spectrum of clinical and personal experience of gastroschisis, participants were recruited across

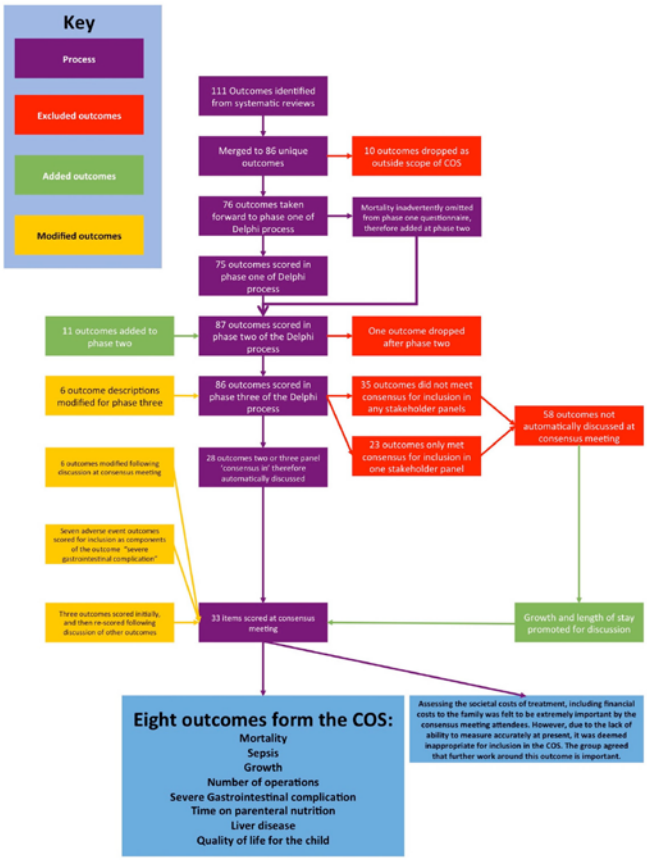

Figure 1 Summary of the gastroschisis core outcome set (COS) development process.

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Table 1 Stakeholder recruitment strategies

Stakeholder group	Panel	Recruitment methods
People born with gastroschisis	Personal experience panel	Mailing lists, websites and Facebook groups of UK and international gastroschisis support groups.
Parents of children born with gastroschisis		Mailing lists and meetings for a Parental Advisory Group established by the National Perinatal Epidemiology Unit.
Paediatric surgeons	Neonatal panel	Direct approaches to experts known to members of the SMG and those identified on a search of the British Association of Paediatric Surgeons (BAPS) register as having a special interest in management of children with gastroschisis. BAPS mailing lists, newsletters and website. Direct approach to clinical leads at each paediatric surgical centre in the UK for the BAPS-CASS gastroschisis study.
Neonatologists	Neonatal panel	Direct approach to experts known to members of the SMG. Mailing lists, bulletin and website of the British Association of Perinatal Medicine.
Fetal medicine specialists	Neonatal panel	Direct approach to experts known to members of the SMG. Mailing list of the fetal medicine clinical study group of the British Maternal and Fetal Medicine Society.
Specialist nurses	Neonatal panel	Direct approaches to experts known to members of the SMG. Mailing list of the Neonatal Nurses Association and the National Neonatal Surgical Benchmarking Group.
Paediatricians	Non-neonatal panel	Direct approach to experts known to members of the SMG. Mailing list of the British Society of Paediatric Gastroenterology Hepatology and Nutrition.
Researchers	Non-neonatal panel	Direct approaches to experts known to members of the SMG and prominent gastroschisis researchers identified through searches of the literature.
Specialist paediatric surgical nurses	Neonatal panel	Direct approach to experts known to members of the SMG.
Dietitians	Non-neonatal panel	Direct approach to experts known to members of the SMG. Mailing list of the British Society of Paediatric Gastroenterology Hepatology and Nutrition.

BAPS-CASS, British Association of Paediatric Surgeons Congenital Anomalies Surveillance System; SMG, Study Management Group.

a range of clinical specialties involved in the treatment of children born with gastroschisis and also from families where one or more people had been born with gastroschisis. Experts were recruited according to the strategies described in table 1 with those selected to participate asked to nominate additional potentially eligible stakeholders. Clinical stakeholders were recruited only from the UK in order to ensure funding could be used to maximise the number of participants attending the consensus meeting while also maintaining the meeting attendee's representativeness of the wider study participants. Prior to inclusion in the study, experts were asked to register their interest via a customised website, where details were collected documenting their experience of gastroschisis. Registrations were reviewed by the Study Management Group (SMG) to ensure that participants had sufficient expertise in gastroschisis management or lived experience of gastroschisis to participate in the study.

Data presentation throughout the Delphi process was simplified by combining stakeholder groups into a neonatal panel, a non-neonatal panel and a personal experience panel as described in table 1, within which, opinions were anticipated to be broadly similar.

Information sources

Two systematic reviews, each with a prospectively registered protocol, were conducted by separate groups who had each set out to develop a COS for use in determining the overall success of treatment for a child born with gastroschisis. The first of these reviews was a broad, scoping review, including all comparative study designs,[7] while the second focused solely on randomised controlled trials and systematic reviews.[8] Outcomes identified from the systematic reviews were assessed by the SMG and mapped to unique terms. Outcomes assessing the success of antenatal interventions were dropped as they were outside of the scope of the COS.

In phase one of the Delphi process, stakeholders were asked to propose additional outcomes that they felt were important but had not been identified by the systematic reviews. These outcomes were reviewed by the SMG, and if within the scope of the COS, were taken forward for assessment in phase two of the Delphi process. See online supplementary material 1 for list of all outcomes considered at any stage.

Dropping and modification of outcomes

No outcomes were dropped between phase one and phase two of the Delphi process. Between phase two and phase three, outcomes were dropped if ≥50% of participants in all panels scored them 1–3 and <50% of participants in any panel scored them 7–9. Outcomes were automatically discussed at the consensus meeting if in phase three of the Delphi process two or more panels deemed them to meet the threshold for inclusion in the COS. As per guidance from the COMET initiative, the threshold for inclusion in the COS was defined as ≥70% of participants scoring an outcome of 7–9, and <15% scoring 1–3.[9] Other outcomes were only discussed and rescored at the consensus meeting if there was unanimous agreement among the meeting attendees that they warranted further discussion.

Comments were sought from participants in relation to clarity of outcome descriptions throughout each phase of the Delphi process. All comments were reviewed by the SMG, and if necessary, outcome descriptions/terminology were modified to improve their clarity and understanding.

Consensus definition

Outcomes were deemed to have met consensus for inclusion in the COS if ≥70% of participants at the consensus meeting scored them 7–9 and <15% scored them 1–3.

Assessment of attrition bias

Median phase one scores for the outcomes included in the COS (or their nearest approximation where the outcome was added after phase one) were compared between participants within each panel who completed all three phases of the Delphi process and those who only completed phase one. Wilcoxon rank-sum test was used to compare scores, and in order to reduce the risk

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of a type I error, the Bonferroni correction was used to set the level of significance at a P value of <0.002.

RESULTS

Protocol modifications

It was initially proposed that people born with gastroschisis and parents of children born with gastroschisis should only be recruited from the UK. However, despite extensive work with gastroschisis charities, it proved difficult to recruit to these stakeholder groups when participation was limited to the UK. It was therefore decided by the SMG that it was more important to ensure a strong voice of personal experience throughout the study than it was to ensure that it was feasible for all participants to have the opportunity to attend the consensus meeting, and recruitment was therefore expanded to include people with personal experience of gastroschisis who were treated in other high-income countries. Participants in other stakeholder groups were still restricted to those based in the UK.

It was initially proposed that no outcomes would be dropped between phases of the Delphi process. However, after publication of the protocol, but prior to phase one of the Delphi process, it was decided by the SMG that in order to allow participants to focus on outcomes likely to be of greater importance, they should instead be retained as described in the *dropping and modification of outcomes section*.

Participants

One hundred and sixty-four people registered to participate in the Delphi process, 102 (62%) of whom completed phase one. Eighty-five (83%) of 102 eligible participants then completed phase two, and 71 (84%) of 85 eligible participants completed phase three (table 2).

Of the 71 participants that completed all three phases of the Delphi process, 19 (27%) were paediatric surgeons, 13 (18%) were neonatologists, 11 (16%) were specialist nurses, 2 (3%) were paediatric gastroenterologists, 2 (3%) were paediatric dieticians and 22 (31%) were parents of children born with gastroschisis. Fourteen (64%) of the parents who completed all three phases of the Delphi process had children born with gastroschisis who were less than 5 years of age at the time of the study, four (18%) had children between 5 and 10 years of age, two (1%) had children over 10 years of age and two (1%) preferred not to say how old their child was.

Outcomes

Following review by the SMG and removal of outcomes outside the scope of the COS, 75 outcomes were carried forward from the systematic reviews to phase one of the Delphi process. Twelve additional outcomes were proposed during phase one, leading to assessment of 87 outcomes in phase two, 86 (99%) of which were carried forward to phase three (online supplementary material 1). Following scoring in phase three, 28 outcomes (33%) met the criteria for automatic discussion at the consensus meeting, with two additional outcomes discussed following unanimous agreement by the meeting attendees that they warranted further review (table 3). Eight outcomes (box 1 and table 4) met the criteria for inclusion in the COS, with the additional outcome *societal cost (including financial cost to the family)* noted as important by the meeting attendees but not included within the COS due to the lack of ability to accurately measure such an outcome at present.

Table 2 Study participants

	Number of participants					
	Registering for round one	Completing round one (% of those eligible)	Completing round two (% of those eligible)	Completing round three (% of those eligible)	Consensus meeting	Measurement meeting
Neonatal panel	58	52 (90)	47 (90)	43 (91)	15	10
Non-neonatal panel	8	8 (100)	7 (88)	6 (86)	4	3
Personal experience panel	98	42 (43)	31 (74)	22 (71)	5	1
Total	164	102 (62)	85 (83)	71 (84)	24	14

Table 3 Outcomes discussed at the consensus meeting, categorised into OMERACT filter 2.0 core areas

Mortality outcomes	Life impact outcomes	Pathophysiological manifestation outcomes	Resource utilisation outcomes	Adverse event outcomes
Mortality	Home parenteral nutrition	Quality of life for the child	Short bowel syndrome	Abdominal compartment syndrome†
	Need for total parenteral nutrition postdischarge	Bowel lengthening procedure required	Cholestasis	Bowel ischaemia
	Reoperation	Time on total parenteral nutrition	Unspecified measures of growth*	Bowel obstruction†
	Societal costs, including financial costs for the family	Time on parenteral nutrition		Bowel resection†
	Rehospitalisation	Liver transplant		Intestinal perforation†
	Length of stay*	Small bowel transplantation		Necrotising enterocolitis†
		Need for a permanent stoma		Infection with systemic sequelae
		Chronic GI symptoms		Anastomotic stricture
		Gastrointestinal dysfunction		Gastrointestinal complication†
		Neurodevelopmental outcomes		Intestinal failure associated liver disease

*Outcomes not meeting criteria for automatic discussion at the consensus meeting and only promoted after unanimous agreement by the meeting attendees.
†Outcomes combined to the composite outcome severe gastrointestinal complication.
GI, gastrointestinal.

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Box 1 The gastroschisis core outcome set

Death
- Number (%) of infants who have died.

Sepsis
- Median (IQR and range) number of times treatment was given for proven or presumed sepsis.
- Number of episodes where sepsis was proven by a positive blood or CSF culture should be reported separately from the number of episodes where treatment was given for sepsis, but the blood or CSF culture was negative.

Growth
- Median (IQR and range) z-score for weight, length and head circumference in studies reporting outcomes at or prior to 1 year of age.
- Median (IQR and range) z-score for weight and height in studies reporting outcomes after 1 year of age.

Number of operations
- Median (IQR and range) number of operations per infant.
- The type of operations undertaken should be categorised according to whether they were performed under general or local anaesthetic and whether they were an abdominal operation, central venous catheter insertion or 'other' operation. 'Other' operations should only be reported when performed under general, not local, anaesthetic.
- Each episode of silo placement, replacement and reapplication should be reported as a separate abdominal operation, with abdominal closure reported separately to silo placement.

Severe gastrointestinal complication
- Median (IQR and range) number of severe gastrointestinal complications per infant.
- Severe gastrointestinal complication *only includes*:
  - intestinal perforation
  - any intestinal resection, regardless of amount of bowel removed or the indication for the resection
  - mechanical intestinal obstruction resulting in a repeat laparotomy
  - abdominal compartment syndrome*
  - enterocolitis.†

Time on parenteral nutrition
- Median (IQR and range) number of days *any* parenteral nutrition was received per infant in studies reporting outcomes at or prior to 1 year of age.
- Number (%) of infants receiving *any* parenteral nutrition in studies reporting outcomes after 1 year of age.

Liver disease
- Number (%) of infants with persistent conjugated hyperbilirubinaemia (>50 µmol/L) for ≥2 weeks with no known other underlying liver disease.

Quality of life for the child
- Median (IQR and range) PedsQL score in each study group.
- If appropriate, the median (IQR and range) score from the PedsQL gastrointestinal symptoms and family impact modules in each study group should also be reported.

*Defined as 'suspected raised intra-abdominal pressure with at least two of oliguria or anuria, respiratory de-compensation, hypotension/shock, or metabolic acidosis, that leads to intervention'.
†Defined as 'suspected enterocolitis with at least one of bilious aspirates or emesis, abdominal distension or occult or gross blood in stool (no

Continued

Box 1 Continued

fissure), and at least one of pneumatosis intestinalis, hepatobiliary gas, pneumoperitoneum'.
CSF, cerebrospinal fluid; PedsQL, pediatric quality of life inventory.

Definition and measurement of outcomes

A literature review informed by a previously published systematic review[7] identified existing definitions, measurement tools and common measurement time-points for outcomes included in the COS. The 14 attendees at the measurement meeting were asked to review summaries of this literature in advance of the meeting in order to guide discussion among the group. Following discussion, unanimous agreement was reached on definitions and methods of measurement for each core outcome (box 1). Appropriate time-points for reporting these core outcomes were also discussed, and it was unanimously agreed that these should be kept as close as possible to standard time-points for reporting surgical and paediatric outcomes (table 5). In order to make future meta-analysis more meaningful, studies using the developed COS should report outcomes at at least one of these time points. Further rationale for selection of these time-points, and for using different time-points for intervention and cohort studies is described in detail in a previously published Hirschsprung's disease COS development study.[10]

Attrition bias

Median phase one scores for the eight outcomes included in the COS, or their nearest approximations, were compared between participants who completed all three phases of the Delphi process and those who completed phase one only. No statistically significant differences were seen between any of these groups (table 6).

DISCUSSION

Using robust consensus methodology, we have enabled key stakeholders to identify eight outcomes as being the most important in determining the overall success of treatment of a child born with gastroschisis. These are: death, sepsis, growth, number of operations, severe gastrointestinal complication, time on parenteral nutrition, liver disease and quality of life for the child. By developing the COS using Delphi methodology combined with detailed discussion of outcomes at a consensus meeting, we anticipate that the included outcomes are relevant to clinical practice, parents and patients and appropriate for differentiating

Table 4 Outcomes meeting consensus for inclusion in the NETS[1G] core outcome set

Core outcome	Score 7–9 (%)	Reporting time-points
Death	100	Cohort or intervention study time-points
Sepsis	100	Cohort or intervention study time-points
Growth	100	Cohort or intervention study time-points
Number of operations	100	Cohort or intervention study time-points
Severe gastrointestinal complication	96	Cohort or intervention study time-points
Time on parenteral nutrition	87	Cohort study time-points only
Liver disease	74	Cohort or intervention study time-points
Quality of life for the child	73	Cohort or intervention study time-points

NETS, Next Stage in Evidence-based paediatric surgical Treatment Strategies 1 - Gastroschisis.

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Table 5 Proposed time-points for measurement of core outcomes

Cohort studies	Intervention studies
28 days of age	30-day postintervention
	90-day postintervention
One year of age	One-year postintervention
Five years of age	Five-year postintervention
Ten years of age	Ten-year postintervention
Every subsequent 10 years	Every subsequent 10 years

the relative merits of gastroschisis treatments. Furthermore, the COS has been designed to be practical to use in multiple study designs. The number of outcomes is relatively small and each has been robustly defined, with an appropriate measure and time-point for reporting identified. This level of detail should enable the immediate practical implementation of the COS.

A particular strength of this process has been the involvement of a wide range of stakeholder groups including parents of children born with gastroschisis. Unfortunately, however, there were no individuals born with gastroschisis who completed all three phases of the study. The difficulty engaging adults treated for gastroschisis as a child may be due to the fact that many have no ongoing active involvement with medical services or charities. It is difficult to know if this population of adults do not have regular contact with medical services because they are symptom free or because they have become detached from these services. If the former is true, the COS will likely remain fully representative of the outcomes that are important in determining treatment success, as the majority of 'experience' of gastroschisis will be from the parental point of view. However, if it is the latter, and there are differences in opinion of which outcomes are important between parents, and adults who were treated for gastroschisis as a child, then the COS may under-represent the treated adult's opinion.

Table 6 Comparison of median phase one scores for outcomes included in the core outcome set between participants in each panel who completed all three phases of the Delphi process and those who only completed phase one

Outcome	Panel	P value from Wilcoxon rank-sum test
Death	Neonatal	0.3
	Non-neonatal	1
	Personal experience	0.9
Sepsis	Neonatal	0.4
	Non-neonatal	0.7
	Personal experience	0.7
Growth	Neonatal	0.4
	Non-neonatal	0.6
	Personal experience	0.2
Number of operations	Neonatal	0.9
	Non-neonatal	1
	Personal experience	0.2
Severe gastrointestinal complication	Neonatal	0.6
	Non-neonatal	0.6
	Personal experience	0.5
Time on parenteral nutrition	Neonatal	0.8
	Non-neonatal	0.7
	Personal experience	0.6
Liver disease	Neonatal	0.5
	Non-neonatal	0.9
	Personal experience	0.1
Quality of life	Neonatal	0.8
	Non-neonatal	0.4
	Personal experience	0.4

In addition to the difficulties that were experienced recruiting people born with gastroschisis to the personal experience panel, the attrition rate in this panel was also higher than in the two other panels. However, this was still in line with other published studies.[11] It is unclear why the attrition rate was higher, but we would speculate that the demographics of those who are likely to be members of the personal experience panel might have influenced their ability to find time to complete all three phases of the study. There were, however, no differences identified in scoring patterns between those participants who completed all three phases of the Delphi process and those who only completed phase one, and we therefore do not believe that the identified attrition will have affected the results of the process.

Currently, many COS development processes conduct interviews with non-medical participants prior to starting the Delphi process. These interviews are used to identify outcomes that are important to patients but not reported by the existing literature. In this COS development process, we opted not to conduct interviews and instead gave participants the opportunity to propose new outcomes in phase one of the Delphi process. This decision was based on our experience of developing a Hirschsprung's disease COS,[10] where analysis of the additional outcomes proposed by participants, and comments left during the Delphi process reassured us that the likelihood of missing important outcomes by not conducting qualitative interviews prior to starting the Delphi process was low. In addition, we believed there to be significant benefit to not conducting qualitative interviews in that it reduced the cost and time necessary to develop the COS and therefore increased the efficiency with which its use could be implemented in future research. Interestingly, despite some methodological differences, there is overlap between the outcomes included in this COS, outcomes included in the recently developed Hirschsprung's disease COS[10] and a paediatric asthma COS.[12] All three have included death and quality of life, as well as a measure of the need for repeated medical intervention. Commonality between these COSs may suggest a role for developing a paediatric COS that is applicable to all conditions with significant childhood morbidity and that can then be augmented with smaller disease-specific COSs. Results of two further paediatric surgical COSs that are currently in development for appendicitis[13] and burns[14] will help to inform this discussion, as will the results of the Core outcomes in neonatology (COIN) study,[15] which is developing a neonatal COS.

While some of the outcomes included in the COS such as time on parenteral nutrition and number of operations were already frequently investigated in gastroschisis studies, there was significant variation in the way they were defined, or the time-point at which they were measured.[7] This has meant that although researchers were investigating outcomes of importance to patients, the fact that they were doing so in different ways was impeding the development of a meaningful evidence base.[4] Developing this COS has allowed key stakeholders to achieve consensus on definitions and measures that should be used for each of these already commonly investigated core outcomes. Promoting the use of these definitions will improve the quality of the evidence base supporting the management of infants with gastroschisis, without significantly altering the outcomes that researchers are investigating. Other core outcomes including growth and quality of life were very infrequently investigated in

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gastroschisis studies.[7] It is likely that these have not previously been frequently investigated, because it is difficult and expensive to collect data in relation to them. Identifying these outcomes as important to key stakeholders therefore has significant implications for researchers, journal editors and funders, as it will alter the way in which studies are designed, funded and reviewed for publication.

While the COS has identified eight outcomes that, because of their importance to key stakeholders, should be investigated in all studies comparing treatments for children born with gastroschisis, there are still further steps that must be taken before the patient benefit of this work is realised. Using the COS in clinical practice, audit, observational studies and randomised controlled trials will start to establish data in the public domain that can be meta-analysed to meaningfully inform the ongoing debate around the ideal management of children born with gastroschisis. If this COS facilitates the generation of high-quality evidence to support optimal management strategy, then patient care can be standardised, and outcomes will begin to improve.

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Contributors BSRA was responsible for the design of the study, day-to-day management of the study, analysis of data and drafting of the manuscript. NJH, ARR, SSM, JJK and MK were responsible for design of the study, management of the study and contributed to critical revisions of the manuscript. Members of NETS1G collaboration contributed critically to the academic content of the study and have reviewed and critically revised the manuscript.

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Appendix 13: *Outcome definition in the NETS^{2G} study*

XIII.I **Primary outcome**

Number of severe gastrointestinal complications in the first 28 days of life included the following five complications, intestinal perforation, unplanned intestinal resection regardless of amount of bowel removed or the indication for the resection, mechanical intestinal obstruction requiring laparotomy, abdominal compartment syndrome, and enterocolitis. For infants treated in Canada, abdominal compartment syndrome was defined as '*an increase in intra-abdominal pressure requiring surgery to relieve pressure*,' whilst for infants treated in the British Isles, it was defined as per the treating clinician. Enterocolitis for both sets of infants was defined as per the treating clinician.

XIII.II **Secondary outcomes**

1. Number of procedures in the first 28 days of life. This included all procedures carried out under a general anaesthetic as well as all abdominal procedures and central venous catheter insertions carried out without a general anaesthetic.
2. The number of episodes of infection in the first 28 days of life. This included only episodes of central nervous system infection, necrotising enterocolitis, lower respiratory tract infection, soft tissue infection, urinary tract infection and clinical sepsis of unknown cause.
3. One or more episode of infection in the first 28 days of life. This included only episodes of central nervous system infection, necrotising enterocolitis, lower respiratory tract infection, soft tissue infection, urinary tract infection or clinical sepsis of unknown cause.

4. Z-score for head circumference and weight at 28 days of age. Z-scores were derived from weight and head circumference measurement data collected in the CNN dataset, and calculated using the LMS Growth add in for excel, based upon the UK 1990 reference growth charts. See Appendix ten for justification of using the UK 1990 reference charts.
5. Diagnosis of liver disease in the first 28 days of life. Liver disease is defined by CAPSNet as two or more consecutive measurements of 50 μmol/l or greater of conjugated bilirubin over a period of at least 14 days at any point in the hospital stay, with no documented bacteremia over that time period. In the original BAPS-CASS study however, liver disease was diagnosed at the discretion of the treating clinician. Using the available data, it was not possible to apply a single definition of liver disease uniformly for both British and Irish, and Canadian infants, and therefore, in order to present the most severe estimate of the rate of liver disease, an infant was deemed to have been diagnosed with liver disease if they met the case definition for the study in which their data were originally used. In order to again represent the most severe estimate of rates of liver disease, where dates of diagnosis were not available, all diagnoses were assumed to have been made prior to 28 days of age.
6. Number of days on which *any* parenteral nutrition was received in the first 28 days of life.
7. All cause mortality prior to 28 days of life.

Appendix 14: *Variable creation in the Canadian master dataset*

Table 53: Variable creation in the Canadian master dataset

Final variable name	Definition	CAPSNet 2010	CAPSNet 2012	CNN 2010	CNN 2012
DOA	Date of Admission	DOA	DOA	-	-
C_LOCATION	CAPSNet location of first closure	location	SurgeryLocation	-	-
C_LOCATION2	CAPSNet location of second closure	clocation	Nlocation	-	-
C_LOCATION_GRP	Grouped location for first closure	C_LOCATION	C_LOCATION	-	-
surgicalfindings	Free text for CAPSNet operations	surgicalfindings	OtherFindings	-	-
C_DATASET	Newly generated variable defining whether an infant is pre or post 2010 CAPSNet dataset	1	2	-	-
M_MAT_AGE	Maternal age at delivery (grouped)	MaternalAge MomDateofBirth	MaternalAge	MotherAge NOT used as doesn't add any more information	
C_LIVER_DISEASE	CAPSNet liver disease	liverdisease	Comp9Chol Comorb2CholLivDis	-	-
C_INTUBATED	Intubated for first closure	intubation	surgeryintubation	-	-
C_GENERAL_ANAE		aninhal	Analg1Inhalation	-	-
C_DATE_CLOSURE	Date of closure	cldate DOA finaldate	ClosureDate if Closuresuccesful==1 NFinalDate if Closuresuccesful==0	-	-
C_DAYS_TO_CLOSURE	Days to closure	DOA C_DATE_CLOSURE	DOA C_DATE_CLOSURE	-	-
C_CLOSURE_28	Closure of the abdominal defect within 28 days of birth	DAYS_TO_CLOSURE clsuccess intent	DAYS_TO_CLOSURE closuresuccesful intent	-	-
C_CLOSURE_SUCCESS	Intended closure strategy employed succesfully	clsuccess	closuresuccessful (also renamed as clsuccess)	-	-
C_CLOSURE_TECH	Closure technique	failtech (contains data for both failtech and cltechnique)	YCoverageTechnique NCoverageTechnique	-	-
C_CLOSURE_TECH_GRP	Closure technique grouped	C_CLOSURE_TECH	C_CLOSURE_TECH	-	-
C_SILO_TYPE	Type of silo used if first closure not succesful	silotype	NTypeOfSilo	-	-

Table 53: Variable creation in the Canadian master dataset - Continued

Final variable name	Definition	CAPSNet 2010	CAPSNet 2012	CNN 2010	CNN 2012
C_OP_ONE	First closure type	intent clsuccess CLOSURE_TECH_GRP INTUBATED GENERAL_ANAE LOCATION_GRP failmesh clsuccess DAYS_TO_CLOSURE ClosureTime	intent clsuccess CLOSURE_TECH_GRP LOCATION_GRP INTUBATED GENERAL_ANAE YMeshUsed DAYS_TO_CLOSURE ClosureTime	-	-
C_OP_TWO	Second op under GA, not under GA, unknown or none	C_OP_ONE CLOSURE_TECH_GRP clsuccess failmesh CLOSURE_CODED	C_OP_ONE CLOSURE_TECH_GRP clsuccess NMeshUsed CLOSURE_CODED	-	-
C_U_1_CLOSE	Unknown GA status of first closure	-	C_OP_ONE C_INTUBATED SUCCESFUL_CLSURE_CODED_TWICE	-	-
C_U_2_CLOSE	Unknown GA status of second closure	C_OP_TWO	C_OP_TWO	-	-
C_U_2_CLOSE_28	Unknown GA status of second closure performed within 28 days	C_OP_TWO CLOSURE_28	C_OP_TWO CLOSURE_28	-	-
All additional operation variables	Variables used to derive number of additional operations	free text from Surgery1 to Surgery16	ProcType1 to ProcType25	-	-
Dates of procedure		surdate1 to surdate 16	ProcDate1 to ProcDate25	-	-
Cause Of Death	Cause of death (only available for 12 infants)	-	-	CauseOfDeath	CauseOfDeath
M_REP_YEAR	Year in which case was reported	DOA	DOA	-	-
M_DAYS_DISCHARGE	Days from birth to discharge	final_disdate	FinalDisDate	-	-
C_ETHNICITY	Ethnicity of infant	Ethnicity patethnic	Ethnicity PatEthnicity	-	Ethnicity (recoded to Methnicity as maternal no infant)
M_ETH_GRP	Ethnicity grouped as white/other	C_ETHNICITY	C_ETHNICITY	-	C_ETHNICITY
M_SEX	Infants sex	Gender	Gender	-	-
M_GA_BIRTH	Gestational age at birth completed weeks	GA	GAWeeks	-	-
M_B_WEIGHT_CONT	Continuous birth weight variable	bthwt	BirthWeight	-	-
M_B_WEIGHT	Birth weight in 50g categories	M_B_WEIGHT_CONT	M_B_WEIGHT_CONT	-	-

Table 53: Variable creation in the Canadian master dataset - Continued

Final variable name	Definition	CAPSNet 2010	CAPSNet 2012	CNN 2010	CNN 2012
Type2	Congenital anomaly Type recoded to categories	-	-	catype	Type
C_ASS_ANOM	Type 2 with multiple anomalies condensed to one row	-	-	-	-
M_ANOMALY	1 or more congenital anomaly	malnone - variable for *confirming* no prenatal malformations detected. Note haven't used malpulm etc in derivation of outcome, as these are only for antenatally *suspected* anomalies.		C_ASS_ANOM2	C_ASS_ANOM2
M_ANOMALY_TYPE	Final variable for type of anomaly	-	-	C_ASS_ANOM2	C_ASS_ANOM2
M_ATRESIA	Confirmed intestinal atresia	atresia surgicalfindings Surgery1 to Surgery16	OtherFindings ProcType1 to ProcType25 IntestinalAtresia	-	-
M_NECROSIS	Intestinal necrosis at presentation	s1necrosis s2necrosis	BISNecrosis	-	-
M_PERFORATION	Intestinal perforation at presentation	s1perforation s2perforation	BISPerforation	-	-
M_MATTING	Intestinal matting at presentation	s1matting s2matting	BISMatting	-	-
M_COMPLEX	Complex gastroschisis as per the definition of Molik et al	M_ATRESIA M_NECROSIS M_PERFORATION	M_ATRESIA M_NECROSIS M_PERFORATION	-	-
M_APGAR_FIVE	APGAR score at five minutes	apgar5	Apgar5	-	-
M_TRANSFERRED	Transferred in to a paediatric surgical centre from a district general/community hospital prior to treatment	outborn	Outborn	-	-
M_C_SECTION	Caesarean section delivery	deliverplan planchanged	Csection	Delivery	-
M_ANT_DX	Antenatally diagnosed gastroschisis, or at least one ultrasound scan conducted	numus	PrenatDiag2GS	-	-
M_SURGEON	Grade of surgeon performing first reduction and closure procedure	surgeon	Surgeon	-	-
M_DISCHARGE_LOCATION	First discharge location (including death)	final_disdest	FinalDisDest	-	-
M_MORTALITY	Infant died	M_DISCHARGE_LOCATION	M_DISCHARGE_LOCATION	-	-
M_MORTALITY_28	Infant died prior to 28 days of age	M_DISCHARGE_LOCATION M_DAYS_DISCHARGE	M_DISCHARGE_LOCATION M_DAYS_DISCHARGE	-	-
M_TREATMENT	First surgical reduction strategy defining primary closure, silo placement or WBR	C_OP_ONE	C_OP_ONE	-	-

Table 53: Variable creation in the Canadian master dataset - Continued

Final variable name	Definition	CAPSNet 2010	CAPSNet 2012	CNN 2010	CNN 2012
M_VENTILATED	Ventilated post-operatively	postimv	PostOpVentDays	-	-
M_VENT_DAYS	Number of days post-operative ventilation	postimv	PostOpVentDays	-	-
M_DAYS_PN	Number of days parenteral nutrition	DaysOnTPN	DaysOnTPN	-	-
M_DAYS_PN_BIRTH	Number of days parenteral nutrition in the first 28 days of life	DaysOnTPN	DaysOnTPN	-	-
M_PN_EVER	Ever received parenteral nutrition	DaysOnTPN	DaysOnTPN	-	-
M_OBSTRUCTION	Number of episodes of intestinal obstruction	bo surgery1 to surgery16 compspecify	ProcType1 to ProcType25 COmpOthSpec Comp3BowelObst	-	-
M_OBSTRUCTION_28	Number of episodes of intestinal obstruction in the first 28 days of life	bo surgery1 to surgery16 compspecify	ProcType1 to ProcType25 COmpOthSpec Comp3BowelObst	-	-
M_PERFORATION_COMP	Number of episodes of intestinal perforation	surgery1 to surgery16 compspecify	ProcType1 to ProcType25 COmpOthSpec	-	-
M_PERFORATION_COMP_28	Number of episodes of intestinal perforation in the first 28 days of life	surgery1 to surgery16 compspecify	ProcType1 to ProcType25 COmpOthSpec	-	-
M_RESECTION	Number intestinal resections	surgery1 to surgery16 compspecify	ProcType1 to ProcType25 COmpOthSpec	-	-
M_RESECTION_28	Number intestinal resections in the first 28 days of life	surgery1 to surgery16 compspecify	ProcType1 to ProcType25 COmpOthSpec	-	-
M_ACS	Number of episodes of Abdominal Compartment Syndrome	acs	Comp2ACS	-	-
M_NEC	Number of episodes of enterocolitis	compspecify	COmpOthSpec	nec	MultipleEpisodes NEC NECDate
M_NEC_28	Number of episodes of enterocolitis in the first 28 days of life	compspecify	COmpOthSpec	nec	MultipleEpisodes NEC NECDate
M_GI_COMP_TOTAL	Total number of severe gastrointestinal complications	sum of appropriate variables above			

Table 53: Variable creation in the Canadian master dataset - Continued

Final variable name	Definition	CAPSNet 2010	CAPSNet 2012	CNN 2010	CNN 2012
M_GI_COMP_TOTAL_28	Total number of severe gastrointestinal complications in the first 28 days of life	sum of appropriate variables above			
M_SEPSIS_NUM	Number of episodes of infection	-	-	type date1	DiagnosisType Date
M_SEPSIS_NUM_28	Number of episodes of infection in the first 28 days of life	-	-	type date1	DiagnosisType Date
C_CENTILE_W_BIRTH	Centile birth weight for gestational age	M_GA_BIRTH M_SEX M_B_WEIGHT_CONT	M_GA_BIRTH M_SEX M_B_WEIGHT_CONT	-	-
C_CENTILE_W_28	Centile for weight at 28 days of age	-	-	Day28Weight	D28Weight
C_CENTILE_HC_28	Centile for head circumference at 28 days of age	-	-	Day28HeadClr	D28HeadCircumference
C_SDS_WEIGHT_28	z-score for weight at 28 days of age	-	-	Day28Weight	D28Weight
C_SDS_HEAD_28	z-score for head circumference at 28 days of age	-	-	Day28HeadClr	D28HeadCircumference
M_SGA	Small for gestational age at birth (<10th centile birth weight for gestational age	C_CENTILE_W_BIRTH	C_CENTILE_W_BIRTH	-	-
M_OP_ONE	First reduction and closure procedure type (all types)	C_OP_ONE	C_OP_ONE	-	-
M_LIVER_DISEASE	Liver disease as per original study definition	C_LIVER_DISEASE	C_LIVER_DISEASE	-	-
M_LIVER_28	Liver disease as per original study definition	C_LIVER_DISEASE M_DAYS_DISCHARGE	C_LIVER_DISEASE M_DAYS_DISCHARGE	-	-
M_SEPSIS_28	One or more infection in the first 28 days of life	-	-	M_SEPSIS_NUM_28	M_SEPSIS_NUM_28

Appendix 15: *Variables without direct equivalence between BAPS-CASS and CAPSNet datasets*

XV.I Small for gestational age at birth, head circumference at 28 days of age, and weight at 28 days of age

Multiple reference standards exist for use in determining an infant's z-score for head circumference, weight, and length, and there is much debate over which is most appropriate (224). However, only the British 1990 reference standards could be used in a unified format for batch calculation of centiles for head circumference and weight in both premature and full-term infants at birth and at 28 days of age. In order to apply one set of standards across all infants, measurements and time-points in the NETS^{2G} study, the British 1990 standards were therefore primarily chosen for calculation of all z-scores.

In order to investigate whether utilising the UK 1990 reference standards may have affected the conclusions of the study, z-scores for birthweight, proportion of infants who were small for gestational age at birth (<10th centile birth-weight for gestational age - SGA), and association of being SGA with number of severe gastrointestinal complications were also calculated for the Canadian cohort using the INTERGROWTH-21st reference standards(225). The INTERGROWTH-21st standards are a set of recently developed growth standards based upon an international population. Z-scores for head circumference and weight at 28 days of age cannot yet be calculated for the NETS^{2G} study population using INTERGROWTH-21st standards. Therefore, the similarity of measures of birth weight between INTERGROWTH-21st and UK 1990 reference standards was used as a proxy for similarity between measures for weight and head circumference at 28 days of age.

When calculated using the UK 1990 reference standards for all infants, the mean z-score for birthweight in the study population as a whole was -0.27 (95% CI -0.33 to -0.21), and when calculated using the INTERGROWTH-21st reference standards for Canadian infants, was -0.27 (95% CI -0.33 to -0.21), p-value for difference on a paired t-test 0.753. Overall, there were 307 infants (19.46%) who were SGA using the UK 1990 reference standards, and 312 infants (19.75%) who were SGA using the INTERGROWTH-21st reference standards for the Canadian infants. On univariable negative binomial regression analysis, there was no statistically significant association between being SGA, as calculated using the UK 1990 reference standards for all infants, and number of severe gastrointestinal complications in the first 28 days of life, IRR, 1.13 (95% CI 0.75-1.70, p=0.564). There was also no statistically significant association when SGA was calculated using the INTERGROWTH-21st reference standards, IRR 1.08 (95% CI 0.71 – 1.63, =0.718).

As using the UK 1990 reference standards for calculation of weight centiles in the Canadian infants did not appear to affect the conclusions of the work, it was determined more robust to use one set of reference standards throughout the study, as opposed to having to use different standards for calculating growth variables dependent upon an infant's gestational age at birth, the point of measurement and their country of birth. Therefore, throughout the study, the UK 1990 reference standards were utilised to calculate an infant's birthweight centile as well as their z-score for weight and head circumference at 28 days of age.

XV.II Intestinal matting

In the CAPSNet data collection form, intestinal matting was defined as none, moderate and severe, whilst in the BAPS-CASS data collection form it was defined as none, less than 50% intestinal matting, ≥50% intestinal matting, and adherent mass. There is no direct equivalence between these two systems of categorisation. Primarily therefore, less than 50% intestinal matting and ≥50% intestinal matting were mapped to the CAPSNet category of mild to moderate matting, with only adherent mass mapped to severe matting. However, in order to investigate whether the mapping affected the conclusions of the study, the univariable analysis was repeated with ≥50% intestinal matting mapped to severe intestinal matting instead of moderate intestinal matting.

Utilising the original mapping, there were 645 infants (44.9%) with no intestinal matting, 617 infants (43.0%) with mild to moderate intestinal matting, and 174 (12.1%) with severe intestinal matting. Using the alternate mapping, there were 645 infants (44.9%) with no intestinal matting, 568 infants (39.6%) with mild to moderate intestinal matting, and 223 (15.5%) with severe intestinal matting. The association of each definition of the variable with number of severe gastrointestinal complications is shown along with results of the univariable analysis in Table 54. Regardless of the mapping used, intestinal matting met criteria for assessment for inclusion in the multivariable model, but did not meet criteria for retention. The original mapping of the variable, with both less than 50% intestinal matting, and ≥50% intestinal matting mapped to mild to moderate intestinal matting, was therefore used throughout all remaining analyses.

Table 54: Univariable analysis utilising differing mapping of intestinal matting variable

	Number of severe gastrointestinal complications in the first 28 days of life							
	0	**1**	**2**	**≥3**				
	N=1430	**N=127**	**N=30**	**N=12**				
	n(%)*	**n(%)***	**n(%)***	**n(%)***	**Unadjusted IRR (95% CI)**	**p-value**	**Adjusted IRR (95% CI)**	**p-value**
Intestinal matting						0.014		
None	588 (45.5%)	45 (42.5%)	7 (25.0%)	5 (45.5%)	Ref.		Not retained	
Mild	559 (43.3%)	42 (39.6%)	13 (46.4%)	3 (27.3%)	1.09 (0.73-1.61)			
Severe	144 (11.2%)	19 (17.9%)	8 (28.6%)	3 (27.3%)	2.12 (1.26-3.54)			
Alternative mapping of severe intestinal matting category						0.003		
None	588 (45.5%)	45 (42.5%)	7 (25.0%)	5 (45.5%)	Ref.		Not retained	
Mild	519 (40.2%)	37 (34.9%)	9 (32.1%)	3 (27.3%)	0.99 (0.67-1.48)			
Severe	184 (14.3%)	24 (22.6%)	12 (42.9%)	3 (27.3%)	2.14 (1.34-3.43)			

*Percentage of those with complete data

Appendix 16: *NETS^{2G} dataset creation*

XVI.I Cleaning of the BAPS-CASS dataset

XVI.I.I Deriving the number of severe gastrointestinal complications variable

Number of severe gastrointestinal complications, as defined in the NETS[1G] gastroschisis core outcome set, is not an outcome that was collected in the original BAPS-CASS study. However, sufficient data were collected to allow this outcome to be derived from other variables contained within the dataset.

Data relating to whether the infant experienced an intestinal perforation or enterocolitis were collected as Yes/No questions, and clarified further in free text comments. Information relating to intestinal resections, mechanical intestinal obstruction requiring laparotomy, and abdominal compartment syndrome were collected as free text descriptions of the operations an infant had undergone. Dates of each complication were collected where provided, but if not available, then reviews of the original data collection forms were undertaken to determine whether the complication was likely to have occurred pre or post 28 days of age. Review of the original paper data collection forms was also used to determine whether multiple reports of the same complication in different parts of the data collection form represented the same or different events. The number of individual complications reported for an infant was summed to create the composite outcome of number of severe gastrointestinal complications.

XVI.I.II Deriving the number of operations prior to 28 days of age variable

In the BAPS-CASS data collection form, a Yes/No question was used to record whether an infant underwent a reoperation. Further details of the operation or

operations performed were recorded in free text comments. Where the date of an operation was missing, the infant's original paper data collection form was again reviewed to determine whether the operation was more likely to have been conducted pre or post 28 days of age. Reported operations were classified into five categories: abdominal operation performed under general anaesthetic, central venous catheter insertion under general anaesthetic, 'other' operation under general anaesthetic, abdominal procedure without general anaesthesia, or central venous catheter insertion without general anaesthesia.

Where multiple procedures of the same category were carried out at the same time, these were counted as one operation. For example, if an infant underwent a Ladd's procedure and an intestinal resection in the same operation, these were counted as one abdominal procedure under general anaesthetic. However, if they underwent two operations of different types at the same time, for example, a Ladd's procedure and insertion of a central venous catheter, these were counted as two separate operations.

All infants who received parenteral nutrition must have undergone insertion of a central venous catheter, and therefore if they did not have a central venous catheter insertion recorded, they were assumed to have undergone insertion of a central venous catheter without general anaesthesia and this was included in the total number of operations that they underwent.

XVI.I.III Deriving infection and liver disease variables

Diagnosis of infections and liver disease were recorded either in free text comments relating to whether the infant had experienced a major complication, or in comments relating to other information that the clinician felt might be important. All free text comments in each of these sections were reviewed to determine whether an infant was known to have been diagnosed with liver disease or an infection. Given the data collection methodology used, it was not possible to reliably determine the number of episodes of infection experienced by an infant, and therefore British and Irish infants only contributed data to the outcome *one or more episode of infection,* not the outcome *number of episodes of infection.*

XVI.I.IV Deriving mortality and days of parenteral nutrition variables

Whether an infant died prior to 28 days of age, and the number of days parenteral nutrition they received in the first 28 days of life were collected in the original BAPS-CASS study, and therefore these outcomes were analysed without any need to derive them from other data points.

XVI.I.V Deriving growth

Growth data were not collected in the BAPS-CASS study, and therefore British and Irish infants did not contribute data to assessment of this outcome.

XVI.II Linkage of CAPSNet and CNN data

Data collected by CAPSNet were linked to data collected by the CNN using the infant's CNN unique identifier.

XVI.III Creating a master Canadian dataset

In 2010, the CAPSNet and CNN data collection systems were updated. Data collection, labelling and storage were therefore different for infants born before and after the change in system. Utilising an infant's CNN unique identifier, CAPSNet and CNN data were merged to create two datasets, one containing all data collected prior to 2010, and one containing all data collected after 2010. Variables required for the secondary analysis were renamed and recoded using common terms, following which the pre and post-2010 datasets were merged.

XVI.IV Collapsing of episode/admission based data

Data relating to any additional congenital anomalies an infant was diagnosed with, and the number of episodes of infection they experienced, were stored with each episode or anomaly as a separate record. These data were collapsed to a single record per infant prior to merging with the master Canadian dataset.

XVI.V Cleaning of the Canadian dataset

XVI.V.I Deriving the number of severe gastrointestinal complications variables

Within the unified Canadian dataset, data relating to the number of severe gastrointestinal complications an infant experienced were extracted from both CAPSNet and CNN variables. CAPSNet variables that were utilised included free text comments relating to the operative interventions an infant underwent, and multiple choice questions and free-text comments relating to the complications the infant experienced. CNN variables utilised included those relating to whether or not an

infant had been diagnosed with an intestinal perforation or necrotising enterocolitis. Where complications data were extracted from the CAPSNet database, the date a complication was diagnosed was only available if the complication had been reported as part of an operation the infant underwent, not if it had been recorded as a complication. Within the CNN dataset, dates of diagnosis were collected for intestinal perforation and enterocolitis. If an infant had the same type of complication reported multiple times, and dates were not available to confirm whether they were separate events, the following assumptions were made.

- Intestinal perforations were assumed to represent the same event
- Episodes of intestinal obstruction were assumed to represent the same event
- Intestinal resections were assumed to represent separate events
- Episodes of NEC were assumed to represent separate events

Where dates were not recorded, assumptions were also made as to whether events occurred pre or post 28 days of age.

- For all events, if an infant had been discharged or died prior to 28 days of age, then the event was assumed to have occurred prior to 28 days.
- Individual case reviews of each episode of intestinal perforation, resection and NEC were undertaken to determine whether they were most likely to have occurred pre or post 28 days of age.
- All episodes of intestinal obstruction were assumed to have occurred after 28 days of age.

- All episodes of abdominal compartment syndrome were assumed to have occurred prior to 28 days of age.

XVI.V.II Deriving the number of operations variable

Details of additional operations an infant underwent were collected by CAPSNet using date selection questions and free text descriptions of the operation performed. Operations were categorized and summed by review of the free text comments using the same rules as for the BAPS-CASS dataset.

XVI.V.III Deriving the infection variables

Each episode of infection an infant experienced was recorded as a separate event in the CNN dataset, and categorised as a central nervous system infection, meningitis, clinical sepsis, lab confirmed blood-stream infection, necrotizing enterocolitis, lower respiratory tract infection, soft tissue infection, urinary tract infection, conjunctivitis, eye infection, gastroenteritis, other eye, nose and mouth infection, other gastrointestinal infection respiratory syncytial virus, skin infection or upper respiratory tract infection. The number of episodes of infection that met the outcome definition were summed to create the composite outcome of number of episodes of infection.

XVI.V.IV Deriving the liver disease variable

Using Yes/No questions, data were collected relating to whether an infant had been diagnosed with liver disease, as per the CAPSNet definition, at any time during their

hospital stay, or at discharge. Infants were deemed to have been diagnosed with liver disease if it were reported at either time point.

XVI.V.V Deriving the growth variables

Weight and head circumference at 28 days of age were collected in the CNN dataset. These data were exported to excel and the LMS Growth add in was used in conjunction with the British 1990 reference tables and the infants gestational age at birth and sex to calculate z-scores.

XVI.V.VI Deriving the mortality and days of parenteral nutrition variables

Whether an infant died prior to 28 days of age, and the number of days parenteral nutrition they received in the first 28 days of life were collected in the original CAPSNet study, and therefore these outcomes were analysed without any need to derive them from other data points.

Appendix 17: *Additional congenital anomaly definitions*

XVII.I Canadian Infants Post-2010

Canadian infants in the post-2010 CNN dataset had congenital anomalies information coded according to International Classification of Diseases 10 standard definitions. Each code was assigned to a category of chromosomal anomaly, cardiac anomaly, central nervous system anomaly, genito-urinary/renal anomaly, pulmonary/airways anomaly, skeletal anomaly, or other single major anomaly. Infants with multiple anomalies were classified as 'multiple additional congenital anomalies'.

XVII.I.I Chromosomal

- Down's Syndrome
- Edwards' Syndrome Or Trisomy 18
- Patau Syndrome Or Trisomy 13
- Other Trisomies And Partial Trisomies Of The Autosomes Not Elsewhere Classified
- Monosomies And Deletions From The Autosomes Not Elsewhere classified
- Balanced Rearrangements And Structural Markers Not Elsewhere Classified
- Turner's Syndrome
- Other Sex Chromosome Abnormalities, Female Phenotype Not Elsewhere Classified
- Other Sex Chromosome Abnormalities, Male Phenotype Not Elsewhere Classified
- Other deletions of part of a chromosome
- Male with sex chromosome mosaicism

XVII.I.II Cardiac

- Double Outlet Right Ventricle
- Transposition Of The Great Vessels (Tgv)
- Ventricular Septal Defect
- Atrial Septal Defect
- Atrioventricular Septal Defect
- Tetralogy Of Fallot
- Pulmonary Valve Stenosis
- Hypoplastic Left Heart Syndrome
- Other Congenital Malformations Of The Heart
- Congenital Heart Block

- Total Anomalous Pulmonary Venous Connection
- Coarctation Of The Aorta
- Congenital Absence And Hypoplasia Of The Umbilical Artery (Single Umbilical Artery)
- Other Congenital Malformations Of The Circulatory System
- Common arterial trunk
- Double outlet right ventricle
- Double outlet left ventricle
- Dextratransposition of aorta
- Complete transposition of great vessels
- Congenitally corrected transposition of great vessels
- Other transposition of great vessels NEC
- Double inlet ventricle
- Discordant atrioventricular connection with corrected transposition
- Discordant atrioventricular connection NEC
- Isomerism of atrial appendages
- Other congenital malformations of cardiac chambers and connections
- Congenital malformation of cardiac chambers and connections, unspecified
- Ventricular septal defect
- Atrial septal defect
- Atrioventricular septal defect
- Tetralogy of Fallot
- Aortopulmonary septal defect
- Other congenital malformations of cardiac septa
- Congenital malformation of cardiac septum, unspecified
- Pulmonary valve atresia
- Congenital pulmonary valve stenosis
- Congenital pulmonary valve insufficiency
- Other congenital malformations of pulmonary valve
- Congenital tricuspid atresia
- Ebstein's anomaly
- Hypoplastic right heart syndrome
- Other congenital malformations of tricuspid valve
- Congenital malformation of tricuspid valve, unspecified
- Congenital stenosis of aortic valve
- Congenital insufficiency of aortic valve
- Congenital mitral stenosis
- Congenital mitral insufficiency
- Hypoplastic left heart syndrome
- Other congenital malformations of aortic and mitral valves
- Congenital malformation of aortic and mitral valves, unspecified
- Dextrocardia
- Laevocardia
- Cor triatriatum
- Pulmonary infundibular stenosis

- Congenital subaortic stenosis
- Malformation of coronary vessels
- Congenital heart block
- Other specified congenital malformations of heart
- Patent ductus arteriosus
- Congenital malformation of heart, unspecified
- Coarctation of aorta
- Atresia of aorta
- Stenosis of aorta
- Other congenital malformations of aorta
- Atresia of pulmonary artery
- Stenosis of pulmonary artery
- Other congenital malformations of pulmonary artery
- Other congenital malformations of great arteries
- Congenital malformation of great arteries, unspecified
- Congenital stenosis of vena cava
- Persistent left superior vena cava
- Total anomalous pulmonary venous connection
- Partial anomalous pulmonary venous connection
- Anomalous pulmonary venous connection, unspecified
- Anomalous portal venous connection
- Portal vein-hepatic artery fistula
- Other congenital malformations of great veins
- Congenital malformation of great vein, unspecified
- Congenital absence and hypoplasia of umbilical artery
- Congenital renal artery stenosis
- Other congenital malformations of renal artery
- Peripheral arteriovenous malformation of upper limb
- Peripheral arteriovenous malformation of lower limb
- Peripheral arteriovenous malformation of digestive system vessel
- Peripheral arteriovenous malformation of renal vessel
- Peripheral arteriovenous malformation of other site
- Congenital phlebectasia
- Other specified congenital malformations of peripheral vascular system
- Congenital malformation of peripheral vascular system, unspecified
- Arteriovenous malformation of precerebral vessels
- Other malformations of precerebral vessels
- Arteriovenous malformation of cerebral vessels
- Other malformations of cerebral vessels
- Other specified congenital malformations of circulatory system
- Congenital malformation of circulatory system, unspecified

XVII.I.III Central Nervous System

- Anencephaly

- Encephalocele
- Microcephaly
- Congenital Hydrocephalus
- Other Congenital Malformations Of The Brain
- Spina Bifida
- Spinal Cord Anomaly Other Than Spina Bifida
- Other Congenital Malformations Of The Nervous System
- Craniorachischisis
- Iniencephaly
- Frontal encephalocele
- Nasofrontal encephalocele
- Occipital encephalocele
- Encephalocele of other sites
- Encephalocele, unspecified
- Microcephaly
- Malformations of aqueduct of Sylvius
- Atresia of foramina of Magendie and Luschka
- Other congenital hydrocephalus
- Congenital hydrocephalus, unspecified
- Congenital malformations of corpus callosum
- Arhinencephaly
- Holoprosencephaly
- Other reduction deformities of brain
- Septo-optic dysplasia
- Megalencephaly
- Congenital cerebral cysts
- Other specified congenital malformations of brain
- Congenital malformation of brain, unspecified
- Cervical spina bifida with hydrocephalus
- Thoracic spina bifida with hydrocephalus
- Lumbar spina bifida with hydrocephalus
- Sacral spina bifida with hydrocephalus
- Unspecified spina bifida with hydrocephalus
- Cervical spina bifida without hydrocephalus
- Thoracic spina bifida without hydrocephalus
- Lumbar spina bifida without hydrocephalus
- Sacral spina bifida without hydrocephalus
- Spina bifida, unspecified
- Amyelia
- Hypoplasia and dysplasia of spinal cord
- Diastematomyelia
- Other congenital cauda equina malformations
- Hydromyelia
- Other specified congenital malformations of spinal cord
- Congenital malformation of spinal cord, unspecified

- Arnold-Chiari syndrome
- Other specified congenital malformations of nervous system
- Congenital malformation of nervous system, unspecified

XVII.I.IV Genitourinary and renal

- Congenital Malformations Of Ovaries, Fallopian Tubes And Broad Ligiaments
- Other Congenital Malformations Of The Female Genitals
- Congenital Malformations Of The Uterus And Cervix
- Hypospadias
- Other Congenital Malformations Of The Male Organs
- Indeterminate Sex And Pseudohermaphroditism
- Renal Agenesis And Other Defects Of The Kidney
- Congenital Renal Cystic Diseases
- Congenital Hydronephrosis
- Other Congenital Malformations Of The Urinary System
- Congenital Posterior Urethral Valves
- Congenital absence of ovary
- Developmental ovarian cyst
- Congenital torsion of ovary
- Accessory ovary
- Ovarian streak
- Other congenital malformations of ovary
- Embryonic cyst of fallopian tube
- Embryonic cyst of broad ligament
- Other congenital malformations of fallopian tube and broad ligament
- Agenesis and aplasia of uterus
- Doubling of uterus with doubling of cervix and vagina
- Other doubling of uterus
- Bicornate uterus
- Unicornate uterus
- Agenesis and aplasia of cervix
- Embryonic cyst of cervix
- Congenital fistulae between uterus and digestive and urinary tracts
- Other congenital malformations of uterus and cervix
- Congenital malformation of uterus and cervix, unspecified
- Congenital absence of vagina
- Doubling of vagina
- Congenital rectovaginal fistula
- Imperforate hymen
- Other congenital malformations of vagina
- Fusion of labia
- Congenital malformation of clitoris
- Other congenital malformations of vulva
- Other specified congenital malformations of female genitalia

- Congenital malformation of female genitalia, unspecified
- Hypospadias, balanic
- Hypospadias, penile
- Hypospadias, penoscrotal
- Hypospadias, perineal
- Congenital chordee
- Other hypospadias
- Hypospadias, unspecified
- Absence and aplasia of testis
- Hypoplasia of testis and scrotum
- Other congenital malformations of testis and scrotum
- Atresia of vas deferens
- Other congenital malformations of vas deferens, epididymis, seminal vesicles and prostate
- Congenital absence and aplasia of penis
- Hypoplasia of penis
- Other congenital malformations of penis
- Other specified congenital malformations of male genital organs
- Congenital malformation of male genital organ, unspecified
- Hermaphroditism, not elsewhere classified
- Male pseudohermaphroditism, not elsewhere classified
- Female pseudohermaphroditism, not elsewhere classified
- Pseudohermaphroditism, unspecified
- Indeterminate sex, unspecified
- Renal agenesis, unilateral
- Renal agenesis, bilateral
- Renal agenesis, unspecified
- Renal hypoplasia, unilateral
- Renal hypoplasia, bilateral
- Renal hypoplasia, unspecified
- Potter's syndrome
- Congenital single renal cyst
- Polycystic kidney, infantile type
- Polycystic kidney, adult type
- Polycystic kidney, unspecified
- Renal dysplasia
- Medullary cystic kidney
- Other cystic kidney diseases
- Cystic kidney disease, unspecified
- Congenital hydronephrosis
- Atresia and stenosis of ureteropelvic junction
- Atresia and stenosis of ureterovesical orifice
- Other atresia and stenosis of ureter
- Congenital megaloureter
- Other obstructive defects of renal pelvis and ureter

- Agenesis of ureter
- Duplication of ureter
- Malposition of ureter
- Congenital vesico-uretero-renal reflux
- Other congenital malformations of ureter
- Accessory kidney
- Lobulated, fused and horseshoe kidney
- Ectopic kidney
- Hyperplastic and giant kidney
- Other specified congenital malformations of kidney
- Congenital malformation of kidney, unspecified
- Epispadias
- Cloacal exstrophy of urinary bladder
- Other exstrophy of urinary bladder
- Congenital posterior urethral valves
- Congenital bladder neck obstruction
- Congenital stricture of urethra
- Congenital stricture of urinary meatus
- Other congenital atresia and stenosis of urethra and bladder neck
- Malformation of urachus
- Congenital absence of bladder and urethra
- Congenital diverticulum of bladder
- Congenital urethrorectal fistula
- Congenital double urethra (or urinary meatus)
- Other congenital malformations of bladder and urethra
- Other specified congenital malformations of urinary system
- Congenital malformation of urinary system, unspecified

XVII.I.V Pulmonary and airways

- Congenital Malformations Of The Nose
- Congenital Malformations Of The Larynx
- Congenital Malformations Of The Trachea And Bronchus
- Congenital Malformations Of The Lung
- Congenital Cystic Lung
- Sequestration of The Lung
- Cleft Palate
- Cleft Lip
- Cleft Palate With Lip
- Choanal atresia
- Agenesis and underdevelopment of nose
- Fissured, notched and cleft nose
- Congenital perforated nasal septum
- Other congenital malformations of nose
- Congenital malformation of nose, unspecified

- Web of larynx
- Congenital subglottic stenosis
- Laryngeal hypoplasia
- Laryngocele
- Congenital laryngeal stridor
- Other congenital malformations of larynx
- Congenital malformation of larynx, unspecified
- Congenital tracheomalacia
- Congenital malformation of tracheal cartilage
- Congenital atresia of trachea
- Congenital stenosis of trachea
- Congenital tracheocele
- Other specified congenital malformation of trachea
- Congenital bronchomalacia
- Congenital stenosis of bronchus
- Other congenital malformations of bronchus
- Congenital cystic lung
- Accessory lobe of lung
- Sequestration of lung
- Agenesis of lung
- Congenital bronchiectasis
- Ectopic tissue in lung
- Hypoplasia and dysplasia of lung
- Other congenital malformations of lung
- Congenital malformation of lung, unspecified
- Anomaly of pleura
- Congenital cyst of mediastinum
- Other specified congenital malformations of respiratory system
- Congenital malformation of respiratory system, unspecified
- Cleft hard palate
- Cleft soft palate
- Cleft uvula
- Cleft palate, unspecified
- Cleft lip
- Cleft palate with cleft lip

XVII.I.VI Musculoskeletal

- Congenital Deformities Of The Hip
- Congenital Deformities Of The Feet
- Congenital Musculoskeletal Deformities Of Head, Face, Spine And Chest
- Congenital Musculoskeletal Deformities Of Arm, Leg, Long Bones
- Polydactyly
- Syndactyly
- Reduction Defects Of The Upper Limb
- Reduction Defects Of The Lower Limb

- Reduction Defects Of Unspecified Limb
- Other Congenital Malformations Of Limbs (Shoulder Girdle, Knee, Arthrogryposis)
- Other Congenital Malformations Of The Skull And Face Bones
- Craniosynostosis
- Congenital Malformations Of The Spine And Bony Thorax
- Congenital Malformations Of The Musculoskeletal System, Not Elsewhere Classified
- Congenital Diaphragmatic Hernia
- Exomphalos
- Congenital dislocation of hip, unilateral
- Congenital dislocation of hip, bilateral
- Congenital dislocation of hip, unspecified
- Congenital subluxation of hip, unilateral
- Congenital subluxation of hip, bilateral
- Congenital subluxation of hip, unspecified
- Unstable hip
- Other congenital deformities of hip
- Congenital deformity of hip, unspecified
- Talipes equinovarus
- Talipes calcaneovarus
- Metatarsus varus
- Other congenital varus deformities of feet
- Talipes calcaneovalgus
- Congenital pes planus
- Other congenital valgus deformities of feet
- Pes cavus
- Other congenital deformities of feet
- Congenital deformity of feet, unspecified
- Facial asymmetry
- Compression facies
- Dolichocephaly
- Plagiocephaly
- Other congenital deformities of skull, face and jaw
- Congenital deformity of spine
- Pectus excavatum
- Pectus carinatum
- Other congenital deformities of chest
- Congenital deformity of sternocleidomastoid muscle
- Congenital deformity of hand
- Congenital deformity of knee
- Congenital bowing of femur
- Congenital bowing of tibia and fibula
- Congenital bowing of long bones of leg, unspecified
- Other specified congenital musculoskeletal deformities

- Accessory finger(s)
- Accessory thumb(s)
- Accessory toe(s)
- Polydactyly, unspecified
- Fused fingers
- Webbed fingers
- Fused toes
- Webbed toes
- Polysyndactyly
- Syndactyly, unspecified
- Congenital complete absence of upper limb(s)
- Congenital absence of upper arm and forearm with hand present
- Congenital absence of both forearm and hand
- Congenital absence of hand and finger(s)
- Longitudinal reduction defect of radius
- Longitudinal reduction defect of ulna
- Lobster-claw hand
- Other reduction defects of upper limb(s)
- Reduction defect of upper limb, unspecified
- Congenital complete absence of lower limb(s)
- Congenital absence of thigh and lower leg with foot present
- Congenital absence of both lower leg and foot
- Congenital absence of foot and toe(s)
- Longitudinal reduction defect of femur
- Longitudinal reduction defect of tibia
- Longitudinal reduction defect of fibula
- Split foot
- Other reduction defects of lower limb(s)
- Reduction defect of lower limb, unspecified
- Congenital absence of unspecified limb(s)
- Phocomelia, unspecified limb(s)
- Other reduction defects of unspecified limb(s)
- Other congenital malformations of upper limb(s), including shoulder girdle
- Congenital malformation of knee
- Other congenital malformations of lower limb(s), including pelvic girdle
- Arthrogryposis multiplex congenital
- Other specified congenital malformations of limb(s)
- Unspecified congenital malformation of limb(s)
- Craniosynostosis
- Craniofacial dysostosis
- Hypertelorism
- Macrocephaly
- Mandibulofacial dysostosis syndrome
- Oculomandibular dysostosis
- Other specified congenital malformations of skull and face bones

- Congenital malformation of skull and face bones, unspecified
- Spina bifida occulta
- Klippel-Feil syndrome
- Congenital spondylolisthesis
- Congenital spondylolysis
- Congenital scoliosis due to congenital bony malformation
- Other congenital malformations of spine, not associated with scoliosis
- Cervical rib
- Other congenital malformations of ribs
- Congenital malformation of sternum
- Other congenital malformations of bony thorax
- Congenital malformation of bony thorax, unspecified
- Achondrogenesis
- Thanatophoric short stature
- Short rib syndrome
- Chondrodysplasia punctate
- Achondroplasia
- Dystrophic dysplasia
- Chondroectodermal dysplasia
- Spondyloepiphyseal dysplasia
- Other osteochondrodysplasia with defects of growth of tubular bones and spine
- Osteochondrodysplasia with defects of growth of tubular bones and spine, unspecified
- Osteogenesis imperfect
- Polyostotic fibrous dysplasia
- Osteopetrosis
- Progressive diaphyseal dysplasia
- Enchondromatosis
- Metaphyseal dysplasia
- Multiple congenital exostoses
- Other specified osteochondrodysplasias
- Osteochondrodysplasia, unspecified
- Congenital diaphragmatic hernia
- Other congenital malformations of diaphragm
- Exomphalos
- Prune belly syndrome
- Other congenital malformations of abdominal wall
- Ehlers-Danlos syndrome
- Other congenital malformations of musculoskeletal system
- Congenital malformation of musculoskeletal system, unspecified

XVII.I.VII Other Major Single Anomaly

- Congenital Anomalies Of Neck Region
- Fetal Alcohol Syndrome (Dysmorphic)

- Congenital malformations of intestinal fixation
- Congenital Malformations Of The Gallbladder, Bile Ducts And Liver
- Atresis Of The Bile Ducts
- Sinus, fistula and cyst of branchial cleft
- Preauricular sinus and cyst
- Other branchial cleft malformations
- Webbing of neck
- Macrostomia
- Microstomia
- Macrocheilia
- Microcheilia
- Other specified congenital malformations of face and neck
- Congenital malformation of face and neck, unspecified
- Congenital malformations of palate, not elsewhere classified
- Other congenital malformations of mouth
- Pharyngeal pouch
- Other congenital malformations of pharynx
- Atresia of oesophagus without fistula
- Atresia of oesophagus with tracheo-oesophageal fistula
- Congenital tracheo-oesophageal fistula without atresia
- Congenital stenosis and stricture of oesophagus
- Oesophageal web
- Congenital dilatation of oesophagus
- Diverticulum of oesophagus
- Other congenital malformations of oesophagus
- Congenital malformation of oesophagus, unspecified
- Congenital hypertrophic pyloric stenosis
- Congenital hiatus hernia
- Other specified congenital malformations of stomach
- Congenital malformation of stomach, unspecified
- Other specified congenital malformations of upper alimentary tract
- Congenital malformation of upper alimentary tract, unspecified
- Meckel's diverticulum
- Agenesis, aplasia and hypoplasia of gallbladder
- Other congenital malformations of gallbladder
- Atresia of bile ducts
- Congenital stenosis and stricture of bile ducts
- Choledochal cyst
- Other congenital malformations of bile ducts
- Congenital malformations of adrenal gland
- Congenital malformations of the oesophagus
- Atresia of oesophagus without fistula

XVII.II **Canadian infants pre-2010**

Additional congenital anomalies data were entered as free text. Each free text entry was reviewed and assigned to the category in which the closest matching International Classification of Diseases 10 code was allocated.

XVII.II.I Cardiac:

- Anomaly of artery or vein, NEC
- Atresia/Stenosis of pulmonary artery
- Atrial septal defect
- Cardiomegaly
- Defect of foramen ovale
- Ostium secundum type atrial septal defect
- Other anomalies of circulatory system
- Other anomaly of heart
- Parachute deformity of mitral valve
- Persistent ductus arteriosus
- Ventricular septal defect

XVII.II.II Central Nervous System

- Hemianencephaly
- Microcephalus
- Other anomalies of brain
- Other anomalies of spinal cord

XVII.II.III Genitourinary and renal

- Agenesis or hypoplasia of kidney(s)
- Congenital hydroureter
- Hypospadias or epispadias
- Multicystic kidney
- Other anomalies of bladder and urethra
- Other anomalies of kidney
- Other anomalies of ureter
- Renal dysplasia or dysgenesis
- Unspecified obstructive defect of renal pelvis and ureter

XVII.II.IV Pulmonary/Airways

- Agenesis, hypoplasia, and dysplasia of lung
- Other anomalies of larynx, trachea, and bronchus
- Stridor, laryngeal, congenital

XVII.II.V Musculoskeletal

- Asymmetry of face
- Cleft lip
- Club foot, unspecified
- Congenital dislocation of hip
- Congenital sternomastoid torticollis
- Generalized flexion contractures of lower limb joints, congenital
- Hemivertebra
- Other anomalies of face and neck
- Other anomalies of lower limb, including pelvic girdle
- Other anomalies of ribs and sternum
- Other anomaly of upper limb
- Plagiocephaly
- Polydactyly
- Syndactyly
- Talipes equinovarus

XVII.II.VI Other single major anomaly

- Accessory spleen
- Congenital diverticulum of colon
- Congenital splenomegaly
- Gastrointestinal vessel anomaly
- Malrotation of cecum or colon
- Meckel's diverticulum
- Microcolon
- Other anomalies of gallbladder, bile ducts, and liver
- Other specified anomalies
- Situs inversus

XVII.III British and Irish infants

Additional anomalies data were recorded on the BAPS-CASS forms as free text, and coded on entry into the customised database as multiple, bowel atresia/volvulus (duodenum, ileum, colon, jejunum), renal, cardiac, biliary atresia, cranial/brain/neurological, talipes, chromosomal (trisomy), Meckel's diverticulum, undescended testis or other. Biliary atresia and Meckel's diverticulum were recoded as 'other single major anomaly', talipes as a 'musculoskeletal anomaly', and

cranial/brain/neurological as a ‘central nervous system anomaly’. If anomalies were coded as ‘other’ the free text description was reviewed and the anomaly recoded to an appropriate category. Intestinal atresia and undescended testis were not included as additional chromosomal or structural anomalies

Appendix 18: *Assumption checking in statistical analyses*

XVIII.I Number of severe gastrointestinal complications

Negative binomial regression analyses were utilised for investigating the association between reduction and closure strategies and number of severe gastrointestinal complications, as the outcome data were over-dispersed count data, as evidenced by a mean of 0.143, standard deviation of 0.485, and a Chi^2 value of 110.32 for the likelihood ratio test of alpha=0.

XVIII.II Number of operations

Poisson regression analyses were used for investigating the association between reduction and closure strategies and number of severe gastrointestinal complications, as the outcome data were count data without any evidence of under or over-dispersion, as evidenced by a mean of 2.72 and a standard deviation of 0.81.

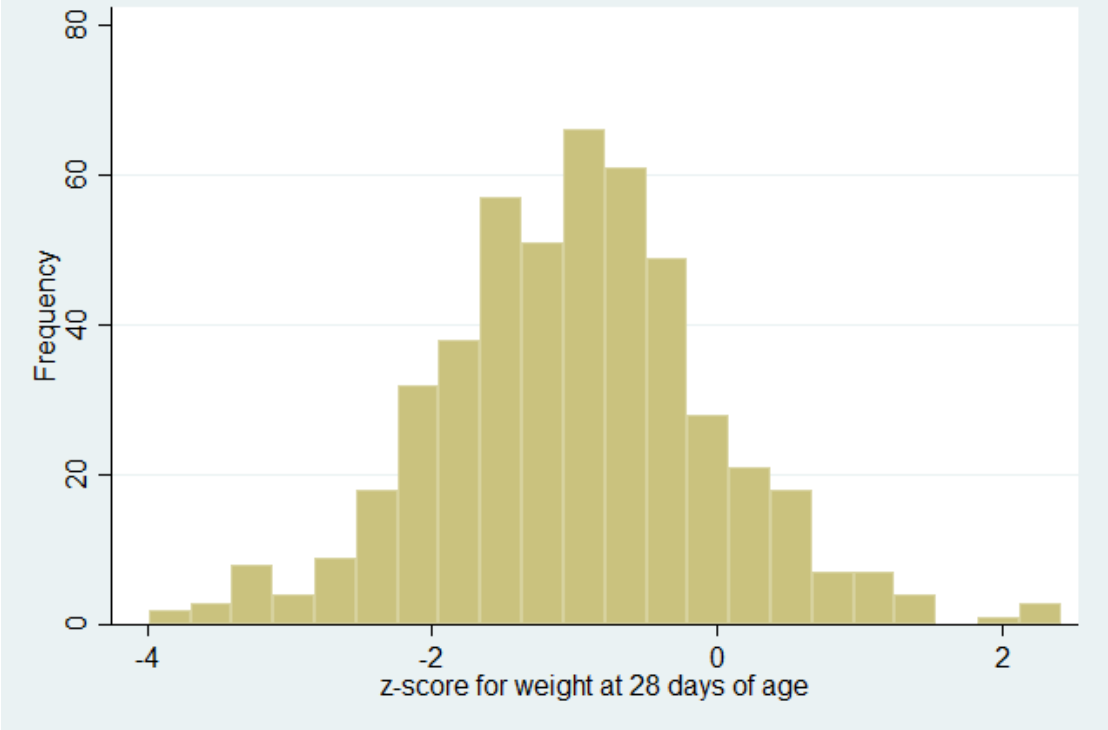
XVIII.III Number of episodes of infection

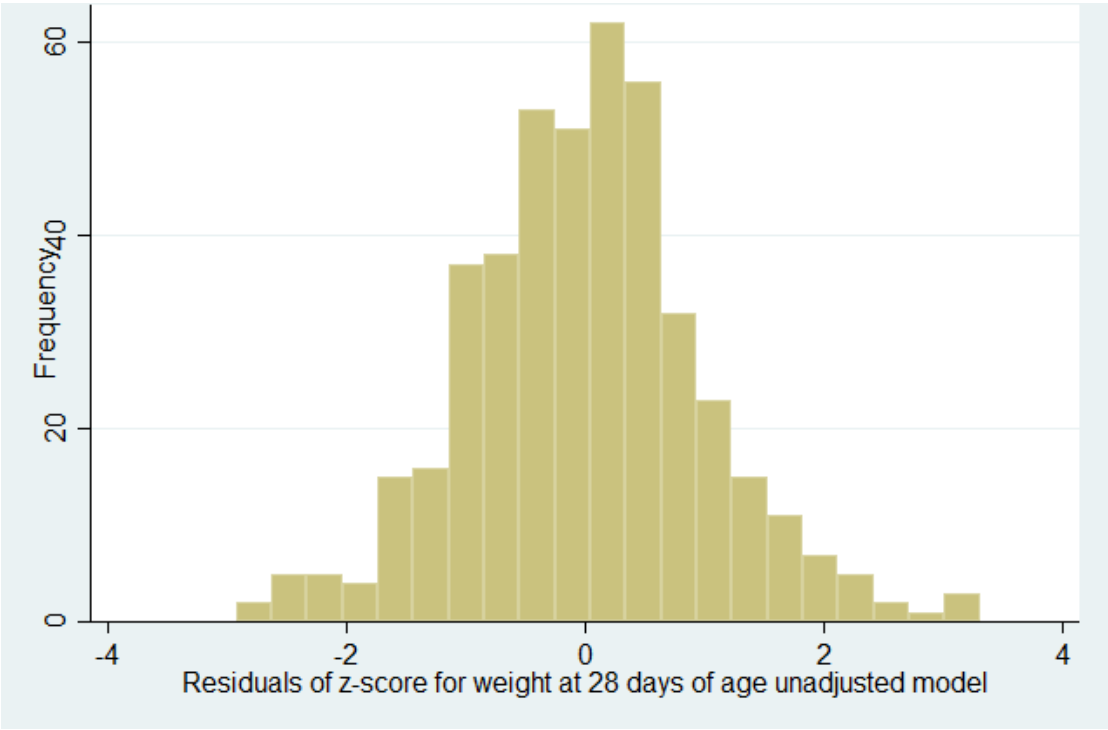
Negative binomial regression analyses were utilised for investigating the association between reduction and closure strategies and number of episodes of infection, as the outcome data were over-dispersed count data, as evidenced by a mean of 0.23, standard deviation of 0.61, and a Chi^2 value of 59.32 for the likelihood ratio test of alpha=0.

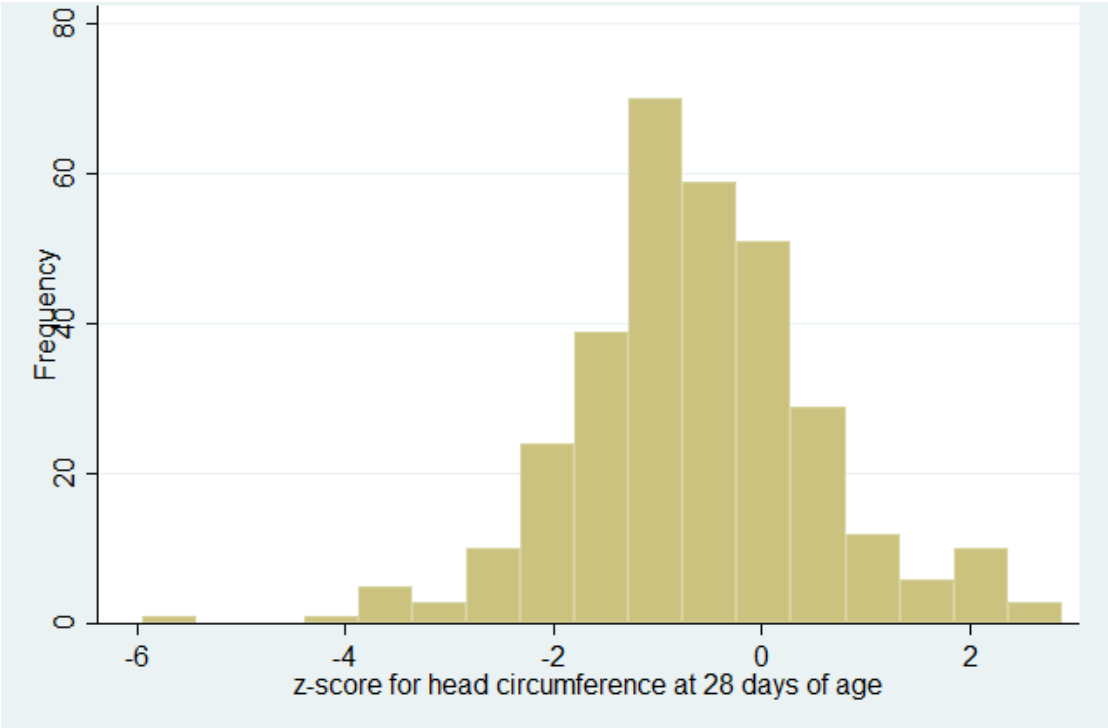
XVIII.IV Z-score for weight and head circumference at 28 days of age

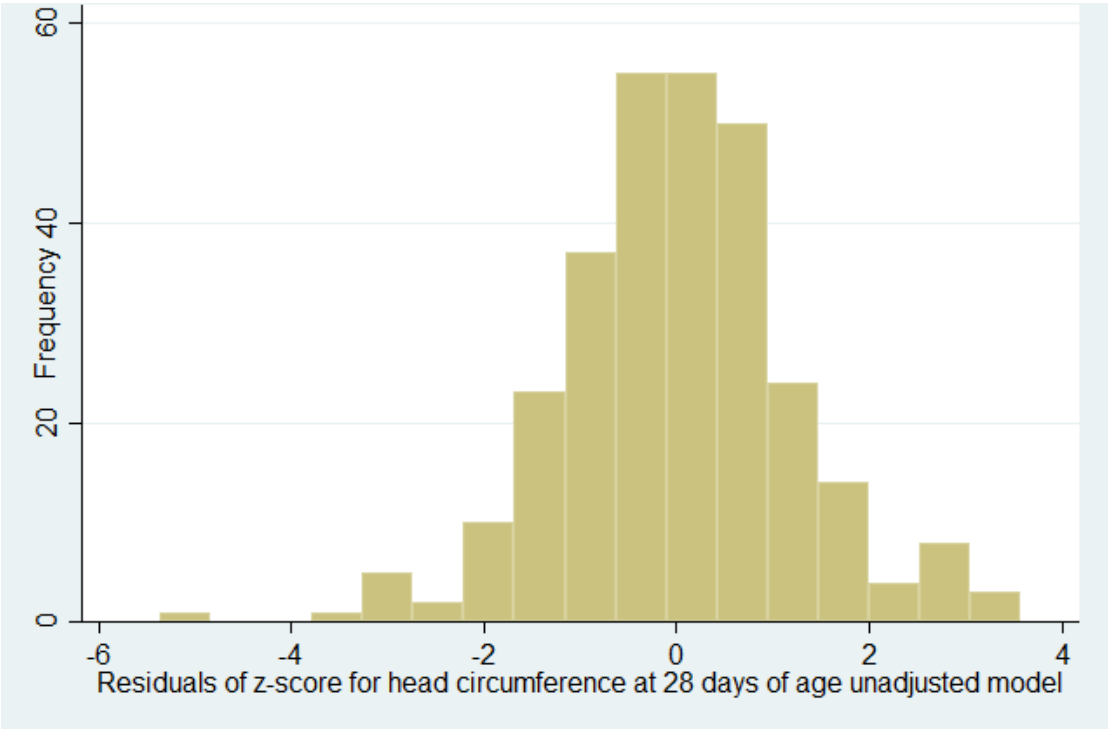
Both weight and head circumference at 28 days of age were normally distributed continuous data and therefore linear regression analyses were used for investigating

their association with number of severe gastrointestinal complications. See figures below for histograms of z-score frequency for each outcome, and residual frequency for each outcome produced from the univariable linear regression analysis investigating association between reduction and closure strategy, and the outcome of interest.




Frequency
0
20
40
60
-4
-2
0
2
4
Residuals of z-score for weight at 28 days of age unadjusted model


Frequency
0
20
40
60
80
-6
-4
-2
0
2
z-score for head circumference at 28 days of age


0
20
40
60
Frequency
-6
-4
-2
0
2
4
Residuals of z-score for head circumference at 28 days of age unadjusted model

Appendix 19: *Investigating whether missing CAPSNet-CNN links affected the conclusions of the study*

XIX.I Methods

Characteristics of Canadian infants with and without linkage established between CAPSNet and CNN data were described. Patient characteristics associated with the number of severe gastrointestinal complications experienced by an infant in the first 28 days of life were investigated using univariable negative binomial regression analysis in the cohort of infants in whom CAPSNet-CNN linkage had been established, with a subsequent multivariable model developed according to the same methodology as the primary analysis. Investigation of the impact of reduction and closure strategy, and country of treatment on core outcomes at 28 days of age were also investigated in the sub-group of infants in whom CAPSNet-CNN linkage had been established. Co-variate adjusted models were adjusted for the patient factors identified as associated with number of severe gastrointestinal complications in the linked cohort only. The outcomes *number of episodes of infection, z-score for weight at 28 days of age,* and *z-score for head circumference at 28 days of age* were not investigated in the sub-group analysis, as data for these outcomes is only available for infants with a link to CNN data, and therefore the sub-group represents the same population as the primary analysis.

XIX.II Characteristics of the linked and unlinked infants

Those infants whose data could not be linked were more likely to be born between 2009 and 2012, more likely to have been transferred in to a paediatric surgical centre, and less likely to have been delivered by caesarean section. Differences in operative strategy also existed between the two groups, with unlinked infants more likely to have undergone OPFC than those whose data were linked (Table 55).

Congenital anomaly data were derived from CNN variables only, and therefore no comparison of rates of additional chromosomal or structural anomalies was undertaken.

Table 55: Comparison of characteristics of Canadian infants in whom linkage to CNN data was and wasn't possible

	Canadian infants without a CNN link	Canadian infants with a CNN link	
	N=227	N=980	
	Median (IQR)	Median (IQR)	p-value
Gestational age at birth			0.047
Completed weeks	36 (35-37)	36 (35-37)	
Birthweight			0.071
Grams	2570 (2220-2890)	2500 (2180-2850)	
	n(%)	n(%)	p-value
Reporting year			<0.001
2005-2008	55 (24.3%)	323 (33.0%)	
2009-2012	165 (73.0%)	299 (30.5%)	
2013-2016	6 (2.7%)	358 (36.5%)	
Transferred in to surgical centre			0.006
No	116 (51.1%)	597 (61.0%)	
Yes	111 (48.9%)	381 (39.0%)	
Antenatal diagnosis			0.083
No	0 (0.0%)	13 (1.4%)	
Yes	212 (100.0%)	913 (98.6%)	
Maternal age			0.31
<25	128 (63.4%)	532 (65.9%)	
25-34	71 (35.1%)	251 (31.1%)	
35 and above	3 (1.5%)	24 (3.0%)	
Caesarean section delivery			0.012
No	35 (85.4%)	648 (66.6%)	
Yes	6 (14.6%)	325 (33.4%)	
Ethnicity			0.7
White	102 (72.3%)	437 (70.7%)	
Other	39 (27.7%)	181 (29.3%)	
Sex			0.73
Male	113 (51.4%)	513 (52.7%)	
Female	107 (48.6%)	461 (47.3%)	
Small for gestational age at birth			0.72
No	183 (84.3%)	811 (83.4%)	
Yes	34 (15.7%)	162 (16.6%)	
Necrosis at admission			0.34
No	171 (97.7%)	876 (96.3%)	
Yes	4 (2.3%)	34 (3.7%)	

*Percentage of those with complete data

Table 55: Comparison of characteristics of Canadian infants in whom linkage to CNN data was and wasn't possible - Continued

	Canadian infants without a CNN link	Canadian infants with a CNN link	
	N=227	N=980	p-value
Intestinal atresia			0.29
No	203 (91.9%)	843 (89.5%)	
Yes	18 (8.1%)	99 (10.5%)	
Intestinal perforation			0.68
No	169 (97.1%)	884 (96.5%)	
Yes	5 (2.9%)	32 (3.5%)	
Intestinal Matting			0.97
None	74 (43.0%)	398 (43.6%)	
Mild	73 (42.4%)	387 (42.4%)	
Severe	25 (14.5%)	127 (13.9%)	
APGAR score at five minutes			0.66
≥7	178 (85.2%)	846 (87.4%)	
4-6	26 (12.4%)	100 (10.3%)	
0-3	5 (2.4%)	22 (2.3%)	
First attempted reduction/closure procedure			<0.001
OPFC	124 (56.1%)	344 (36.6%)	
Operative primary reduction, sutureless closure	12 (5.4%)	59 (6.3%)	
Silo placement and staged reduction	64 (29.0%)	395 (42.1%)	
Mesh	3 (1.4%)	2 (0.2%)	
WBR	18 (8.1%)	139 (14.8%)	

* Percentage of those with complete data

XIX.III **Association of patient factors with complications**

There were 1224 infants (89%) who experienced no severe gastrointestinal complications in the first 28 days of life, 108 (8%) who experienced one, 28 (2%) who experienced two, and 12 (1%) who experienced three or more.

With the exception of ethnicity, the same factors as in the primary model met criteria for assessment in the multivariable model (Table 56) However, in addition to the four factors, gestational age at birth, birth weight, intestinal perforation and intestinal atresia that were retained in the primary model, year of birth was also retained in the sensitivity analysis model. Following adjustment in the multivariable model, relationships between the retained patient characteristics and number of severe gastrointestinal complications were clinically similar to the relationships described in the primary model (Table 57).

Table 56: Association of patient factors with number of severe gastrointestinal complications in the first 28 days of life – excluding Canadian infants without a CAPSNet-CNN link

	Number of severe gastrointestinal complications							
	0	1	2	≥3				
	N=1224	N=108	N=28	N=12				
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Unadjusted IRR (95% CI)	p-value	Adjusted IRR (95% CI)	p-value
Gestational Age at Birth						0.001		
Completed weeks	36 (35-37)	36 (34-37)	36 (35-36.5)	36 (35-37)	0.85 (0.77-0.9) per week increase		0.96 (0.86-1.1) per week increase	0.441
Birthweight						<0.001		
Grams	2490 (2166-2810)	2280 (1915-2620)	2210 (1670-2420)	2243 (2000-2600)	0.96 (0.95-0.98) per 50g increase		0.97 (0.95-0.99) per 50g increase	0.002
	n(%)*	n(%)*	n(%)*	n(%)*	Unadjusted IRR (95% CI)	p-value	Adjusted IRR (95% CI)	p-value
Reporting year						0.01		
2005-2008	623 (50.9%)	65 (60.2%)	18 (64.3%)	9 (75.0%)	Ref.		Ref.	
2009-2012	274 (22.4%)	20 (18.5%)	2 (7.1%)	3 (25.0%)	0.6 (0.4-0.9)		0.5 (0.3-0.9)	0.02
2013-2016	327 (26.7%)	23 (21.3%)	8 (28.6%)	0 (0.0%)	0.6 (0.4-0.9)		0.7 (0.4-1.1)	0.1
Country of treatment						<0.001		
British Isles	331 (27.0%)	41 (38.0%)	13 (46.4%)	7 (58.3%)	Ref.		Not retained	
Canada	893 (73.0%)	67 (62.0%)	15 (53.6%)	5 (41.7%)	0.5 (0.3-0.7)			
Transferred in to surgical centre						0.6		
No	756 (61.9%)	76 (71.0%)	16 (57.1%)	4 (33.3%)	Ref.		Not retained	
Yes	466 (38.1%)	31 (29.0%)	12 (42.9%)	8 (66.7%)	1.1 (0.8-1.6)			

* Percentage of those with complete data
IRR – Incidence Rate Ratio

Table 56: Association of patient factors with number of severe gastrointestinal complications in the first 28 days of life – excluding Canadian infants without a CAPSNet-CNN link - Continued

	Number of severe gastrointestinal complications							
	0	1	2	≥3				
	N=1224	N=108	N=28	N=12				
	n(%)*	n(%)*	n(%)*	n(%)*	Unadjusted IRR (95% CI)	p-value	Adjusted IRR (95% CI)	p-value
Antenatal diagnosis						0.6		
No	15 (1.3%)	2 (1.9%)	1 (3.8%)	0 (0.0%)	Ref.		Not retained	
Yes	1156 (98.7%)	105 (98.1%)	25 (96.2%)	12 (100.0%)	0.7 (0.2-2.7)			
Maternal age						0.4		
<25	727 (68.5%)	61 (67.8%)	14 (63.6%)	11 (91.7%)	1.2 (0.8-1.8)		Not retained	
25-34	307 (28.9%)	27 (30.0%)	8 (36.4%)	1 (8.3%)	Ref.			
35 and above	28 (2.6%)	2 (2.2%)	0 (0.0%)	0 (0.0%)	0.5 (0.1-2.6)			
Caesarean Section Delivery						0.5		
No	797 (65.6%)	64 (59.3%)	16 (59.3%)	9 (75.0%)	Ref.		Not retained	
Yes	418 (34.4%)	44 (40.7%)	11 (40.7%)	3 (25.0%)	1.2 (0.8-1.7)			
Ethnicity						0.3		
White	689 (77.5%)	69 (93.2%)	12 (63.2%)	9 (81.8%)	Ref.		Not retained	
BME	200 (22.5%)	5 (6.8%)	7 (36.8%)	2 (18.2%)	0.7 (0.4-1.3)			
Sex						0.5		
Male	619 (50.9%)	51 (47.2%)	13 (46.4%)	6 (50.0%)	Ref.		Not retained	
Female	598 (49.1%)	57 (52.8%)	15 (53.6%)	6 (50.0%)	1.1 (0.8-1.6)			

* Percentage of those with complete data
IRR – Incidence Rate Ratio
BME – Black or minority ethnicity

Table 56: Association of patient factors with number of severe gastrointestinal complications in the first 28 days of life – excluding Canadian infants without a CAPSNet-CNN link - Continued

	Number of severe gastrointestinal complications							
	0	1	2	≥3				
	N=1224	N=108	N=28	N=12				
	n(%)*	n(%)*	n(%)*	n(%)*	Unadjusted IRR (95% CI)	p-value	Adjusted IRR (95% CI)	p-value
SGA at birth						0.6		
No	973 (80.1%)	87 (80.6%)	18 (66.7%)	10 (83.3%)	Ref.		Not retained	
Yes	241 (19.9%)	21 (19.4%)	9 (33.3%)	2 (16.7%)	1.1 (0.7-1.7)			
Additional chromosomal or structural congenital anomaly						0.7		
No	993 (84.2%)	82 (81.2%)	23 (88.5%)	10 (83.3%)	Ref.		Not retained	
Yes	186 (15.8%)	19 (18.8%)	3 (11.5%)	2 (16.7%)	1.1 (0.7-1.8)			
APGAR score at five minutes						0.6		
≥7	1059 (88.5%)	92 (89.3%)	22 (84.6%)	12 (100.0%)	Ref.		Not retained	
04-Jun	111 (9.3%)	11 (10.7%)	3 (11.5%)	0 (0.0%)	0.9 (0.5-1.7)			
0-3	27 (2.3%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0.5 (0.1-2.4)			
Necrosis at admission						0.002		
No	1119 (97.5%)	88 (90.7%)	22 (84.6%)	10 (90.9%)	Ref.		Not retained	
Yes	29 (2.5%)	9 (9.3%)	4 (15.4%)	1 (9.1%)	3.4 (1.6-7.6)			
Matting						0.02		
None	518 (45.7%)	41 (43.6%)	7 (26.9%)	5 (45.5%)	Ref.		Not retained	
Mild	493 (43.5%)	36 (38.3%)	12 (46.2%)	3 (27.3%)	1.0 (0.7-1.6)			
Severe	122 (10.8%)	17 (18.1%)	7 (26.9%)	3 (27.3%)	2.1 (1.2 -3.6)			

*Percentage of those with complete data
IRR – Incidence rate ratio
SGA – Small for gestational age

Table 56: Association of patient factors with number of severe gastrointestinal complications in the first 28 days of life – excluding Canadian infants without a CAPSNet-CNN link - Continued

	Number of severe gastrointestinal complications							
	0	1	2	≥3				
	N=1224	N=108	N=28	N=12				
	n(%)*	n(%)*	n(%)*	n(%)*	Unadjusted IRR (95% CI)	p-value	Adjusted IRR (95% CI)	p-value
Intestinal atresia						<0.001		
No	1078 (91.3%)	78 (75.0%)	17 (65.4%)	8 (66.7%)	Ref.		Ref.	
Yes	103 (8.7%)	26 (25.0%)	9 (34.6%)	4 (33.3%)	3.3 (2.1-5.2)		2.3 (1.4-3.7)	0.001
Perforation						<0.001		
No	1131 (97.8%)	89 (88.1%)	22 (84.6%)	7 (63.6%)	Ref.		Ref.	
Yes	26 (2.2%)	12 (11.9%)	4 (15.4%)	4 (36.4%)	5.4 (2.8-10.6)		4.4 (2.2-8.9)	<0.001
Complex gastroschisis (94)						<0.001		
Simple	1014 (82.8%)	67 (62.0%)	15 (53.6%)	5 (41.7%)	Ref.		Not retained#	
Complex	122 (10.0%)	33 (30.6%)	11 (39.3%)	6 (50.0%)	4.0 (2.6 -6.0)			
Unknown	88 (7.2%)	8 (7.4%)	2 (7.1%)	1 (8.3%)	1.4 (0.7-2.7)			
Grade of surgeon						0.3		
Consultant	445 (51.3%)	26 (41.9%)	7 (50.0%)	4 (80.0%)	Ref.		Not retained	
Trainee	316 (36.4%)	22 (35.5%)	4 (28.6%)	1 (20.0%)	0.9 (0.5-1.5)			
Consultant and Trainee	106 (12.2%)	14 (22.6%)	3 (21.4%)	0 (0.0%)	1.5 (0.8-2.9)			

*Percentage of those with complete data
Not assessed for inclusion in multivariable model, as composite of other characteristics
IRR – Incidence rate ratio

Table 57: Comparison of primary multivariable model and model developed excluding Canadian infants in whom a link to CNN data was not possible

	All infants		CNN Linked only	
	Adjusted IRR (95% CI)	**p-value**	**Adjusted IRR (95% CI)**	**p-value**
Gestational age at birth		0.5		
Per completed week increase	0.97 (0.88-1.10)		0.96 (0.86-1.1)	0.441
Birthweight		<0.001		
Per 50g increase	0.96 (0.95-0.98)		0.97 (0.95-0.99)	0.002
Intestinal atresia		<0.001		
No	Ref.		Ref.	
Yes	2.36 (1.50-3.71)		2.3 (1.4-3.7)	0.001
Intestinal perforation		<0.001		
No	Ref.		Ref.	
Yes	3.75 (1.96-7.15)		4.4 (2.2-8.9)	<0.001
Reporting year grouped				
2005-2008			Ref.	
2009-2012	Not retained in multi-variable model		0.5 (0.3-0.9)	0.02
2013-2016			0.7 (0.4-1.1)	0.1

IRR – Incidence Rate Ratio

XIX.IV Reduction and closure excluding unlinked infants

XIX.IV.I First reduction and closure strategies

Excluding the 227 infants in whom linkage between CAPSNet and CNN data were not possible, there were 547 (40%) who underwent OPFC, 533 (39%) who underwent SR, 165 (12%) who underwent WBR, 84 (6%) who underwent other first reduction and closure procedures, and 44 (3%) who were missing information on the first reduction and closure procedure.

XIX.IV.II Association with core outcomes at 28 days of age

There were no clinically or statistically significant differences between the estimates of effect calculated in the primary analysis and those calculated in the sub-group analysis excluding infants in whom a link could not be established between CAPSNet and CNN data. Full results of the analysis are presented in Table 58.

Table 58: Core outcomes at or up to 28 days of age in each reduction and closure group excluding Canadian infants in whom a link to CNN data was not possible

	OPFC	SR	WBR	Crude estimate of treatment effect in comparison to OPFC				Propensity score and covariate# adjusted estimate of treatment effect in comparison to OPFC			
	N=547	N=533	N=165	SR		WBR		SR		WBR	
	n(%)*	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Severe gastrointestinal complications											
None	477 (87.4%)	487 (91.4%)	149 (90.3%)								
One	53 (9.7%)	34 (6.4%)	10 (6.1%)	0.75 (0.50-1.12)	0.157	0.86 (0.48-1.53)	0.597	0.72 (0.45-1.12)	0.183	1.61 (0.81-3.22)	0.174
Two	12 (2.2%)	8 (1.5%)	5 (3.0%)								
Three or more	4 (0.7%)	4 (0.8%)	1 (0.6%)								
Operations											
One	0 (0.0%)	1 (0.2%)	0 (0.0%)								
Two	376 (70.4%)	6 (1.2%)	48 (29.3%)	1.34 (1.25 – 1.44)	<0.001	1.16 (1.04-1.29)	0.007	1.33 (1.22-1.46)	<0.001	1.16 (1.02-1.32)	0.022
Three	124 (23.2%)	426 (84.0%)	110 (67.1%)								
Four or more	34 (6.4%)	74 (14.6%)	6 (3.7%)								
	n(%)*	n(%)*	n(%)*	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Mortality											
No	536 (98.2%)	521 (98.3%)	157 (96.9%)	0.93 (0.37 – 2.30)	0.868	1.71 (0.57-5.07)	0.335	1.03 (0.33-3.16)	0.961	1.43 (0.38-5.29)	0.597
Yes	10 (1.8%)	9 (1.7%)	5 (3.1%)								

*Percentage of those with complete data

IRR – incidence rate ratio, OR- Odds ratio, 95% CI – 95% Confidence Interval

OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

Table 58: Core outcomes at or up to 28 days of age in each reduction and closure group excluding Canadian infants in whom a link to CNN data was not possible - Continued

	OPFC	SR	WBR	Crude estimate of treatment effect in comparison to OPFC				Propensity score and covariate# adjusted estimate of treatment effect in comparison to OPFC			
	N=671	N=597	N=183	SR		WBR		SR		WBR	
	n(%)*	n(%)*	n(%)*	OR (95% CI)		p-value		OR (95% CI)		p-value	
One or more Infection											
No Yes	460 (84.1%) 87 (15.9%)	426 (80.4%) 104 (19.6%)	144 (87.3%) 21 (12.7%)	1.29 (0.94 – 1.77)	0.111	0.77 (0.46-1.29)	0.320	1.60 (1.10-2.34)	0.015	1.14 (0.62-2.11)	0.668
Liver Disease											
No Yes	501 (95.2%) 25 (4.8%)	512 (99.0%) 5 (1.0%)	160 (99.4%) 1 (0.6%)	0.20 (0.07 -0.52)	<0.001	0.13 (0.02-0.93)	0.042	0.41 (0.14-1.16)	0.094	0.22 (0.03-1.86)	0.164
	Median (IQR)	Median (IQR)	Median (IQR)	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Parenteral nutrition											
Number of days use	26 (17-28)	28 (21-28)	23 (17-28)	1.08 (1.06-1.11)	<0.001	0.96 (0.93-1.00)	0.048	1.06 (1.03-1.10)	<0.001	0.97 (0.93-1.01)	0.155

*Percentage of those with complete data

IRR – incidence rate ratio, OR- Odds ratio, 95% CI – 95% Confidence Interval

OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

Appendix 20: *Additional estimates of effect comparing reduction and closure strategies*

Table 59: Covariate and propensity score alone adjusted estimates of effect for comparison of reduction and closure strategies

	OPFC	SR	WBR	Covariate adjusted estimate of treatment effect				Propensity score adjusted estimate of treatment effect			
	N=671	N=597	N=183	SR		WBR		SR		WBR	
	n(%)*	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Severe gastrointestinal complications											
None	586 (87.5)	549 (92.0%)	164 (89.6%)	0.79 (0.54-1.16)	0.221	0.79 (0.54-1.16)	0.221	0.79 (0.54-1.16)	0.221	0.79 (0.54-1.16)	0.221
One	67 (10.0%)	35 (5.9%)	13 (7.1%)								
Two	13 (1.9%)	9 (1.5%)	5 (2.7%)								
Three or more	4 (0.6%)	4 (0.7%)	1 (0.5%)								
Operations											
One	0 (0.0%)	1 (0.2%)	0 (0.0%)	1.4 (1.3-1.5)	<0.001	1.4 (1.3-1.5)	<0.001	1.4 (1.3-1.5)	<0.001	1.4 (1.3-1.5)	<0.001
Two	461 (71.1%)	6 (1.1%)	64 (35.4%)								
Three	149 (23.0%)	476 (83.4%)	111 (61.3%)								
Four or more	38 (5.9%)	88 (15.4%)	6 (3.3%)								
infections											
None	286 (83.1%)	317 (80.3%)	120 (86.3%)	1.12 (0.79-1.62)	0.495	1.12 (0.79-1.62)	0.495	1.12 (0.79-1.62)	0.495	1.12 (0.79-1.62)	0.495
One	46 (13.4%)	61 (15.4%)	14 (10.1%)								
Two	9 (2.6%)	14 (3.5%)	5 (3.6%)								
Three or more	3 (0.9%)	3 (0.8%)	0 (0.0%)								
	n(%)*	n(%)*	n(%)*	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Mortality											
No	657 (98.1%)	582 (98.1%)	175 (97.2%)	0.9 (0.4-2.2)	0.9	0.9 (0.4-2.2)	0.9	0.9 (0.4-2.2)	0.9	0.9 (0.4-2.2)	0.9
Yes	13 (1.9%)	11 (1.9%)	5 (2.8%)								

*Percentage of those with complete data

IRR – incidence rate ratio, OR- Odds ratio, 95% CI – 95% Confidence Interval

OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

Table 59: Covariate and propensity score alone adjusted estimates of effect for comparison of reduction and closure strategies - Continued

	OPFC	SR	WBR	Covariate adjusted estimate of treatment effect				Propensity score adjusted estimate of treatment effect			
	N=671	N=597	N=183	SR	WBR	SR	WBR				
	n(%)*	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Infection in first 28 days											
No	460 (84.1%)	426 (80.4%)	144 (87.3%)	1.36 (0.98-1.87)	0.065	1.36 (0.98-1.87)	0.065	1.36 (0.98-1.87)	0.065	1.36 (0.98-1.87)	0.065
Yes	87 (15.9%)	104 (19.6%)	21 (12.7%)								
Liver Disease											
No	610 (95.8%)	568 (99.1%)	173 (97.7%)	0.2 (0.1-0.6)	0.002	0.2 (0.1-0.6)	0.002	0.2 (0.1-0.6)	0.002	0.2 (0.1-0.6)	0.002
Yes	27 (4.2%)	5 (0.9%)	4 (2.3%)								
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**	**Difference in z-score (95% CI)**	**p-value**	**Difference in z-score (95% CI)**	**p-value**	**Difference in z-score (95% CI)**	**p-value**	**Difference in z-score (95% CI)**	**p-value**
Head circumference											
z-score	-0.60(-0.81 to -0.38)	-0.69 (-0.90 to -0.48)	-0.59 (-1.0 to -0.17)	-0.16 (-0.28 to 0.248)	0.9	0.03 (-0.33 to 0.392)	0.9	0.10 (-0.27 to 0.46)	0.601	0.03 (-0.47 to 0.52)	0.918
Weight											
z-score	-0.9 (-1.0 to -0.76)	-1.05 (-1.20 to -0.90)	-1.12 (-1.37 to 0-.86)	-0.06 (-0.018 to 0.065)	0.4	-0.078 (-0.25 to 0.96)	0.4	0.04 (-0.18 to 0.26)	0.712	-0.11 (-0.44 to 0.21)	0.496
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
Parenteral nutrition											
Number of days use	26 (17-28)	28 (21-28)	23 (17-28)	1.10 (1.07 - 1.12)	<0.001	1.10 (1.07 - 1.12)	<0.001	1.10 (1.07 - 1.12)	<0.001	1.10 (1.07 - 1.12)	<0.001

*Percentage of those with complete data

IRR – incidence rate ratio, OR- Odds ratio, 95% CI – 95% Confidence Interval

OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

Appendix 21: *Effect of early deaths on number of severe gastrointestinal complications*

XXI.I Number of severe gastrointestinal complications experienced by infants who died prior to 28 days of age

Of the 29 infants who underwent one of the reduction and closure strategies of interest and who died prior to 28 days of age, 21 (72%) experienced no severe gastrointestinal complications prior to their death, six (21%) experienced one severe gastrointestinal complication prior to their death, none experienced two severe gastrointestinal complications prior to their death, and two (7%) experienced three or more severe gastrointestinal complications prior to their death (Table 60).

Table 60: Number of severe gastrointestinal complications experienced by infants who died in each reduction and closure group

	OPFC	SR	WBR
	N=13 infants	N=11 infants	N=5 infants
Complications experienced prior to death	**n(%)**	**n(%)**	**n(%)**
None	7 (54%)	9 (82%)	5 (100%)
One	5 (38%)	1 (9%)	0 (%)
Two	0 (0%)	0 (%)	0 (%)
Three or more	1 (8%)	1 (9%)	0 (%)

XXI.II Sensitivity analysis assuming all infants who died experienced six complications prior to their death

The maximum number of severe gastrointestinal complications experienced in the first 28 days of life by any infant in the study was six. When the 29 infants who were known to have died prior to 28 days of age were assumed to have experienced six severe gastrointestinal complications prior to their death, there were 16 infants (2.4%) in the OPFC group who experienced three or more severe gastrointestinal complications, 14 (2.3%) in the SR group, and 6 (3.3%) in the WBR group. Assuming that all infants who died prior to 28 days of age experienced six severe gastrointestinal complications prior to their death did not affect the clinical or statistical significance of any of the four estimates of treatment effect on number of severe gastrointestinal complications (Table A21.2 and A21.3).

XXI.III Complications in infants who survived to 28 days of age

In addition to the 29 infants who were confirmed to have died prior to 28 days of age, there were a further nine infants in whom it was not known whether they had died prior to 28 days of age or not. When the primary analysis was repeated following the exclusion of these 38 infants to limit the population to those who were confirmed to have survived to 28 days of age, no clinically or statistically significant changes were seen in any of the estimates of treatment effect on number of severe gastrointestinal complications (Table 61 and 62).

Table 61: Impact of mortalities prior to 28 days of age on number of severe gastrointestinal complications, crude and covariate plus propensity score adjusted estimates of effect

	OPFC	SR	WBR	Crude estimate of treatment effect in comparison to OPFC				Propensity score and covariate# adjusted estimate of treatment effect in comparison to OPFC			
	N=671	N=597	N=183								
	n(%)*	n(%)*	n(%)*	SR		WBR		SR		WBR	
Number of severe gastrointestinal complications				**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
None	586 (87.5%)	549 (92.0%)	164 (89.6%)	0.73 (0.5-1.06)	0.094	0.91 (0.53-1.55)	0.719	0.72 (0.45-1.13)	0.149	1.74 (0.91 - 3.32)	0.093
One	67 (10.0%)	35 (5.9%)	13 (7.1%)								
Two	13 (1.9%)	9 (1.5%)	5 (2.7%)								
Three or more	4 (0.6%)	4 (0.7%)	1 (0.5%)								
Number of severe gastrointestinal complications, six complications pre-death				**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
None	579 (86.4%)	540 (90.5%)	159 (86.9%)	0.83 (0.54-1.28)	0.399	1.49 (0.80 - 2.78)	0.214	0.88 (0.52-1.50)	0.638	1.53 (0.71-3.30)	0.276
One	62 (9.3%)	34 (5.7%)	13 (7.1%)								
Two	13 (1.9%)	9 (1.5%)	5 (2.7%)								
Three or more	16 (2.4%)	14 (2.3%)	6 (3.3%)								
Number of severe gastrointestinal complications in infants who were confirmed to have survived to 28 days of age				**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
None	578 (88.1%)	537 (92.3%)	156 (89.1%)	0.81 (0.55 - 1.21)	0.308	1.33 (0.78-2.26)	0.299	0.72 (0.45-1.15)	0.172	1.89 (0.98-3.63)	0.056
One	62 (9.5%)	33 (5.7%)	13 (7.4%)								
Two	13 (2.0%)	9 (1.5%)	5 (2.9%)								
Three or more	3 (0.5%)	3 (0.5%)	1 (0.6%)								

*Percentage of those with complete data

IRR – incidence rate ratio, OR- Odds ratio, 95% CI – 95% Confidence Interval

OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

Table 62: Impact of mortalities prior to 28 days of age on number of severe gastrointestinal complications, covariate and propensity score alone adjusted estimates of effect

	OPFC	SR	WBR	Covariate# adjusted estimate of effect of treatment in comparison to OPFC				Propensity score adjusted estimate of effect of treatment in comparison to OPFC			
	N=671	N=597	N=183								
	n(%)*	n(%)*	n(%)*	SR		WBR		SR		WBR	
Number of severe gastrointestinal complications				**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
None	586 (87.5%)	549 (92.0%)	164 (89.6%)	0.79 (0.54-1.16)	0.221	1.18 (0.70-2.01)	0.53	0.77 (0.49-1.22)	0.275	1.71 (0.87-3.37)	0.118
One	67 (10.0%)	35 (5.9%)	13 (7.1%)								
Two	13 (1.9%)	9 (1.5%)	5 (2.7%)								
Three or more	4 (0.6%)	4 (0.7%)	1 (0.5%)								
Number of severe gastrointestinal complications, six complications pre-death				**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
None	579 (86.4%)	540 (90.5%)	159 (86.9%)	0.83 (0.54-1.28)	0.399	1.49 (0.80 - 2.78)	0.214	0.96 (0.57 - 1.64)	0.893	1.58 (0.72 - 3.43)	0.251
One	62 (9.3%)	34 (5.7%)	13 (7.1%)								
Two	13 (1.9%)	9 (1.5%)	5 (2.7%)								
Three or more	16 (2.4%)	14 (2.3%)	6 (3.3%)								
Number of severe gastrointestinal complications in infants who were confirmed to have survived to 28 days of age				**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
None	578 (88.1%)	537 (92.3%)	156 (89.1%)	0.81 (0.55 - 1.21)	0.308	1.33 (0.78-2.26)	0.299	0.75 (0.47 - 1.21)	0.24	1.83 (.92-3.62)	0.084
One	62 (9.5%)	33 (5.7%)	13 (7.4%)								
Two	13 (2.0%)	9 (1.5%)	5 (2.9%)								
Three or more	3 (0.5%)	3 (0.5%)	1 (0.6%)								

*Percentage of those with complete data

IRR – incidence rate ratio, OR- Odds ratio, 95% CI – 95% Confidence Interval

OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

Appendix 22: *Outcomes in infants without intestinal necrosis, perforation or matting*

Table 63: Outcomes in infants without intestinal necrosis, perforation or matting, covariate and propensity score adjusted estimates of effect

	OPFC	SR	WBR	Covariate# adjusted estimate of effect of treatment in comparison to OPFC				Propensity score adjusted estimate of effect of treatment in comparison to OPFC			
	N=241	N=202	N=117	SR		WBR		SR		WBR	
	n(%)*	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Severe GI complications											
None	215 (89.2%)	194 (96.0%)	107 (91.5%)	0.32 (0.14-0.75)	0.009	1.09 (0.53-2.25)	0.814	0.29 (0.11-0.75)	0.011	1.39 (0.58-3.36)	0.458
One	21 (8.7%)	8 (4.0%)	5 (4.3%)								
Two	3 (1.2%)	0 (0.0%)	4 (3.4%)								
Three or more	2 (0.8%)	0 (0.0%)	1 (0.9%)								
Operations											
One	0 (0%)	0 (0%)	0 (0%)	1.43 (1.27-1.61)	<0.001	1.22 (1.06-1.41)	0.005	1.39 (1.22-1.59)	<0.001	1.19 (1.01-1.39)	0.037
Two	192 (81.0%)	2 (1.0%)	41 (35.0%)								
Three	39 (16.5%)	168 (86.6%)	72 (61.5%)								
Four or more	6 (2.5%)	24 (12.4%)	4 (3.4%)								
Episodes of infection											
None	107 (86.3%)	93 (77.5%)	75 (86.2%)	1.55 (0.82 - 2.96)	0.179	0.88 (0.41-1.89)	0.735	1.61 (0.79-3.29)	0.192	1.52 (0.63-3.69)	0.349
One	14 (11.3%)	23 (19.2%)	9 (10.3%)								
Two	2 (1.6%)	3 (2.5%)	3 (3.4%)								
Three or more	1 (0.8%)	1 (0.8%)	0 (0.0%)								
	n(%)	n(%)	n(%)	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Infection in first 28 days											
No	180 (87.0%)	149 (81.0%)	92 (87.6%)	1.54 (0.89-2.68)	0.124	0.88 (0.43-1.79)	0.72	2.06 (1.10-3.86)	0.023	1.24 (0.54-2.88)	0.611
Yes	27 (13.0%)	35 (19.0%)	13 (12.4%)								
Liver Disease											
No	215 (95.1%)	193 (99.5%)	110 (97.3%)	0.10 (0.013-0.78)	0.028	0.49 (0.13-1.82)	0.289	0.15 (0.02-1.24)	0.078	0.61 (0.14-2.72)	0.516
Yes	11 (4.9%)	1 (0.5%)	3 (2.7%)								

*Percentage of those with complete data, IRR – incidence rate ratio, OR- Odds ratio, 95% CI – 95% Confidence Interval, OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

Table 63: Outcomes in infants without intestinal necrosis, perforation or matting, covariate and propensity score adjusted estimates of effect - Continued

	OPFC	SR	WBR	Crude estimate of effect of treatment in comparison to OPFC				Propensity score and covariate# adjusted estimate of effect of treatment in comparison to OPFC			
	N=241	N=202	N=117	SR		WBR		SR		WBR	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value
Head circumference											
z score	-0.35 (-2.62 to 1.92)	-.68 (-2.42 to 1.06)	-.46 (-2.30 to 1.38)	-0.21 (-0.60 to 0.17)	0.278	-0.19 (-0.44 to 0.40)	0.927	-0.44 (-0.91 to 0.03)	0.070	-0.17 (-0.70 to 0.36)	0.526
Weight											
z-score	-.87 (-2.87 to 1.13)	-1.04 (-2.49 to 0.41)	-1.17 (-2.80 to 0.46)	-0.11 (-0.32 to 0.10)	0.304	-0.13 (0.36-0.10)	0.278	-0.10 (-0.45 to 0.25)	0.575	-0.25 (-0.64 to 0.14)	0.212
	Median (IQR)	Median (IQR)	Median (IQR)	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Parenteral nutrition											
Number of days use	23 (16-28)	27 (20-28)	22 (16-28)	1.12 (1.07-1.16)	<0.001	1.01 (0.96-1.06)	0.753	1.08 (1.03-1.13)	0.001	0.97 (0.92-1.02)	0.270

IRR – incidence rate ratio, OR- Odds ratio, 95% CI – 95% Confidence Interval, OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

Appendix 23: ***Outcomes in infants with intestinal necrosis,*** *perforation or matting*

Table 64: Outcomes in infants with intestinal necrosis, perforation or matting. Covariate and propensity score alone adjusted estimates of effect

	OPFC	SR	WBR	Covariate adjusted[#] estimate of effect of treatment in comparison to OPFC				Propensity score adjusted estimate of effect of treatment in comparison to OPFC			
	N=349	N=348	N=59	SR		WBR		SR		WBR	
	n(%)*	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Severe GI complications											
None	300 (86.0%)	316 (90.8%)	50 (84.7%)								
One	37 (10.6%)	21 (6.0%)	8 (13.6%)	0.98 (0.62 - 1.55)	0.924	1.17 (0.50-2.74)	0.712	1.09 (0.63 - 1.89)	0.758	1.63 (0.57 - 4.71)	0.363
Two	10 (2.9%)	8 (2.3%)	1 (1.7%)								
Three or more	2 (0.6%)	3 (0.9%)	0 (0.0%)								
Operations											
One	0 (0%)	0(0%)	0(0%)								
Two	208 (62.1%)	4 (1.2%)	19 (33.3%)	1.31 (1.19-1.43)	<0.001	1.09 (0.91-1.29)	0.344	1.30 (1.17 -1.45)	<0.001	1.10 (0.90-1.34)	0.350
Three	96 (28.7%)	273 (82.2%)	36 (63.2%)								
Four or more	31 (9.3%)	55 (16.6%)	2 (3.5%)								
Episodes of infection											
None	158 (81.4%)	202 (80.8%)	41 (85.4%)								
One	29 (14.9%)	36 (14.4%)	5 (10.4%)	0.98 (0.63 - 1.52)	0.919	0.81 (0.36-1.80)	0.600	1.04 (0.62 - 1.74)	0.882	1.17 (0.47-2.92)	0.738
Two	5 (2.6%)	11 (4.4%)	2 (4.2%)								
Three or more	2 (1.0%)	1 (0.4%)	0 (0.0%)								
	n(%)*	n(%)*	n(%)*	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR(95%CI)	p-value
Mortality											
No	342 (98.3%)	336 (97.4%)	57 (96.6%)	1.38 (0.48-3.98)	0.548	1.65 (0.32-8.60)	0.551	2.47 (0.74-8.26)	0.141	2.16 (0.34-13.93)	0.416
Yes	6 (1.7%)	9 (2.6%)	2 (3.4%)								
Infection in first 28 days											
No	247 (82.6%)	240 (78.7%)	47 (85.5%)	1.37 (0.90-2.07)	0.142	0.89 (0.39-2.03)	0.785	1.39 (0.87-2.41)	0.172	1.14 (0.45-2.86)	0.784
Yes	52 (17.4%)	65 (21.3%)	8 (14.5%)								
Liver Disease											
No	321 (95.3%)	331 (98.8%)	58 (98.3%)	0.32 (0.10-1.01)	0.053	0.87 (0.10-7.31)	0.900	0.56 (0.17-1.89)	0.347	1.05 (0.12-9.21)	0.966
Yes	16 (4.7%)	4 (1.2%)	1 (1.7%)								

*Percentage of those with complete data,

IRR – incidence rate ratio, OR- Odds ratio, 95% CI – 95% Confidence Interval, OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

Table 64: Outcomes in infants with intestinal necrosis, perforation or matting. Covariate and propensity score alone adjusted estimates of effect

	OPFC	SR	WBR	Crude estimate of effect of treatment in comparison to OPFC				Propensity score and covariate[#] adjusted estimate of effect of treatment in comparison to OPFC			
	N=349	N=348	N=59	Silo placement		WBR		Silo placement		WBR	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value
Head circumference											
z-score	-.74 (-3.15 to 1.67)	-.0.62 (-3.12 to 1.89)	-.84 (-4.61 to 2.95)	0.17 (-0.19 to 0.53)	0.347	0.05 (-0.59 to 0.68)	0.884	0.45 (-0.07 to 0.96)	0.090	0.04 (-0.88 to 0.96)	0.932
Weight											
z-score	-.90 (-2.84 to 1.04)	-1.03 (-3.21 to 1.15)	-1.01 (-3.40 to 1.38)	0.08 (-0.18 to 0.34)	0.539	-0.09 (-0.42 to 0.24)	0.589	0.11 (-0.18 to 0.39)	0.472	0.01 (-0.54 to 0.56)	0.969
	Median (IQR)	Median (IQR)	Median (IQR)	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Parenteral nutrition											
Number of days use	28 (20-28)	28 (22-28)	24 (18-28)	1.07 (1.04-1.11)	<0.001	0.98 (0.92-1.04)	0.528	1.06 (1.02-1.10)	0.003	0.98 (0.92-1.05)	0.590

*Percentage of those with complete data,

IRR – incidence rate ratio, OR- Odds ratio, 95% CI – 95% Confidence Interval, OPFC – Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure, WBR – Ward-based reduction with sutureless closure

#Identified covariates are gestational age at birth, birthweight, intestinal atresia, and intestinal perforation at presentation.

Appendix 24: *Benefits and drawbacks to the minimally invasive approaches to the pull-through procedure*

XXIV.I Benefits to the minimally invasive approaches

Proposed benefits of the laparoscopic approach over the open approach include improved cosmesis, reduced operative time, length of stay, financial cost, and risk of forming intra-abdominal adhesions(226-228). Some authors suggest that the trans-anal approach further improves these outcomes. However, assessments of the benefit of the trans-anal approach have mainly been made using short-term markers of success such as operative time, or bowel function prior to the age at which an infant can be expected to be continent (229, 230). When patients are followed-up over a longer period of time, it has been suggested that the purely trans-anal approach may be associated with poorer outcomes than the open or laparoscopically assisted approaches(231-234).

XXIV.II Drawbacks to the minimally invasive procedures

The point in the bowel at which the nerves of the myenteric plexus stop developing properly in infants with Hirschsprung's Disease varies, meaning that the length of the aganglionic section of bowel will differ from infant to infant. Most commonly, the point at which the transition between abnormal and normal bowel occurs is either in the distal sigmoid colon, or the proximal rectum. This is referred to as 'short segment' Hirschsprung's Disease. The transition zone can however be located in the proximal colon (long-segment Hirschsprung's Disease), or in the most severe cases, the entirety of the colon can be affected (total colonic Hirschsprung's Disease). In order to identify the location of the transition zone, and thereby aid surgical planning, a pre-operative contrast enema is commonly performed. In approximately 10% of infants however, it is not possible to identify the transition zone on contrast

studies, and in a further 8%, the transition zone is more proximal than suggested pre-operatively(235).

In infants with a proximal transition zone it is technically challenging to perform a purely trans-anal pull-through, leading to a putative increased risk of complications. It has therefore been proposed that infants with long-segment or total colonic Hirschsprung's disease are more appropriately managed using one of the other approaches (236, 237). In the open approach and the laparoscopic approach, confirmation of the location of the transition zone is one of the first stages of the procedure. Histologically identifying the transition zone early in the operation allows the surgeon to modify their rectal dissection and anastomotic technique as required. However, in the trans-anal pull-through procedure, it is not possible to identify the location of the transition zone prior to starting the rectal dissection by which stage it is difficult to modify the planned procedure(226). This inability to identify the transition zone prior to starting rectal dissection is one of the major drawbacks of the trans-anal approach, as it leads to a significant risk of attempting to perform a potentially inappropriate operation on infants with long-segment or total colonic Hirschsprung's Disease, a disease characteristic that is present in approximately 20% of cases(3).

Appendix 25: *Handling of discrepancies between parent and clinician outcome reports*

Data relating to several outcomes were collected from both parents and clinicians, and where this was the case, all analyses were based upon combining data from both sources. Where discrepancies occurred between parent and clinician reporting of an outcome, these were described, and the following assumptions made in deriving the summary variable:

- Parent reporting of faecal incontinence and severity of faecal incontinence was assumed to be more up to date than clinician reporting.
- Parent reporting of need for enemas or colonic or rectal irrigation to maintain voluntary bowel movements was assumed to be more up to date than clinician reporting.
- Parent reporting of urinary incontinence was assumed to be more up to date than clinician reporting.
- Surgeon reporting of admission and treatment for HAE was assumed to be more accurate than parent reporting.
- Presence of a permanent stoma was determined based upon review of the original BAPS-CASS and NETS^{2HD} data collection forms, and further discussion with the reporting surgeon to seek clarification if necessary.

Data relating to unplanned reoperations were only collected from clinicians, and data relating to quality of life, psychological stress and bowel function score were only collected from parents.

Appendix 26: *Characteristics and management of infants with and without five to seven year clinician follow-up*

Table 65: Characteristics and management of infants with and without five to seven year clinician follow-up

	No follow-up	Follow-up	
	N=67	N=185	
	n(%)*	n(%)*	p-value
Diagnosed in a low volume centre			0.015
No	38 (56.7%)	73 (39.5%)	
Yes	29 (43.3%)	112 (60.5%)	
Ethnicity			0.01
White	52 (77.6%)	164 (90.1%)	
BME	15 (22.4%)	18 (9.9%)	
Gestational age at birth			0.75
Term	56 (84.8%)	159 (86.4%)	
Pre-term	10 (15.2%)	25 (13.6%)	
Birthweight			0.76
2500g or more	54 (85.7%)	157 (87.2%)	
Less than 2500g	9 (14.3%)	23 (12.8%)	
Sex			0.043
Male	58 (86.6%)	138 (74.6%)	
Female	9 (13.4%)	47 (25.4%)	
Family history of HD			0.23
No	64 (97.0%)	170 (92.9%)	
Yes	2 (3.0%)	13 (7.1%)	
Associated chromosomal or structural anomaly			0.50
Isolated HD	49 (74.2%)	135 (73.4%)	
Syndromic	14 (21.2%)	33 (17.9%)	
Isolated additional anomaly	3 (4.5%)	16 (8.7%)	
Age at presentation			1
1-7 days	58 (86.6%)	161 (87.0%)	
8-28 days	3 (4.5%)	8 (4.3%)	
More than 28 days	6 (9.0%)	16 (8.6%)	
Age at diagnosis			0.88
<31 days	56 (83.6%)	157 (85.8%)	
31-60 days	2 (3.0%)	8 (4.4%)	
61-90 days	5 (7.5%)	8 (4.4%)	
91-120 days	1 (1.5%)	3 (1.6%)	
121-150 days	1 (1.5%)	1 (0.5%)	
>150 days	2 (3.0%)	6 (3.3%)	

* Percentage of those with complete data
BME – Black or minority ethnicity

Table 65: Characteristics and management of infants with and without five to seven year clinician follow-up - Continued

	No follow-up	Follow-up	
	N=67	N=185	
	n(%)*	n(%)*	p-value
Transition zone (as defined at surgery)			0.82
Rectosigmoid	47 (75.8%)	121 (73.8%)	
Long segment (proximal to sigmoid colon)	12 (19.4%)	37 (22.6%)	
Total colonic aganglionosis	3 (4.8%)	6 (3.7%)	
Stoma created prior to pull-through			0.46
No	44 (65.7%)	112 (60.5%)	
Yes	23 (34.3%)	73 (39.5%)	
Definitive surgery prior to one year			0.66
No	6 (9.1%)	13 (7.4%)	
Yes	60 (90.9%)	163 (92.6%)	
Staged definitive procedure			0.42
No	44 (71.0%)	109 (65.3%)	
Yes	18 (29.0%)	58 (34.7%)	
First attempted approach to the pull-through			<0.001
Definitive surgery not performed prior to one year	4 (6.1%)	9 (5.1%)	
Open	28 (42.4%)	63 (36.0%)	
Laparoscopic	4 (6.1%)	37 (21.1%)	
Trans-anal	8 (12.1%)	42 (24.0%)	
Combined laparoscopic and trans-anal	22 (33.3%)	24 (13.7%)	
Rectal dissection technique			0.015
Soave	28 (45.2%)	91 (55.2%)	
Swenson	1 (1.6%)	16 (9.7%)	
Duhamel	33 (53.2%)	58 (35.2%)	
	Median (IQR)	**Median (IQR)**	
Weight at stoma formation			0.55
Grams	3667 (2700-4200)	3425 (3000-4000)	
Weight at definitive surgery			0.32
Kilograms	5.5 (4.68-7)	5.4 (4.14-6.4)	

* Percentage of those with complete data

Appendix 27: *Outcomes for infants with and without five to seven year clinician follow-up*

Table 66: Outcomes for infants with and without five to seven year clinician follow-up

	No follow-up	Follow-up	
	N=52	N=150	
	n(%)*	n(%)*	p-value
Revision surgery within one year of diagnosis			0.94
No	50 (98.0%)	137 (97.9%)	
Yes	1 (2.0%)	3 (2.1%)	
Post pull-through stoma within a year of diagnosis			0.97
No	37 (90.2%)	123 (90.4%)	
Yes	4 (9.8%)	13 (9.6%)	
Post-operative HAE suspected			0.85
No	36 (69.2%)	101 (67.8%)	
Yes	16 (30.8%)	48 (32.2%)	
One or more unplanned reoperation within a year of diagnosis			0.3
No	41 (82.0%)	123 (87.9%)	
Yes	9 (18.0%)	17 (12.1%)	
Total number of unplanned operations within a year of diagnosis			0.55
None	41 (82.0%)	123 (87.9%)	
One	6 (12.0%)	8 (5.7%)	
Two	2 (4.0%)	6 (4.3%)	
Three	1 (2.0%)	3 (2.1%)	

* Percentage of those with complete data
HAE – Hirschsprung's Associated Enterocolitis

Appendix 28: *Characteristics of children who survived to five years post-diagnosis. Comparison of those with and without five to seven year parent follow-up*

Table 67: Characteristics of children who survived to five years post-diagnosis. Comparison of those with and without five to seven year parent follow-up

	No follow-up	Follow-up	
	N=159	N=81	
	n(%)*	n(%)*	p-value
Diagnosed in a low volume centre			0.003
No	60 (37.7%)	47 (58.0%)	
Yes	99 (62.3%)	34 (42.0%)	
Ethnicity			0.26
White	133 (84.7%)	72 (90.0%)	
BME	24 (15.3%)	8 (10.0%)	
Gestational age at birth			0.65
Term	137 (86.7%)	71 (88.8%)	
Pre-term	21 (13.3%)	9 (11.3%)	
Birthweight			0.54
2500g or more	133 (86.9%)	70 (89.7%)	
Less than 2500g	20 (13.1%)	8 (10.3%)	
Sex			0.55
Male	127 (79.9%)	62 (76.5%)	
Female	32 (20.1%)	19 (23.5%)	
Family history of HD			0.19
No	150 (95.5%)	73 (91.3%)	
Yes	7 (4.5%)	7 (8.8%)	
Associated chromosomal or structural anomaly			0.93
Isolated HD	122 (77.2%)	60 (75.0%)	
Syndromic	25 (15.8%)	14 (17.5%)	
Isolated additional anomaly	11 (7.0%)	6 (7.5%)	
Age at presentation			0.49
1-7 days	139 (87.4%)	70 (86.4%)	
8-28 days	5 (3.1%)	5 (6.2%)	
More than 28 days	15 (9.4%)	6 (7.4%)	
Age at diagnosis			0.67
<31 days	132 (83.5%)	71 (87.7%)	
31-60 days	5 (3.2%)	4 (4.9%)	
61-90 days	11 (7.0%)	2 (2.5%)	
91-120 days	3 (1.9%)	1 (1.2%)	
121-150 days	1 (0.6%)	1 (1.2%)	
>150 days	6 (3.8%)	2 (2.5%)	

* Percentage of those with complete data
BME – Black or minority ethnicity

Table 67: Characteristics of children who survived to five years post-diagnosis. Comparison of those with and without five to seven year parent follow-up - Continued

	No follow-up	Follow-up	
	N=159	N=81	
	n(%)*	n(%)*	p-value
Transition zone (as defined at surgery)			0.74
Rectosigmoid	114 (75.5%)	51 (70.8%)	
Long segment (proximal to sigmoid colon)	31 (20.5%)	18 (25.0%)	
Total colonic aganglionosis	6 (4.0%)	3 (4.2%)	
Stoma created prior to pull-through			0.35
No	104 (65.4%)	48 (59.3%)	
Yes	55 (34.6%)	33 (40.7%)	
Definitive surgery prior to one year			0.072
No	9 (5.7%)	10 (12.3%)	
Yes	149 (94.3%)	71 (87.7%)	
Staged definitive procedure			0.74
No	104 (67.5%)	47 (65.3%)	
Yes	50 (32.5%)	25 (34.7%)	
First attempted approach to the pull-through			0.002
Definitive surgery not performed prior to one year	4 (2.5%)	9 (11.1%)	
Open	62 (39.5%)	28 (34.6%)	
Laparoscopic	20 (12.7%)	20 (24.7%)	
Trans-anal	40 (25.5%)	10 (12.3%)	
Combined laparoscopic and trans-anal	31 (19.7%)	14 (17.3%)	
Rectal dissection technique			0.32
Soave	82 (53.6%)	35 (49.3%)	
Swenson	13 (8.5%)	3 (4.2%)	
Duhamel	58 (37.9%)	33 (46.5%)	
	Median (IQR)	**Median (IQR)**	
Weight at stoma formation			0.18
Grams	3641 (3058-4240)	3525 (2650-3800)	
Weight at definitive surgery			0.23
Kilograms	5.5 (4.49, 6.65)	5.1 (4, 6.36)	

* Percentage of those with complete data

Appendix 29: *Outcomes one-year post diagnosis for children who had undergone definitive surgery prior to one year of age. Comparison of those with and without five to seven year follow-up*

N=235 children who were alive at five to seven years of age, who had undergone definitive surgery prior to one year of age in one of the 20 participating hospitals, and who had one year data returned to BAPS-CASS

Table 68: Outcomes one-year post diagnosis for children who had undergone definitive surgery prior to one year of age. Comparison of those with and without five to seven year follow-up

	No follow-up	Follow-up	
	N=176	N=59	
	n(%)*	n(%)*	p-value
Revision surgery within a year of diagnosis			0.96
No	163 (98.2%)	51 (98.1%)	
Yes	3 (1.8%)	1 (1.9%)	
Post pull-through stoma within a year of diagnosis			0.80
No	137 (89.0%)	46 (90.2%)	
Yes	17 (11.0%)	5 (9.8%)	
Post-operative HAE suspected			0.29
No	122 (70.1%)	37 (62.7%)	
Yes	52 (29.9%)	22 (37.3%)	
One or more unplanned reoperation within a year of diagnosis			0.82
No	145 (86.3%)	49 (87.5%)	
Yes	23 (13.7%)	7 (12.5%)	
Total number of unplanned operations within a year of diagnosis			0.84
None	145 (86.3%)	49 (87.5%)	
One	14 (8.3%)	3 (5.4%)	
Two	6 (3.6%)	3 (5.4%)	
Three	3 (1.8%)	1 (1.8%)	

* Percentage of those with complete data
HAE – Hirschsprung's Associated Enterocolitis

Appendix 30: *Infant characteristics associated with faecal incontinence*

Univariable logistic regression analysis was utilised to investigate the association between key infant characteristics and faecal incontinence at five years of age. Those characteristics that were shown on univariable anlaysis to have a statistically significant association with faecal incontinence, as evidenced by a p-value of <0.1 were eligible for assessment for inclusion in the multi-variable model. However, no factors met this statistical criteria, and therefore a multi-variable model was not developed. Results from the univariable analysis are presented in Table 69.

Table 69: Association of infant characteristics with faecal incontinence

	Continent of faeces	Not continent of faeces		
	N=75	N=113		
	n(%)*	n(%)*	Unadjusted OR (95% CI)	p-value
Ethnicity				0.353
White	64 (86.5%)	101 (91.0%)	Ref.	
BME	10 (13.5%)	10 (9.0%)	0.64 (0.25-1.63)	
Gestational age at birth				0.961
Term	66 (88.0%)	99 (88.4%)	Ref.	
Pre-term	9 (12.0%)	13 (11.6%)	0.98 (0.40-2.41)	
Birthweight				0.858
2500g or more	64 (88.9%)	97 (88.2%)	Ref.	
Less than 2500g	8 (11.1%)	13 (11.8%)	1.09 (0.43-2.77)	
Sex				0.466
Male	59 (78.7%)	84 (74.3%)	Ref.	
Female	16 (21.3%)	29 (25.7%)	1.29 (0.65-2.59)	
Family history of HD				0.145
No	72 (97.3%)	103 (92.0%)	Ref.	
Yes	2 (2.7%)	9 (8.0%)	3.19 (0.67-15.20)	
Associated anomaly				0.42
Isolated HD	55 (73.3%)	88 (78.6%)	Ref.	
Syndromic	12 (16.0%)	18 (16.1%)	0.95 (0.43-2.13)	
Isolated additional anomaly	8 (10.7%)	6 (5.4%)	0.48 (0.16-1.45)	
Age at presentation				0.868
1-7 days	64 (85.3%)	99 (87.6%)	Ref.	
8-28 days	5 (6.7%)	4 (3.5%)	0.53 (0.14-2.03)	
More than 28 days	6 (8.0%)	10 (8.8%)	1.09 (0.38-3.16)	
Age at diagnosis				0.543
28 days or less	63 (86.3%)	94 (83.2%)	Ref.	
More than 28 days	10 (13.7%)	19 (16.8%)	1.29 (0.56-2.96)	

* Percentage of those with complete data
BME – Black or minority ethnicity
HD – Hirschsprung's disease

Table 69: Association of infant characteristics with faecal incontinence - Continued

	Continent of faeces	Not continent of faeces		
	N=75	N=113		
	n(%)*	n(%)*	Unadjusted OR (95% CI)	p-value
Enterocolitis pre-operatively				0.122
No	60 (80.0%)	100 (88.5%)	Ref.	
Yes	15 (20.0%)	13 (11.5%)	0.53 (0.24-1.19)	
Transition zone				0.399
Rectosigmoid	52 (78.8%)	77 (71.3%)	Ref.	
Long segment (proximal to sigmoid colon)	10 (15.2%)	28 (25.9%)	1.93 (0.86-4.30)	
Total colonic aganglionosis	4 (6.1%)	3 (2.8%)	0.52 (0.11-2.40)	

* Percentage of those with complete data