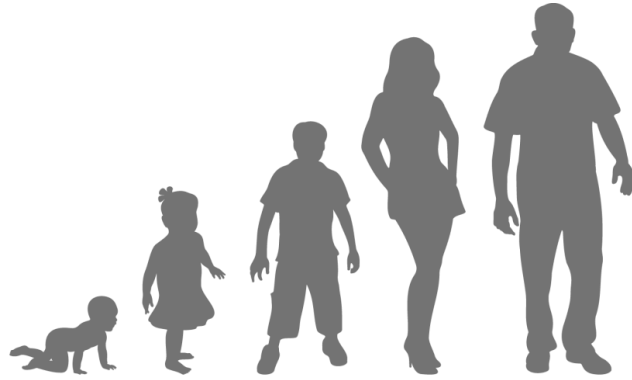




Short and long-term outcomes of children born with abdominal wall defects

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Abstract

Background

Very occasionally, when a fetus is developing in the womb, problems occur with the normal processes controlling closure of the muscles of the abdominal wall and, as a result, some of the abdominal contents develop outside of the body. This is known as an abdominal wall defect. If the pregnancy continues to term, the newborn infant will need specialised surgical care. This situation occurs so infrequently that even a dedicated surgical centre will care for very few of these women and their babies in a year. Many centres have shared their experiences of managing these babies in the published literature but the majority of reports have included only a few infants. The focus of most previous studies has been to describe what happens to these newborn infants between birth and first discharge from hospital from a purely clinical perspective.

Aim

To explore methodologies to holistically understand the short and longer-term outcomes of children born with abdominal wall defects and to use the information to improve the care of future affected infants.

Methods

The quality of the published literature on short-term outcomes of children born with gastroschisis was scrutinised in a systematic review. The accompanying meta-analysis used published data as a means of identifying population outcome estimates.

Two national population-based cohort studies were undertaken, exploring the short-term outcomes of children born with exomphalos and the outcomes at seven to ten years of children born with gastroschisis. The latter study included an assessment of childhood outcomes from the point of view of the children themselves, along with their parents. Further parental perspectives on experiences of care were explored in a qualitative analysis of in-depth interviews with parents of children born with exomphalos.

Findings

Short-term outcomes of children born with gastroschisis have been published in a large number of small studies. Pooling the published data, where possible allowed the production of population estimates but heterogeneity between studies was marked. One in fourteen children born with gastroschisis died before their first birthday when managed in developed countries. Those who developed bowel complications *in utero*, had an increased risk of dying before one-year. The assessment of childhood outcomes for this latter group of children, who made up 11% of the population cohort, revealed a bleak outlook for many, of with one in three either dying or requiring complex surgery to gain allow them to be able to be fed via their gut, before their ninth birthday.

Due to methodological limitations, the extent of neurological and gastrointestinal morbidity among survivors in the cohort is unclear, but the findings of both the highly selected responses from the parent report and those of the clinical study provide enough concern to suggest that alternative methodologies need to be explored to identify the extent of ongoing sequelae as children grow older.

The live-born population of children with exomphalos is highly varied and a large burden of comorbidity was identified, however, two-thirds of infants were able to have their abdominal wall defect surgically closed with a low-rate of early complications. A variety of techniques are employed by UK surgeons when the defect cannot be easily closed and evidence to guide management choice will be difficult to obtain using standard techniques due to the small number of these infants born annually in the UK. Parental experiences echoed the variability in management approach and in some cases highlighted a lack of respect for parental perspectives on management choice.

Conclusion

Children born with abdominal wall defects represent a spectrum from those with severe comorbidity who will need ongoing care, to those who have a straightforward course and a relatively short stay in hospital. Methods of risk-stratifying infants for the purposes of outcome assessment have been explored. This approach is crucial to contextualising the progress of an individual infant and counselling their parents about their likely prognosis.

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List of Abbreviations

Abbreviation	Full text
AN	Antenatal
ASBO	Adhesive (Small) Bowel Obstruction
ASD	Autistic Spectrum Disorder
AUC	Area Under the Curve
AWD	Abdominal Wall Defect
BAPS	British Association of Paediatric Surgeons
BAPS-CASS	BAPS- Congenital Anomaly Surveillance Service
BINOCAR	British and Irish Network of Congenital Anomaly Researchers
BMI	Body Mass Index
BSPGHAN	British Society of Paediatric Gastroenterology, Hepatology and Nutrition
BWS	Beckwith Wiedemann Syndrome
BW	Birth weight
CAPSNET	CANadian Paediatric Surgery NETwork
CDH	Congenital Diaphragmatic Hernia
CDOP	Child Death Overview Panel
CHARGE	A cluster of abnormalities which may include, Coloboma (an eye defect), Heart defects, choanal Atresia (narrowing of the nasal passages), growth Retardation, Genital abnormalities, and Ear abnormalities
CHU-9D	Child Health Utility 9D
CLP	Cleft Lip and Palate
CMPI	Cow Milk Protein Intolerance
COS	Core Outcome Set
DCF	Data Collection Form
DOH	Department of Health
DWR	Defect /Weight Ratio
EUROCAT	European Surveillance of Congenital Anomalies
IFALD	Intestinal Failure Associated Liver Disease
IDEAL	Idea, Development, Assessment, Long-term Follow-up, Improving the Quality of Research in Surgery
IRAS	Integrated Research Application System
FASP	Fetal Anomaly Screening Programme
FGID	Functional Gastrointestinal Disorders
GMC	General Medical Council
GOR (D)	Gastro-Oesophageal Reflux (Disease)
HERG	Health Experiences Review Group
HES	Hospital Episode Statistics
HrQOL	Health related Quality of Life
HSCIC	Health and Social Care Information Centre
HUI	Health Utilities Index
IF	Intestinal Failure
IFALD	Intestinal Failure Associated Liver Disease
IQR	Interquartile Range
ISD	Information Services Division
LGA	Large for Gestational Age
LOS	Length of Stay

List of Abbreviations - cont

Abbreviation	Full text
MBRRACE-UK	Mothers and Babies, Reducing Risk through Audits and Confidential Enquires across the UK
MNI-CORP	Maternal Newborn and Infant Clinical Outcome Review Programme
NCEPOD	National Confidential Enquiry into Peri-Operative Death
NEC	Necrotising EnteroColitis
NGA	Normal for Gestational Age
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health Research
NOS	Newcastle Ottawa Scale
NPEU	National Perinatal Epidemiology Unit
OEIS	A cluster of abnormalities comprising: Omphalocele, Extrophy of the Cloaca, Imperforate Anus, Spinal Abnormalities
OFC	Operative Fascia Closure
OSOP	One Sheet of Paper
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
PFS	Pre-Formed Silo
PIC	Participant Identification Centre
PICU	Paediatric Intensive Care Unit
PN	Parenteral Nutrition
PROM	Patient Reported Outcome Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	Post-Traumatic Stress Disorder
QPGS-RIII	Questionnaire on Pediatric Gastrointestinal Symptoms (Rome III Criteria)
RCS	Royal College of Surgeons
ROC	Receiver Operating Characteristic
SGA	Small for Gestational Age
UDT	Undescended Testis
UKOSS	UK Obstetric Surveillance System
WHO	World Health Organisation

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Chapter 1

Introduction

1.1 Background to this work

As author of this thesis, I am a UK doctor close to completion of six years of specialist training in paediatric surgery. Like all medical practitioners, I wish to select the appropriate treatment strategies for future children in my care in order to assure safety, efficacy and cost effectiveness as well as ensuring the experiences of the child and family are as good as they can be. This desire was the main driver for the work presented here.

Paediatric surgery has only been considered to be a speciality in its own right for approximately 50 years (Grosfeld 2012). This means that the generation of surgeons that have recently retired were the pioneers in defining the scope of the speciality, developing technical and peri-operative medical expertise and setting standards of care. As a result it is a speciality in relative infancy. It is a discipline that deals with a number of high-burden, low incidence structural abnormalities that develop in-utero and have a potential life-long impact on affected children and their families. Expertise in management has largely developed through experiential learning and institutional sharing of retrospective data. As a consequence of the rarity of the conditions encountered, an individual practitioner has little opportunity to gather evidence from their own practice about the safety and efficacy of a given management strategy.

The published literature, as a resource for paediatric surgeons to obtain evidence about the efficacy or safety of a particular treatment strategy for the conditions they treat, is woefully lacking (Allin, Aveyard et al. 2016). In 2009 a group of researchers set out to develop a robust process by which new surgical management strategies, in particular, operative procedures, should be introduced and evaluated.

This is known as the IDEAL framework and refers to the step-wise processes of idea, development, exploration, assessment and long-term follow-up (Barkun, Aronson et al. 2009). The IDEAL group reaffirmed that randomised controlled trials are the optimum methodology to evaluate the efficacy of interventions over the short-term (Cook, McCulloch et al. 2013). Such studies have long been accepted as the gold standard for the generation of the highest quality evidence of short-medium term efficacy of drug therapies (Atkins, Best et al. 2004). The group also suggested that well-designed population-based studies represented the best methodology to evaluate the long-term effects of treatment. A recent systematic review identified that only 12% of recently published studies concerning conditions treated by paediatric surgeons used a design recommended by the IDEAL collaboration. (Allin, Aveyard et al. 2016). Allin et al (2016) found that about half of the studies meeting the review inclusion criteria were retrospective case series. In the paediatric surgical literature these are most frequently produced by a single centre and, due to the infrequency with which these infants present, often include data gathered over a long period of time, during which treatment strategies and other aspects of care have evolved and outcomes may drastically change.

Large-scale blinded randomised controlled trials conducted in other specialities have beneficially influenced practice, ensured that safe and effective treatments are provided to millions of individuals and saved an incalculable amount of money for the National Health Service (NHS) (Marshall 2003). The conduct of such trials in paediatric surgery has been challenging to date. The reasons for this are outlined in Table 1.1

Table 1.1 Challenges to conducting randomised controlled trials in paediatric surgery

1. Rarity	Many conditions treated are encountered infrequently by individual surgeons, meaning that multi-centre and even multi-national collaboration is essential to enable studies of sufficient statistical power to detect an effect. Trials are therefore challenging and expensive
2. Emotional upheaval affecting recruitment	The clinical questions which many trials would address are encountered in situations that occur as an emergency or are upsetting and challenging for parents (who will most often be consenting for enrolment by proxy). This may affect their ability to process the information that will help them decide whether to enrol their children in research studies. A growing number of highly successful neonatal clinical trials suggests that this can, however, be achieved (Azzopardi, Strohm et al. 2014, Darlow, Marschner et al. 2014, Costeloe, Bowler et al. 2016).
3. Expertise	Surgeons frequently learn one surgical technique for the management of a given condition from their tutors. Many procedures have a 'learning curve' associated with them whereby mistakes may be more likely to be made during the early phase of use (Oomen, Hoekstra et al. 2010). For this reason there may not always be an option to offer the choice of two techniques performed by the same surgeon or even within the same department.
4. Perceived lack of equipoise	Similar to point 3, surgeons may feel that a certain technique works well 'in their hands', will be reluctant to change their own practice and therefore believe that they are not in equipoise.
5. Funding and patient burden/ value for money	Trials are expensive (see point 1) and for the funding of trials into conditions that occur only very rarely in the population, it may be hard to convince funders that their investment will bring benefit to a large number of individuals.

The challenges outlined in Table 1 are not insurmountable. An alternative means of generating evidence to guide practice using a robust methodology, well suited to rare conditions is the conduct of population-based prospective cohort studies. This is a strategy that was adopted first in the UK in paediatrics, with the establishment of the British Paediatric Surveillance Unit (BPSU) in 1986, where rare but significant conditions affecting neonates and children were reported on a population basis (Knowles, Friend et al. 2012). This, and other paediatric surveillance systems, was followed, for obstetric practice, by the establishment of the UK Obstetric Surveillance System (UKOSS) (Knight, Kurinczuk et al. 2005).

After the successes of the BPSU and UKOSS, the National Perinatal Epidemiology Unit of Oxford University (NPEU) who oversee UKOSS, collaborated with the British Association of Paediatric Surgeons to create a similar system, titled the 'British Association of Paediatric Surgeons Congenital Anomaly Surveillance System' (BAPS-CASS). The BAPS-CASS system has completed seven population based cohort studies to date and has collected both early and one-year outcome data on infants requiring early surgery for a range of perinatal conditions. These studies have begun to generate data to guide practice and continue to do so following publication and dissemination of their findings (Owen, Marven et al. 2010, Bradnock, Marven et al. 2011). The work contained within this thesis builds on these achievements and in the case of three of the studies presented here, utilised the existing collaboration between surgical centres to obtain national population-based data about infants born with abdominal wall defects.

In the remaining two studies, alternative methodological strategies were used to generate evidence to inform practice as well as valuable information for parental counselling. The first of these was the conduct of a systematic review and meta-analysis to assess the short-term outcomes of infants born with gastroschisis. The second used qualitative analysis to explore the experiences of parents. This, in turn, informed the interpretation of the related quantitative studies within this work.

1.1.1 Why study infants with abdominal wall defects?

Development of the fetus from the embryonic cells that form after fertilisation is a complex process involving intricate intracellular signalling to coordinate the formation of distinct cellular populations, their differential proliferation, migration and in some cases programmed cell death. Errors within these processes can lead to structural malformations within the fetus. Some of these malformations are lethal before birth while others persist in live-born infants. Many of these so-called 'congenital anomalies' require no treatment but significant structural malformations may require early surgical intervention. Two clinical manifestations of the abnormal development of the abdominal wall occur most frequently and require surgical correction. These are gastroschisis and exomphalos and are the abdominal wall defects studied within this thesis. In order to understand how these two abnormalities may arise, a brief overview of the normal processes of abdominal wall closure is provided included in Appendix 1.

Gastroschisis

Gastroschisis is an abnormality characterised by a full-thickness hole in the abdominal wall, adjacent to the insertion of the umbilical cord, through which the viscera, usually the majority of the intestines, protrude and float freely *in utero* in the amniotic fluid (Figure 1.1). There is strong evidence of environmental influences on the development of this abnormality *in utero*, which usually occurs in isolation in an affected fetus (Mac Bird, Robbins et al. 2009).

The extra-abdominal bowel is at risk of damage through contact with the amniotic fluid. Some authors have suggested that fetal meconium passed in this fluid is responsible for the inflammation identified in the bowel wall seen on macroscopic and microscopic examination of the bowel after birth (Correia-Pinto, Tavares et al. 2002). In addition to this, compression at the level of the umbilical defect may affect the blood supply to the bowel outside of the fetal body. In the most severe cases, the defect may even close around the neck of the external bowel, leading to the loss of a significant amount of intestinal length prior to birth (Houben, Davenport et al. 2009).

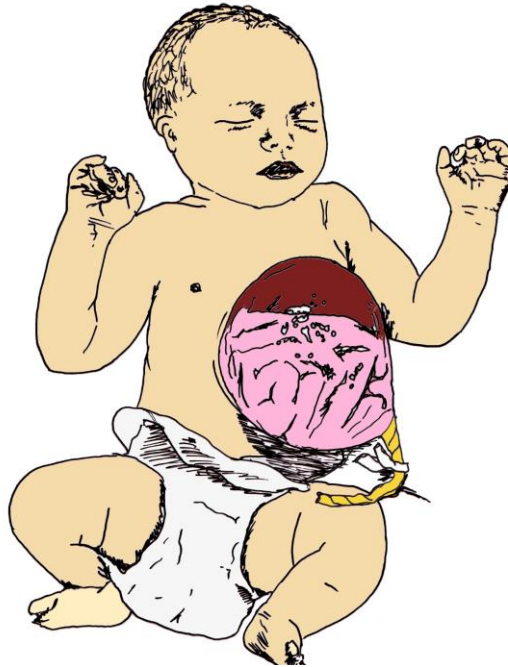
Figure 1.1 An infant with gastroschisis



Exomphalos

Exomphalos is also known as omphalocele in some parts of the world. Although this abnormality is also characterised by a defect in the abdominal wall muscles at the site of the umbilical cord insertion, is an entirely distinct abnormality from gastroschisis. Here, the area of the abdominal wall musculature at the site of the insertion of the umbilical cord is variably deficient. Through this, the viscera, most usually the bowel but often the liver, protrude. In these infants, unlike those with gastroschisis, the viscera are covered by a sac formed of the layers of the umbilical cord (Figure 1.2). Rarely, the protective sac may rupture, leading to protrusion of the bowel and liver into the amniotic cavity. Unlike gastroschisis, exomphalos has no known environmental aetiology and an association with genetic abnormalities is common (Christison-Lagay, Kelleher et al. 2011). Structural malformations affecting other body systems also frequently occur alongside exomphalos; this too is distinct from gastroschisis, where such associations are rare.

Figure 1.2. An infant with exomphalos



Gastroschisis and exomphalos, although occurring infrequently in the population as a whole, are two of the most common malformations requiring early surgery that are managed by paediatric surgeons. Although these defects are anatomically and epidemiologically distinct, they share common features: both can be diagnosed antenatally, frequently require a prolonged hospital stay and children born with them may have significant ongoing medical problems into later life. Gastroschisis has been identified as an ‘index’ neonatal condition by the British Association of Paediatric Surgeons (BAPS) and the Royal College of Surgeons (RCS), the outcomes of which could be scrutinised as part of professional appraisal (RCS 2013). One set of authors recently described gastroschisis as a ‘bellwether’ condition[†] for assessing the quality of neonatal surgical care in developing world settings (Ford, Poenaru et al. 2016). Its relative frequency and the anticipation of favourable outcomes in the majority of infants have clearly been of utility to those responsible for defining and scrutinising neonatal surgical standards.

[†] ‘Bellwether’ is a term that refers to something that ‘leads the way’ or is indicative of a trend. In the surgical literature it has been used to identify surgical procedures that may act as more general indicators of care quality and institutional capacity (Ford, Poenaru et al. 2016)

In all conditions requiring early surgery, a favourable outcome has benefits to the individual and their family that are lifelong. Conversely, adverse early events may lead to death or long-term disability and or morbidity and have a far-reaching impact on those affected, their family and society as a whole. In common with most, if not all, other similar conditions, there is no consensus on the safest and most effective treatment strategies for gastroschisis and exomphalos either before or after birth and there is no clear picture of the long-term outcomes of these treatments. In addition, no robust prognostic information exists that relates to the condition of the infant and their extra-abdominal viscera at birth. The generation of information to fill these knowledge gaps will be of clear benefit to health-care practitioners caring for these infants as well as the infants themselves and their families. There are thus key research gaps in both of these conditions that will be investigated within this thesis.

1.1.2 Gastroschisis – What we do and do not know

Gastroschisis has an interesting and unique epidemiology. There has been recent global public-health concern about the growing birth-prevalence of this condition. The speed of increase in the number of new cases was termed by some an ‘epidemic’ and in 2005 the Chief Medical Officer for England mentioned the rising prevalence of gastroschisis as a significant cause for concern in his annual report (Donaldson 2005, Keys, Drewett et al. 2008). The rapid rise in prevalence, the sporadic occurrence of the condition within families and the absence of other structural malformations have led many to speculate as to an environmental aetiology (Feldkamp and Botto 2008). There is known to be a strong association between gastroschisis and sociodemographic factors such as young maternal age, lower socioeconomic status, and maternal drug use (Draper, Rankin et al. 2008, Mac Bird, Robbins et al. 2009). Biological factors such as low maternal weight, maternal stress, poor diet and genitourinary infection during pregnancy are also implicated in the causal pathway (Feldkamp, Carmichael et al. 2011, Paranjothy, Broughton et al. 2012, Palmer, Evans et al. 2013, Yazdy, Mitchell et al. 2014).

For the vast majority of infants born with gastroschisis, the defect is detected antenatally. Appendix 2 shows the normal antenatal screening that women in the UK are offered during pregnancy. This illustrates the pathway taken by most mothers before they give birth. Due to a positive outlook for the majority of infants, parents are antenatally counselled optimistically and most affected pregnancies continue until term (Springett, Budd et al. 2013).

Babies born with gastroschisis represent a spectrum, ranging from those with relatively normal looking bowel at birth to those with loss of a significant amount of intestinal length due to complications *in utero*. A commonly used risk stratification divides infants into those with 'simple' or 'complex' gastroschisis. In the latter group there is found to be either, a blockage, a twist, dead areas of tissue, or a hole in the bowel at birth. In simple gastroschisis, none of these are present (Molik, Gingalewski et al. 2001). A recent systematic review identified that key short-term outcomes such as death during the initial hospitalisation, as well as significant infective complications, are more common in infants born with complex gastroschisis (Bergholz, Boettcher et al. 2014). The precise implications of *in utero* bowel compromise, both in the long and short term have not, however, been fully elucidated. This is an area where accurate prognostic information could inform parental counselling as well as guiding practitioners as to how to improve outcomes for these infants over the course of their life-time.

When a baby is born with gastroschisis, the exposed bowel must be managed as soon as possible to provide protection, prevent loss of body fluid due to evaporation from the bowel surface and facilitate feeding. In the majority of infants, the bowel can be returned to the abdomen easily and the defect either closed with sutures (under general anaesthesia), a procedure known as operative fascial closure (OFC), or left to close without sutures, using the umbilical cord as a 'cap' (a procedure performed with or without general anaesthesia) (Bianchi and Dickson 1998, Marven and Owen 2008).

In some centres, the bowel is routinely placed in a cylindrical plastic covering with a rim that sits inside the abdominal wall defect known as a 'pre-formed silo' (PFS)(Marven and Owen 2008) (Figure 1.3). This silo is then removed at the bedside, and often a general anaesthetic is avoided. If the size of the abdomen is too small compared to the amount of exposed bowel, alternative strategies must be considered such as application of a PFS or, instead in a 'custom' silo, the latter constructed by the surgeon using synthetic sheeting and sutures (Figure 1.4) (Marven and Owen 2008).

Figure 1.3. A preformed silo (PFS) applied to the bowel in an infant with gastroschisis



Figure 1.4. A 'custom' silo applied to the bowel in an infant with gastroschisis



The main debate about the optimal treatment for simple gastroschisis exists between advocates of primary operative fascial closure (OFC) and those who favour the application of a PFS for all infants suitable for primary bowel reduction. One randomised controlled trial and a number of systematic reviews have been conducted to evaluate the safety and efficacy of one over the other (Pastor, Phillips et al. 2008, Allin, Tse et al. 2015, Ross, Eaton et al. 2015). These have not been able to identify any appreciable difference in outcome beyond a slight difference in the number of days that infants require artificial ventilation in favour of those managed with PFS. To date, studies have focussed on the short-term outcomes of these treatments and no studies have yet compared them based on their long-term consequences.

The challenges of generating data from randomised controlled trials as well as the low-quality of published research in paediatric surgery are clearly evident within the gastroschisis literature. Published studies in this area are predominantly small retrospective case-series with the limitations already described previously. Due to the rarity of adverse events in conditions such as gastroschisis, differences in outcome may be subtle and require large-scale carefully conducted studies to tease out these differences and the factors that may be associated with them. The published studies that have utilised the BAPS-CASS data collection system assessing population-based outcomes to one year in infants born with gastroschisis, (Owen, Marven et al. 2010, Bradnock, Marven et al. 2011) along with those described in Chapters Five and Six of this thesis, looking over a longer period of time, take just such an approach.

Very little has been published to date regarding the longer-term outcomes of infants born with gastroschisis. Reports have largely been restricted to providing information on the period from birth to discharge from hospital, looking at parameters such as early surgical complications, time to initiation or delivery of the full complement of enteral feeds, length of hospital stay or early death. Paediatric surgeons are well aware that some children with gastroschisis may have problems in the longer term and those studies which have included older cohorts of patients have hinted at long-term morbidity (Ludman, Spitz et al. 1993, Davies and Stringer 1997).

It is imperative that a careful and systematic assessment is made of how children born with gastroschisis fare in the longer term. This will provide valuable information to the parents of these children about what the future may hold throughout their life, from the point of diagnosis onwards. Careful recording of patient characteristics and the mapping of these to outcome will assist in the risk-stratification of patients to aid prognostication. The mapping of antecedent factors could also potentially identify modifiable effectors that influence outcome and monitoring the outcomes of varying surgical strategies in gastroschisis in the longer term will inform evidence based-practice.

Most of the studies published to date have been limited to reporting surgical outcomes only, neglecting other areas such as ongoing abdominal symptomatology, growth, nutrition, development and quality of life. Generation of data concerning these issues is of vital importance to produce a holistic picture of the long-term outlook for infants born with gastroschisis. As a group of researchers suggested 25 years ago in a paper about children requiring early surgery: *“if the goal for children who have required surgical repair of congenital malformations is to achieve normal growth and development, then complete evaluation of all aspects of that development-physical, social, intellectual, and psychological-should be considered”* (Ginn-Pease, King et al. 1991). It is evident that for gastroschisis, little progress has been made since then.

Assessing the success of an intervention from the perspective of patients (or by proxy, their parents) is an approach that is gaining velocity within all specialities (Black 2013). This methodology has been incorporated within the National Health Service (NHS) Outcomes Framework, UK government strategy for providing *“a national overview of how the NHS is performing”* (NHS 2015). Since inception in 2010, this process set out to have a, *“relentless focus on the outcomes that matter most to people”* (Department of Health 2012).

Although some authors have added such evaluations to their long-term studies, response rates have been poor and loss to follow-up is high (Gorra, Needelman et al. 2012, Harris, Hart et al. 2012, van Manen, Hendson et al. 2013). An aim of this work was to explore methodologies to address the need to understand parent and child perspectives of outcomes in children born with gastroschisis.

1.1.3 Exomphalos – What we do and do not know

Unlike gastroschisis, exomphalos has no proven epidemiological associations and genetic associations are frequent. These range from whole chromosomal anomalies to smaller genetic aberrations that result in characteristic clinical features, including this abdominal wall defect (Chen 2007a, Chen 2007b, Chen 2007c). In addition, exomphalos is a feature of over 70 known malformation syndromes, many with no identifiable genetic cause (Christison-Lagay, Kelleher et al. 2011). Even in the absence of a syndromic pattern or cluster of structural abnormalities, major structural defects affecting other body systems are common in these infants (Brantberg, Blaas et al. 2005, Chen 2007a, Chen 2007b, Chen 2007c).

The abdominal wall defect itself has a variety of structural variations in infants with exomphalos and a spectrum of associated clinical sequelae may occur, including pulmonary hypoplasia, gastro-oesophageal reflux, distortion of hepatic venous drainage, intestinal non-rotation and bowel dilatation. These associations may significantly affect both the short and long-term outcomes of infants born with exomphalos and have a major impact on their quality of life.

Exomphalos is frequently detected on antenatal ultrasound scanning, usually at the 20 week 'anomaly scan' (Appendix 2). Due to the frequent association of exomphalos with major genetic and structural abnormalities as well as its severe associated clinical sequelae, many pregnancies diagnosed antenatally as being affected by exomphalos are terminated (Lakasing, Cicero et al. 2006, Springett, Budd et al. 2014) and only 34% are born alive (95%CI 27-41%) (Appendix 3). This is a parental decision that follows a counselling process with fetal medicine specialists and in many cases, invasive prenatal testing for associated problems.

The majority of live-born infants undergo surgery. The two ultimate aims in the surgical management of exomphalos are to return the extra-abdominal viscera to the abdominal cavity and to close the fascial defect. The timing of this procedure will depend on a number of factors including the severity of comorbidities, most importantly the infant's cardiorespiratory status, and the anatomical characteristics of the sac and its contents.

The term 'exomphalos' describes a spectrum of abdominal wall defects, from a slightly widened opening of the umbilical cord insertion that may allow a small amount of bowel to herniate through (Figure 1.5), to a large-scale failure of abdominal wall muscular development with a significant proportion of the viscera (the liver and the bowel) being extra-corporeal (Figure 1.6). In the latter variant, the two surgical aims may not be achievable due to a lack of space within the abdominal cavity along with a deficiency of muscle and fascia to close the defect. This situation is known as viscerocranial disproportion.

Figure 1.5. An infant with a small exomphalos defect containing bowel only



Where the defect is very small and there is no attachment of the bowel to the sac, infants may be treated without surgery. In such infants, the bowel is pushed back into the abdomen and the umbilical cord is tied with a sterile thread on the neonatal unit.

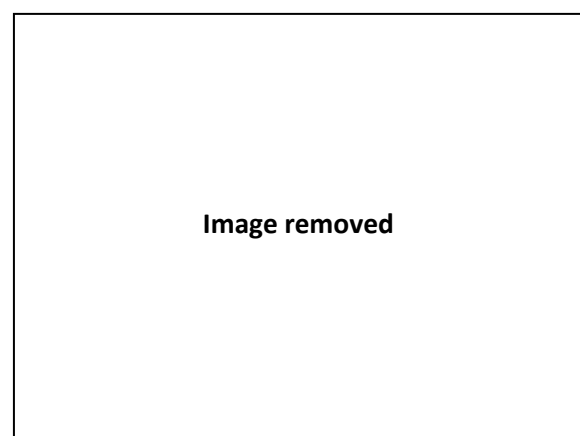
In infants with a larger abdominal wall deficiency, if the defect is felt to be small enough and in the absence of viscerο-abdominal disproportion, the infant will undergo primary operative fascial closure (OFC) under general anaesthesia. Here the viscera are reduced into the abdomen and the fascia closed directly with sutures. The sac is usually removed and the skin closed over the top. When viscerο-abdominal disproportion, unfavourable morphology of the liver or comorbidities preclude OFC, the infant must then undergo 'staged closure'.

A number of methods of staged closure have been described. Broadly these fit into four categories; primary skin closure alone with later ventral hernia repair (closure of the fascial defect), patch application, silo application and finally, escharotic therapy (Morgan, Hanna et al. , Pacilli, Spitz et al. 2005, Rijhwani, Davenport et al. 2005, Charlesworth, Ervine et al. 2009, Mitanchez, Walter-Nicolet et al. 2010, van Eijck, Aronson et al. 2011, Ein and Langer 2012, Lakhoo 2012). The latter of these, known informally as 'paint and wait' involves leaving the sac intact and applying dressings or topical treatments in most infants (Figures 1.6 and 1.7). Gradual epithelialisation of the sac is then allowed to occur. This process happens over the course of months and the infant is left with a large fascial defect which is then closed at a later date.

Figure 1.6 An infant with a large exomphalos defect undergoing escharotic therapy



Figure 1.7. A child with an epithelialised exomphalos sac



Infants requiring staged closure represent the most complex and challenging to manage from a surgical point of view and there remains a lack of consensus about the optimal management approach. Studies describing the staged management of exomphalos have been limited to single institutional series which, like those in gastroschisis, contain data on small numbers of infants, often collected over a long period of time (Pacilli, Spitz et al. 2005, Charlesworth, Ervine et al. 2009, van Eijck, van Vlimmeren et al. 2013). Outcomes of surgical management in exomphalos have never been assessed at a population level or through the use of prospective data collection.

Ensuring that people have a positive experience of care is a key assessment domain within the NHS Outcomes Framework (Department of Health 2016). The literature on parental experiences of early surgical care is, however, conspicuously lacking. Within this thesis the experiences of parents who had a baby diagnosed with exomphalos will be explored in order to identify ways in which these can be improved.

1.2 Research aim, objectives, research questions addressed and thesis structure

1.2.1 Aim

The overarching aim of the work contained within this thesis is to improve the lives of infants born with abdominal wall defects as well of those of their families by producing robust data to inform both the style and content of parental counselling as well as the choice of management strategy by clinicians. The specific objectives are outlined below.

1.2.2 Objectives

1. To pool contemporary published data from high-income countries using a robust methodology to produce population-based outcome estimates in gastroschisis to aid parental counselling and drive discussion about the most robust ways of assessing outcomes in this population.

1.2.2 Objectives – cont.

2. To obtain contemporary, population-based data about the management and outcomes of infants born with gastroschisis and exomphalos in the UK and Ireland and to examine the relationship with birth characteristics and management strategies in order generate prognostic information and assess the potential superiority of one strategy over another.
3. To explore the experiences of parents and children who are affected by a diagnosis of an abdominal wall defect in depth and identify ways in which these experiences could be improved.
4. To Identify and explore strategies to describe the long-term health and well-being of a population-based cohort of infants born with gastroschisis.
5. To use the information from the component studies to inform the design and evaluation of future studies of the management of infants born with abdominal wall defects.

1.2.3. Specific research questions and thesis structure

The aims and objectives outlined in 1.2.1 and 1.2.2 have been addressed in the chapters of this thesis as outlined below.

Chapter 2. Identification of population estimates for short-term outcomes of infants born with gastroschisis: a systematic review and meta-analysis

Research Question:

Can the findings from systematic review and meta-analysis of published data be used to produce outcome standards for the surgical management of gastroschisis?

Chapter 3. A population-based prospective cohort study using the BAPS-CASS system to collect data about the characteristics, management and short-term outcomes of infants born with exomphalos over a two-year period in the UK and Ireland.

Research Questions:

What is the live-birth prevalence of exomphalos in the UK and Ireland. What are the characteristics of the population of infants born alive with exomphalos, what management do they receive and what are their short-term outcomes?

Chapter 4. A qualitative analysis of the experiences of parents who have had a child born with exomphalos.

Research Question:

What are the experiences of parents following a diagnosis of exomphalos and what can healthcare professionals do to improve these?

Chapter 5. A description of a population cohort of children born with gastroschisis at the age of seven to nine years from the perspective of their parents.

Research Question;

What are the parent and child reported outcomes for children aged seven to nine born with gastroschisis?

Chapter 6. A population-based prospective cohort study using the BAPS-CASS system to collect data on childhood clinical outcomes of children born with gastroschisis.

Research Question:

What are the clinical outcomes of children born with gastroschisis at seven to nine years of age?

A variety of methodologies were used to address broader issues as well as the specific research questions outlined above. This process has allowed the evaluation of the various merits of the different approaches and identified their strengths as well as their limitations. By combining methodologies, for example, undertaking both qualitative and quantitative analyses to assess the experiences and outcomes of infants with exomphalos and their families or by assessing both clinician and parent-reported outcomes for infants with gastroschisis, the aim was to undertake a holistic approach to address the main research question. This is in line with the three-part definition of high quality health-care that now sits at the core of health-care evaluation in the NHS: effectiveness, patient experiences and safety (Darzi 2008).

Chapter 2

Identification of population estimates for short-term outcomes of infants born with gastroschisis: a systematic review and meta-analysis

2.1 Introduction

What does the future hold for an infant born in the 21st Century with gastroschisis? This, and the many questions concealed within it, will be firmly in the mind of any expectant parent who has been told that their unborn baby has this diagnosis. A large number of short and long-term outcomes of gastroschisis have been reported in the literature. This chapter concerns the investigation of the former, and Chapters Five and Six, investigate the latter.

The generation of robust data about short-term outcomes is not only of value to prospective parents, but has become a key obligation of practicing doctors. The concept of continuously improving the quality of clinical care through on-going assessment of practice in the form of research and audit has been undertaken within healthcare institutions since Victorian times (RCS 2013). This focus was endorsed and formalised within the concept of clinical governance, first introduced in the UK in the 1997 white paper 'The New NHS, Modern, Dependable' (Department of Health 1997). The culture of continuous improvement has flourished, as has a growing demand for transparency within the workings of healthcare organisations, and greater access to the outcome data of clinical teams following the Kennedy Report (Kennedy 2001). The report of the public enquiry into the deaths of children following cardiac surgery at Bristol Royal Infirmary triggered a number of cultural changes within the NHS.

In June 2013, NHS England began the staged publication of mortality rates of individual surgical specialists (NHS England 2013). Their aim was that more detailed outcome data, relevant to each specialty, will become available with time. Professor Sir Bruce Keogh, NHS England's National Medical Director stated:

"The data results show mortality levels. But in the majority of patients the issue is, how will an operation or procedure improve the quality of a patient's life? Over time, the information that will be available will expand to include more indicators which reflect this important quality measure."

(NHS England 2013)

2.1.1. Revalidation

All practicing doctors in the United Kingdom are required to be registered with the General Medical Council (GMC). In 2012 the GMC introduced the process of revalidation. This requires doctors to undergo a formal review every five years, whereby they must demonstrate that they are able to provide a 'good level of care', are fit to practice and keep themselves up-to-date in the field in which they work (GMC 2016).

For paediatric surgeons, 'maintaining a good level of care' means the outcomes for the infants and children they manage must be robustly reported to ensure that they are in-line with what would be expected of others in the same field. In order to set standards for these outcomes, the Royal College of Surgeons charged each of the surgical speciality associations with identifying index conditions, the outcomes of which could be scrutinised as part of the revalidation process. In 2013 the British Association of Paediatric Surgeons (BAPS), identified gastroschisis as one of three index neonatal surgical conditions, which should have outcomes reported as part of revalidation (RCS 2013a). The four chosen outcomes for analysis in gastroschisis were: length of stay (median), unplanned readmissions at 28 days, Reoperation or re-intervention at 28 days and mortality at 30 days. What has not been defined is the appropriate outcome standard for each criterion, nor how this might be agreed.

2.1.2. Methods of identifying outcome standards

The statement produced by BAPS suggests that in the first instance, an individual surgeon's outcomes should be compared to routinely collected national data (RCS 2013). Sources of such data in the UK include Hospital Episode Statistics for England (HES), Patient Episode Database for Wales (PEDW), the Information Services Division, Scotland (ISD) and the Department of Health, Northern Ireland. These databases collect information on all episodes of care in secondary (hospital) services that have been cleaned and validated after submission by Trusts/ Health-boards (HSCIC 2016). They have the potential to provide a repository of valuable information on surgical outcomes (Spencer 2011). To date, however, they have been plagued by inaccuracies due to reporting errors caused in part by incorrect coding of inpatient episodes (Spencer 2011). Authors from other surgical specialities have debated the utility of routinely collected data as a means of identifying standards for key performance indicators (Slavin, Deakin et al. 2012). Nouraei et al undertook an analysis of institutional outcomes in head and neck cancer using HES data and used logistic regression to construct risk-adjusted standardised mortality ratios (Nouraei, Middleton et al. 2013). They noted that highly disease-specific complications were less likely to be coded accurately and this could potentially affect conditions such as gastroschisis with a low prevalence of highly specific morbidities occurring in a low prevalence abnormality.

BAPS and the Royal College of Surgeons have stated that the 'gold standard' for measurement of outcomes should be 'national clinical audit' (RCS 2013). One such audit tool, for prospectively collecting data and assessing outcomes has so far been established with the speciality, for hypospadias surgery (BAPS 2016). A similar tool for use in gastroschisis known as an 'outcomes register' was launched in 2016. A concern that has been raised about registries of this kind, which rely on voluntary submission of data as well as parental consent for data inclusion is that these characteristics may introduce reporting bias and lead to gaps in data collection which could limit their validity and thus utility (Nouraei, Middleton et al. 2013).

When this has been assessed in the adult surgical literature, significant discrepancies were found between levels of activity according to data collected via a colorectal registry and that recorded on HES (Garout, Tilney et al. 2008). In addition, others found that units which did not submit data to the colorectal registry had higher mortality rates when HES data was used to assess this (Almoudaris, Burns et al. 2011).

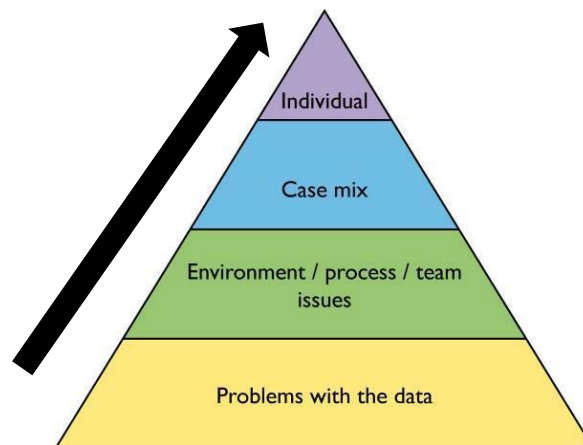
It could be argued that a recent British national cohort study of gastroschisis, to which all paediatric surgical centres contributed data, over an 18 month period, served the purpose of a national audit (Owen, Marven et al. 2010, Wiskin, Cole et al. 2011). The British cohort study provided a useful snapshot of contemporary outcomes in gastroschisis. A similar study has taken place in Canada, where outcome data continue to be collected prospectively (Youssef, Laberge et al. 2015).

The surgical literature contains a large number of studies reporting outcomes from a single centre or a small collection of centres, usually as retrospective cohorts. The relative rarity of conditions such as gastroschisis means that data reported from individual centres is frequently collected over a long period of time, during which practices and outcomes may have changed dramatically. The national cohort studies from the UK and Canada have sought to remedy this and have produced data on the outcomes of large, contemporary infant groups.

2.1.3. The importance of case mix in outcome assessment

The Royal College of Surgeons places a strong emphasis on assessment of outcomes in the context of an individual surgeon's 'case mix' (Figure 2.1) (RCS 2013). 'Case-mix' pertains to the complexity of the infants operated on and to the understanding of their outcomes in this context. The importance of 'case mix adjustment' was highlighted after a recent cessation of children's cardiac surgical services in a specialist centre. This was due in part to the incorrect interpretation of mortality data that were not sufficiently well risk adjusted (Scott-Moncrieff 2014).

Figure 2.1. The process of investigation of outliers in surgeon specific outcome assessment



(RCS 2013)

In the gastroschisis literature, a widely adopted risk-stratification system was proposed by Molik et al in 2001 (Molik, Gingalewski et al. 2001). Since then, many authors have reported outcomes in gastroschisis according to these criteria. This system divides infants into two groups. The first of these groups is termed 'complex' gastroschisis, and refers to infants where, at delivery, there is noted to either, be intestinal atresia (a blockage to the bowel), necrosis (areas where the bowel wall has suffered a lack of blood supply and perished), perforation (a hole in the bowel wall) or a twist affecting the bowel (volvulus). This is in contrast to 'simple' gastroschisis, where none of these features are present.

Molik's risk stratification was utilised within the systematic review described in this chapter, in order to allow clinicians to understand short-term outcomes according to case-mix and to provide more accurate prognostic information for outcomes of infants born with simple and complex gastroschisis.

2.1.4. Study aim

The aim of this study was to systematically review the recent literature to address the question: can meta-analytical techniques be used to amalgamate published outcome data to produce meaningful estimates of contemporary outcomes in gastroschisis?

Secondary aims were to generate useful prognostic information for the purposes of parental counselling both pre- and postnatally. Assessing the quality of studies reporting outcomes in the literature, will, in addition, provide an overview of the utility of using the literature to estimate population outcomes in neonatal conditions such as gastroschisis.

2.1.5. Research question

Can the findings from systematic review and meta-analysis of published data be used to produce outcome standards for the surgical management of gastroschisis?

2.2 Methods

A systematic review and meta-analysis protocol was drafted and registered on the Prospero International Prospective Register of Systematic Reviews (CRD42014009172) prior to commencing the study.

2.2.1 Search strategy and eligibility criteria

The *Embase* and *Medline* electronic databases were searched as well as the Cochrane Library and the International Register of Controlled Trials. Papers published between the 1st January 2000 and the 8th of December 2015 were reviewed. In addition, a search of *Google Scholar* was undertaken on 15th of April 2014.

The search strategy included terms relating to both the population and the outcomes of interest. Both MeSH terms and searches within the title and abstract were performed. No search limits were applied to intervention in order to capture the widest possible number of studies; no language limits were applied. Reference lists of all included papers were searched by-hand to identify papers which may have been missed by the initial search strategy. The search strategies for *Medline* and *Embase* are shown in Table 2.1.

Table 2.1. Electronic database search strategy

Population	Outcome
<i>Gastroschisis</i>	<i>Treatment Outcome</i>
Gastroschisis	<i>Ventilation</i>
Laparoschisis	<i>Artificial Ventilation</i>
Not “developing countr*”	<i>Parenteral Nutrition</i>
Not “low resource”	<i>Newborn Sepsis</i>
Not “resource-poor”	<i>Sepsis or infection</i>
Not “low income”	<i>Infant Mortality</i>
	<i>Mortality</i>
	<i>Survival</i>
	<i>Survival Rate</i>
	<i>Length of Stay</i>
	<i>Hospital Readmission</i>
	<i>Long term survival or overall survival or short term survival or survival rate or survival time</i>
	Outcome*
	Ventilat*
	Feed*
	Nutrition
	Failure*
	Sepsis or bacter* or infection
	Dehiscence
	“compartment syndrome”
	Complication*
	Readmi*
	Admi*
	Mortal*
	Morbid*
	“length of stay”
	Fatal*
	necr*
	Reoperat*
	Ischaemi*
	Parenteral
	Stay

(*Mesh terms*) (terms searched in title and abstract)

In order that the findings of this study are relevant to clinicians practicing in high resource settings such as the UK, only studies published from centres located in countries classified as 'High Income' by the World Bank were included (World Bank 2014). In addition, to enable assessment of contemporary outcomes, only studies published after the year 2000 were included and only published data were included.

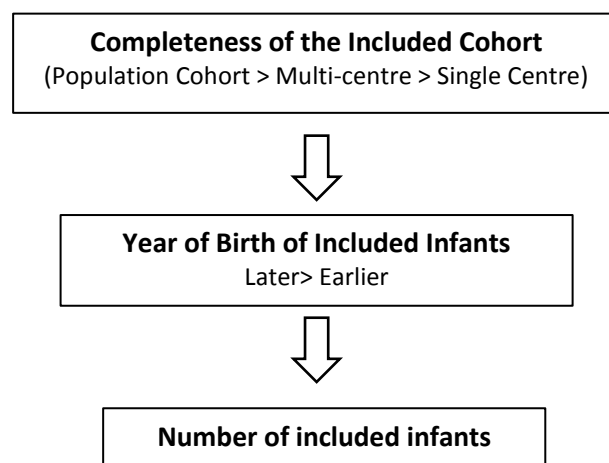
Thus, the population included in this review was: infants born with gastroschisis whose outcomes are reported in studies published after the year 2000. Comparisons were made between the outcomes of infants with simple gastroschisis, complex gastroschisis and those representing a mixed group. The outcomes assessed were: mortality to 30 days and one-year after birth, length of hospital stay and unplanned reoperation within 28 days. Studies in any language were eligible for inclusion and only published data were included.

2.2.2 Exclusion criteria

Studies reporting the outcomes of fewer than five infants were excluded, as were those which did not represent a consecutive cohort treated within a given centre or group of centres. In order to make the results generalisable to the entire population of infants born with gastroschisis, studies that had specific inclusion criteria or omitted a subgroup of infants such as those with comorbidities or chromosomal abnormalities were excluded.

In order that outcome data for individual infants were not duplicated in the analysis, overlapping cohorts containing the same infant data were not included and a system of rules was devised to select the most comprehensive and contemporary sample. The decision 'tree' for deciding which of the overlapping cohorts to use is shown in Figure 2.2.

Figure 2.2. Decision tree illustrating how studies with overlapping cohorts were selected



2.2.3 Data extraction

The above search strategy was used to retrieve titles and abstracts of studies. These were then reviewed by the author and a second reviewer[†], working independently to identify any that met the inclusion criteria outlined above. The full text of potentially eligible studies was then reviewed by the author and two further reviewers[‡] working independently to assess eligibility for inclusion. Any disagreement over study inclusion was resolved through discussion with a third reviewer[‡].

After studies had been selected to be included in the review, the data extracted were entered into a standardised form, independently by the author and a second reviewer[‡]. Discrepancies were identified and resolved through discussion with a third reviewer[‡].

[†] A medical student [‡] One medical student and one surgical trainee.

[‡] Professor Marian Knight, one of the author's supervisors.

[‡] Data were extracted by the author and second surgical trainee, working independently

Table 2.2. Criteria established *a priori* for inclusion of data based on outcome reporting

Outcome	Included	Excluded
Death before 30 days after birth	• ‘Neonatal mortality’ • Individual deaths reported < 30 days after birth • Death within 30 days of first operation	• ‘Infant mortality’ • In-hospital mortality • ‘Postnatal deaths’
Death before one-year after birth	• Individual deaths described or total number of deaths reported with apparently robust one-year follow up	• Individual deaths described where there was no apparently robust one-year follow up on all infants
Length of hospital stay	• Median reported	• Mean reported • Unclear if mean or median reported
Unplanned reoperation before 28 days	• Individual, unplanned reoperations reported $\leq$ 28 days after birth	• Unclear information as to timing of reoperations • Unclear information as to whether reoperations were planned or unplanned

2.2.4 Risk of bias assessment

Studies selected after full-text review for inclusion in the meta-analysis were assessed for risk of bias. These were marked out of nine using a modification of the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies (Wells GA 2014) (Appendix 4). The NOS in its original form was inappropriate to be used to assess the studies included in this meta-analysis because they did not contain a non-exposed cohort. For this reason, the section ‘selection of the non-exposed cohort’ was replaced with the question relating to sample size selection from the version of the NOS adapted for cross sectional studies (Wells GA 2014).

In addition, the section from the original NOS regarding ‘comparability of the cohorts’ was replaced with the corresponding section from the version adapted for cross-sectional studies assessing comparability of those in the outcome groups (Appendix 4).

2.2.5 Data synthesis

Categorical outcomes were analysed using the *metaprop* function in *Stata 13 SE*. The summary measures used in these analyses to estimate risk were: case fatality before thirty days and one year after birth, proportion of unplanned readmissions and proportion of reoperations before 28 days. A random effects model was used due to potential heterogeneity between included populations caused by the small numbers of individuals in included studies (Eaton 2013). *Review Manager 5.3* was used to compare the outcomes between infants with simple or complex gastroschisis.

Length of stay is not normally distributed and therefore could not be assessed using standard meta-analytical techniques. For this outcome, the median of the published medians was used as the summary measure. Median length of stay between infants within different groups was compared using the Mann-Whitney test in *Stata 13*.

Heterogeneity was assessed using the I-squared and Chi-squared statistics.

2.2.6 Assessment of publication bias

Where comparisons between the outcomes of infants with simple and complex gastroschisis were undertaken, funnel plots were produced where possible in order to assess evidence of publication bias.

2.2.7 Additional analysis

The search strategy identified studies published after the year 2000. Many of these contained infants born many years before the year 2000. An additional assessment was undertaken to investigate whether there was evidence of any change in outcomes with time. Cohorts including infants born before the year 2000 were assessed independently of cohorts with all infants born after the year 2000 as well as amalgamating all cohorts together to assess the outcome from all cohorts. Difference in median length of stay between these two groups of cohorts was assessed using the Mann-Whitney test in *Stata 13 SE*.

2.2.8 Alterations to the registered protocol

When the original review protocol was registered it was proposed that sixteen primary outcomes would be assessed. The heterogeneity encountered in the way that the outcomes were reported led to complexity in the process of study identification beyond that described in the methods. It was therefore decided to focus on the four analyses described in this chapter because three have been identified by BAPS and the Royal College of Surgeons as necessary for assessment of performance and the other, death before one year, was chosen *a priori* as being essential to provide a longer-term assessment of mortality data.

Due to other commitments of the original co-reviewer (a medical student), two additional reviewers provided assistance with the full-text review and risk-of-bias assessment. These were two surgical trainees as described previously.

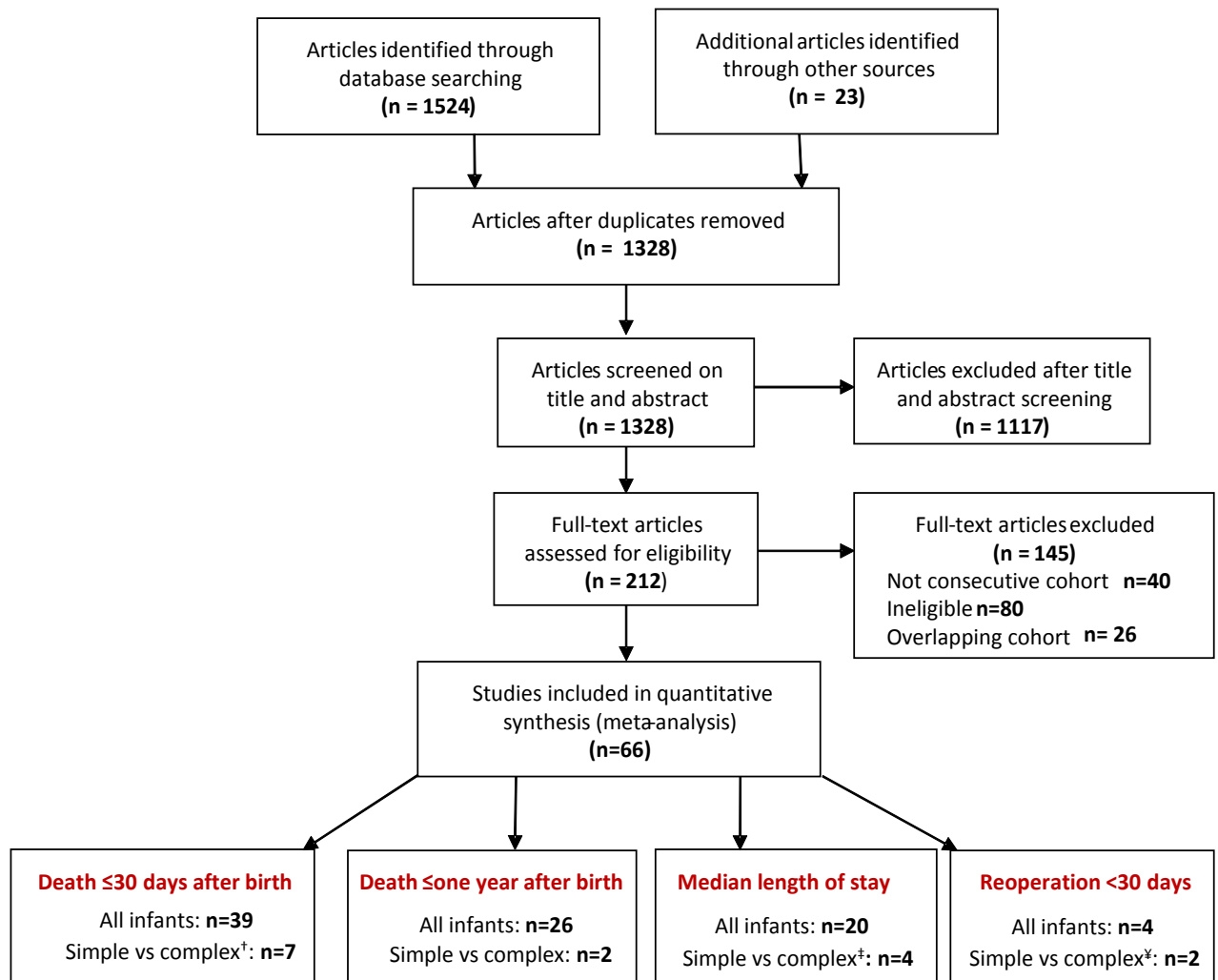
2.3 Results

The methods described above identified 1547 articles. The PRISMA flow diagram in Figure 2.3 shows the process of selection (Moher, Liberati et al. 2009). The full text analysis included 212 articles. Thirty-nine articles contributed to the meta-analysis of risk of death within 30 days after birth; 26 to risk of death within one year of birth; 20 to the length of stay analysis; and four to the risk of reoperation within 28 days. Included studies are described in Table 2.3.

Following a number of unsuccessful requests to authors of published abstracts, no missing or unpublished data were obtained from authors.

Excluded studies and the reasons for exclusion are shown in Appendix 5. No randomised controlled trials met the criteria for inclusion as these studies were undertaken on a select subset of infants with strict inclusion criteria. Their results were, therefore not applicable to the population of infants with gastroschisis treated in any given centre.

Figure 2.3. The PRISMA flow diagram for study selection



'n' refers to the number of studies.

†7/7 contained outcome data for infants with simple gastroschisis, 6/7 contained outcome data for infants with complex gastroschisis

‡4/4 contained outcome data for infants with simple gastroschisis, 3/4 contained outcome data for Infants with complex gastroschisis

§2/2 contained outcome data for infants with simple gastroschisis, 1/2 contained outcome data for Infants with complex gastroschisis

Table 2.3. Studies included in the meta-analysis (First author A-J)

Author, Year published	Country, Recruitment period	Meta-analyses	Study design	Total (N)	Simple n*	Complex n*	NOS Score/ 9
Allotey, 2007	UK 2000-2006	ED ^M	SI RC	53			4
Andrea, 2007	Germany 1993-2005	ED ^M , LD ^M	SI RC	28			4
Badillo, 2008	USA 2000-2007	ED ^M	SI RC	61			4
Barrett 2014	Eire 2007-2011	LOS ^M	NPopn RC	70			6
Bradnock, 2011	UK 2006-2008	ED ^M , ED ^{SC} , LD ^M , LD ^{SC} , LOS ^{SC}	NPopn PC ^o	393	45	336	6
Brantberg, 2004	Norway 1988-2001	ED ^M , LD ^M	SI PC	60			4
Bucher 2012	USA 2001-2010	LOS ^M	SI RC	118			5
Capelle 2007	Belgium 1992-2003	LD ^M	SI RC	22			4
Car, 2011	Croatia 2005-2010	ED ^M	SI RC	10			4
Charlesworth 2007	UK 1993-2005	LOS ^M	SI RC	110			5
Charlesworth 2014	UK 1993-2012	ReOp ^{SC}	SI RC	156	156	0	5
Chiu, 2006	USA 1994-2004	ED ^M	SI RC	48			4
Choi, 2012	USA 1999-2010	ED ^{SC} , LOS ^{SC}	SI RC	70	70	0 (18†)	4
Cohen-Overbeek, 2008	Netherlds 1991-2003	ED ^M	SI RC	28			5
Dimitriou, 2000	UK 1993-1998	ED ^M , LD ^M , LOS ^M	SI RC	32			5
Driver 2001	UK 1992-1998	LOS ^M	SI RC	91			5
Durfee 2002	USA 1993-1998	LD ^M , LOS ^M	SI RC	24			4
Eggink, 2006	USA 1983-2003	ED ^M , LD ^M	SI RC	72			4
Emil, 2012	USA 2001-2007	ED ^M , ED ^{SC} , LD ^M , LD ^{SC}	MI RC	83	64	19	5
Fallon, 2012	USA 2000-2007	ED ^M , LD ^M	SI RC	59			4
Friedmacher 2014	Austria 1975-2008	ReOp ^M , ReOp ^{SC}	SI RC	108	94	14	5
Garne, 2002	Denmark 1980-1993	ED ^M , LD ^M	RPopn RC	6			5
Gelas, 2008	France 1990-2004	LOS ^{SC}	SI RC	69	61	8	5
Goetzinger, 2014	USA 2001-2010	ED ^M , ED ^{SC}	SI RC	94	87	18	5
Guida, 2013	Italy 1976-2009	ED ^M , LOS ^M	SI RC	12			4
Harris 2014	Australia 1992-2005	ED ^M	MI RC	103			5
Henrich, 2008	Germany 1994-2004	ED ^M	SI RC	40			4
Hwang 2004	USA 1982-1999	LD ^M	SI RC	79			4
Jager, 2007	Netherlds 1988-2005	ED ^M , ED ^{SC} , LD ^M , LOS ^M	SI RC	59	49	10	4
Janoo, 2013	USA 1998-2002	ED ^M	SI RC	19			4
Jona, 2003	USA 2001-2001	ED ^M , ReOp ^M	SI RC	16			5

Key – ED^M Death <30d (Mixed), ED^{SC} Death <30d (Simple/ Complex) LD^M Death <1yr (Mixed), LD^{SC} Death <1yr (Simple/ Complex)

SI: Single Institution, MI: Multiple Institutions, NPopn: National Population RPopn: Regional Population, RC: Retrospective Cohort, PC: Prospective Cohort,

NOS: Newcastle Ottawa Score ^oStudies collecting data specifically for outcome assessment LOS^M: Length of hospital stay (Mixed)

LOS^{SC}: Length of hospital stay (Simple/ Complex) ReOp^M: Reoperation (Mixed) ReOp^{SC}: Reoperation (Simple/ Complex) † All excluded

*N^os given only for studies where groups were included in meta-analysis

Table 2.3. (cont) Studies included in the meta-analysis (First author K-Y)

Author, Year published	Country(s), Recruitment period		Meta-analyses	Study design	Total (N)	Simple n	Complex n	NOS Score/ 9
Kassa 2011	Sweden	1989-2009	LOS ^M	SI RC	79			4
Keys 2008	UK	1996-2005	LOS ^M	SI RC	96			5
Khalil 2008	UK	1999-2004	LOS ^M	SI RC	72			5
Kuleva, 2012	France	1999-2010	ED ^M , ED ^{SC}	SI RC	103	89	14	5
Lato, 2013	Germany	1997-2009	ED ^M	SI RC	71			5
McNamara 2011	USA	2002-2008	ReOp ^M	SI RC	32			5
Mesas-Burgos 2015	Sweden	2010-2014	LOS ^M	SI RC	52			5
Minutillo 2013	Australia	1997-2010	LD ^M	RPopn RC	117			5
Molik, 2001	USA	1992-1997	ED ^M , ED ^{SC}	SI RC	103	71	32	4
Murphy, 2007	Eire	1998-2004	ED ^M , LD ^M	NPopn RC	53			5
Nichol, 2004	USA	Not Given	ED ^M , ReOp ^M	SI RC	16			4
Orion, 2011	USA	2000-2009	ED ^M , LD ^M	SI RC	80			4
Overcash 2014	USA	2007-2012	ED ^M	MI RC	191			4
Payne 2009	USA	1990-2007	LOS ^M	SI RC	155			5
Reigstad, 2011	Norway	1993-2008 [‡]	ED ^M , LD ^M , LOS ^M	SI RC	30			4
Salihu, 2002	Germany	1989-1996	ED ^M	SI RC	13			5
Santiago-Munoz, 2007	USA	1998-2006	ED ^M , LOS ^M	SI RC	63			5
Savoie 2014	USA	2008-2013	ED ^M	MI RC	528			5
Sawicka, 2000	Poland	1992-1997	ED ^M , LD ^M	SI RC	23			5
Sawicka 2013	Poland	2000-2010	ED ^M , LD ^M	SI RC	32			4
Schlatter, 2003	USA	1991-2000	ED ^M , LD ^M	SI RC	65			5
Schlueter, 2015	USA	2001-2013	LOS ^M	SI RC	155			5
Sharp, 2000	Australia	1986-1996	LD ^M , LOS ^M	RPopn RC	58			5
Singh, 2003	Australia	1990-2000	LD ^M	MI RC	181			4
Sipek, 2006	Czech Replc	1994-2004	ED ^M , LD ^M	NPopn RC	302			6
Snyder, 2011	USA	1999-2009	LD ^M	SI RC	167			5
Sydorak 2002	USA	1999-2009	ED ^M	SI RC	69			4
Tam, 2011	USA	2000-2008	ED ^M , LD ^M , LOS ^M	SI RC	104			5
Vachharajani, 2007	USA	2001-2005	LD ^M , LOS ^{SC}	SI RC	70 [§]	42	16	4
Vegunta, 2005	USA	1998-2002	ED ^M , LOS ^M	SI RC	30			4
Wang, 2011	USA	1983-2006	ED ^M , LD ^M	RPopn RC	777			5
Youssef 2015	Canada	2005-2013	LOS ^M	NPopn PC [®]	692			5

Key – ED^M Death <30d (Mixed), ED^{SC} Death <30d (Simple/ Complex) LD^M Death <1yr (Mixed), LD^{SC} Death <1yr (Simple/ Complex) SI: Single Institution MI: Multiple Institutions

NPopn: National Population RPopn: Regional Population, RC: Retrospective Cohort, PC: Prospective Cohort NOS: Newcastle Ottawa Score

[®]Studies collecting data specifically for outcome assessment LOS^M: Length of hospital stay (Mixed) LOS^{SC}: Length of hospital stay (Simple/ Complex) Reop^M: Reoperation (Mixed)

Reop^{SC}: Reoperation (Simple/ Complex) *N^os given only for studies where groups were include in meta-analysis

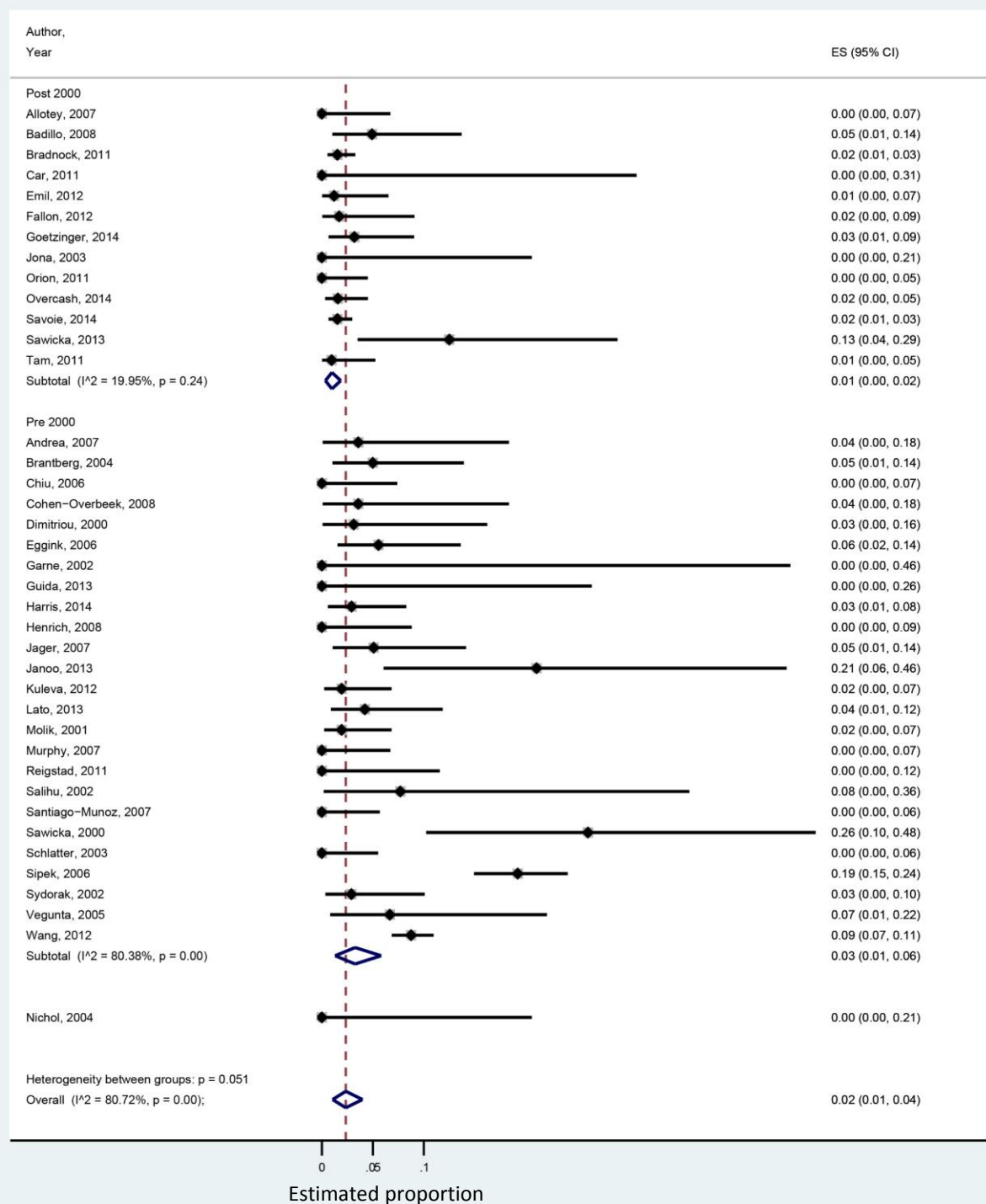
[‡]LOS 1998-2008 n=20 [§]LOS n=58

2.3.1 Death within 30 days of birth

Of the 212 studies included in the full text review, 39 had sufficient data to be included in the meta-analysis of death before 30 days after birth. These studies contained information about the 30 day case fatality in 3925 infants; 192 of these infants died in this time period. The results of the meta-analysis are shown in Figure 2.4. The pooled estimate showed that 2% of all infants died in the first 30 days after birth, (95% CI 1-4%). This represents the proportion of all infants who died, including those with simple and complex gastroschisis. There was a difference in the pooled estimate derived from studies that only included infants born after the year 2000 compared with those including infants born before 2000 (1%, 95% CI 0-3%, compared with 3% 95% CI 1-6% respectively), although this difference was not statistically significant.

The overall I^2 statistic of 80.7% suggests substantial heterogeneity between studies which, was statistically significant ($p < 0.01$). A high degree of variation is clearly observed in the differing estimated proportions between studies and their wide confidence intervals (Figure 2.4). There was less variation in studies published with cohorts born after 2000, with an I^2 statistic of 19.95% ($p = 0.24$). There was only one clear outlier in this later group, a small study published from Poland which reported four neonatal deaths among a group of 32 infants (Sawicka, Wieprzowski et al. 2013). Characteristics of the Polish healthcare service may also have contributed and these will be discussed in 2.4.2i.

Figure 2.4. Estimates of 30 day case fatality for all studies reporting this outcome

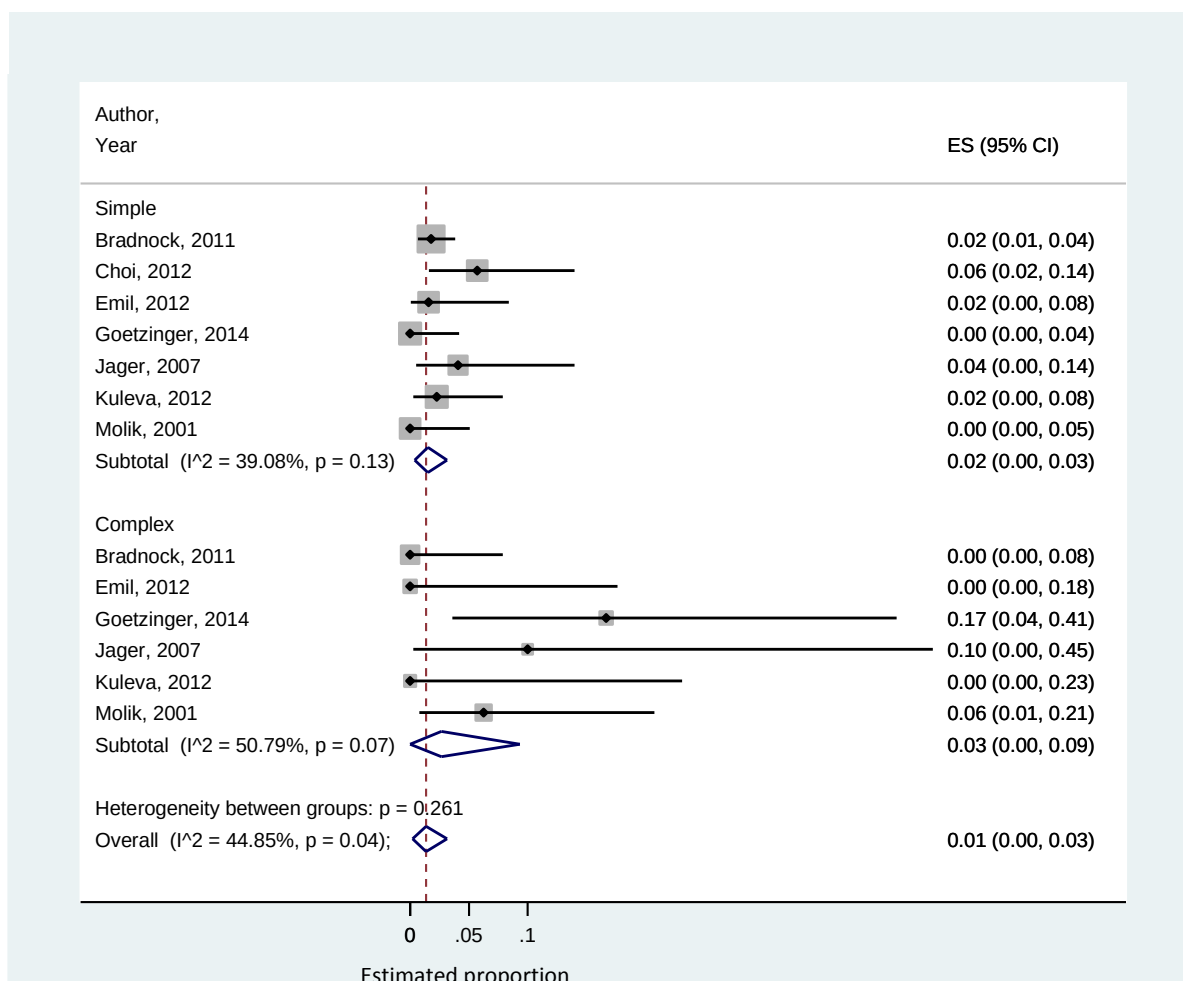


ES – Estimated proportion

In the study by Nichol et al 2004, it was not possible to ascertain whether all infants were born after the year 2000

Seven studies contributed towards the assessment of death before 30 days in infants born with simple and complex gastroschisis. These studies reported this outcome in 766 infants with simple and 138 infants with complex gastroschisis. The pooled estimate for the proportion of infants with simple gastroschisis that died within thirty days after birth was 2%, (95% CI 0-3%) and 3% of those with complex gastroschisis (95% CI 0-9%), (Figure 2.5). These studies were heterogeneous with an I^2 statistic of 44.85% ($p=0.04$). The study by Goetzinger et al. is an outlier within this analysis where three deaths were seen within the 18 infants in their series with gastroschisis. There is no indication of the cause of death in these neonates, but the small number of infants with complex gastroschisis in this and the other studies mean that confidence intervals around the estimates are wide.

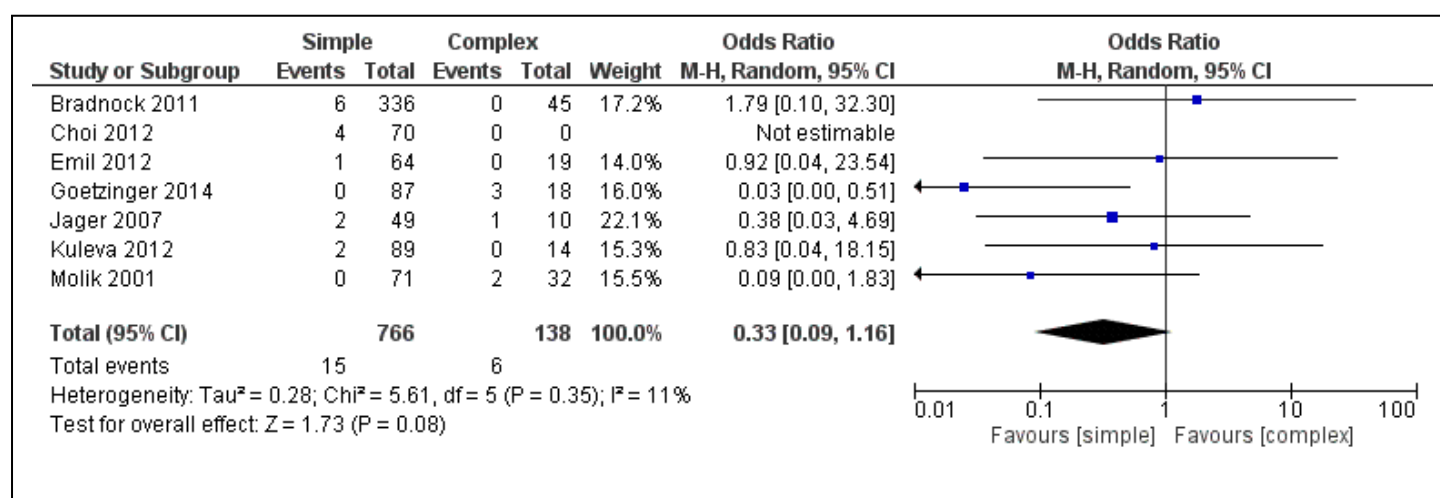
Figure 2.5. Estimates of rates of death before 30 days after birth for infants with simple and complex gastroschisis



ES: Estimated proportion

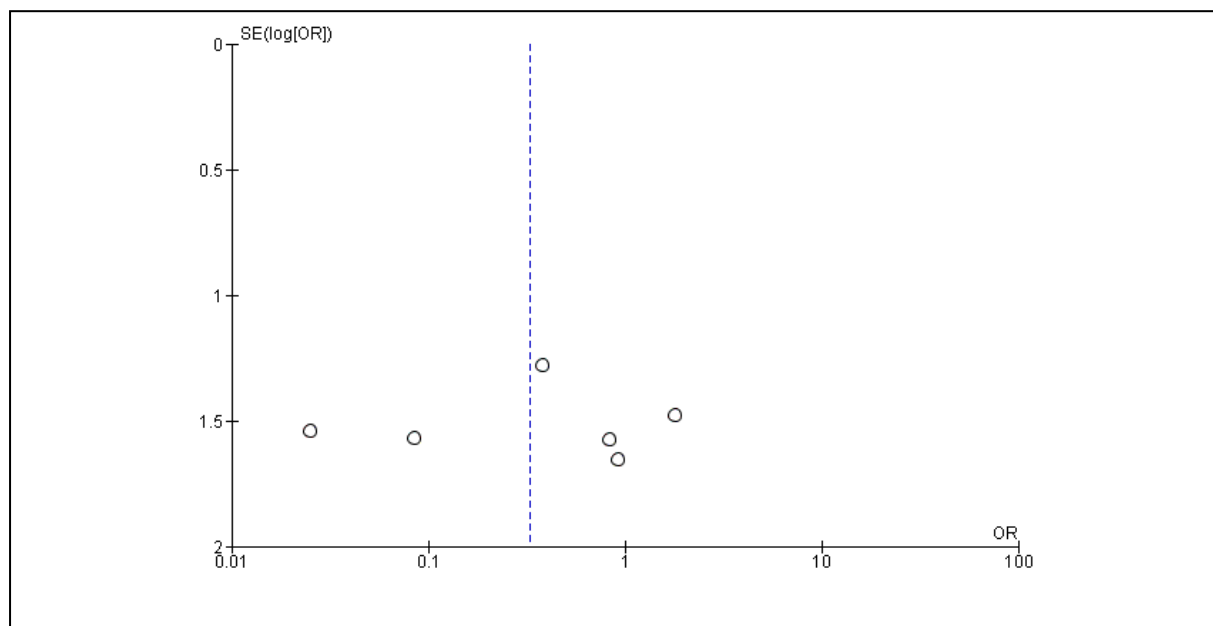
No statistically significant difference was identified in this outcome between these risk groups when they were directly compared; the pooled odds ratio was 0.33 (95%CI 0.09-1.16) ($p=0.08$) which favours a better outcome for simple cases (Figure 2.6). There was low level of heterogeneity between studies with an I^2 statistic of 11% ($p=0.35$).

Figure 2.6. Comparison of the odds of death before 30 days after birth for infants with simple vs complex gastroschisis



An analysis of possible publication bias was undertaken using a funnel plot as shown in Figure 2.7. This illustrates that the studies contributing to this analysis are fairly evenly distributed on either side of the pooled odds ratio providing evidence against publication bias although the small number of data points mean this is difficult to assess conclusively.

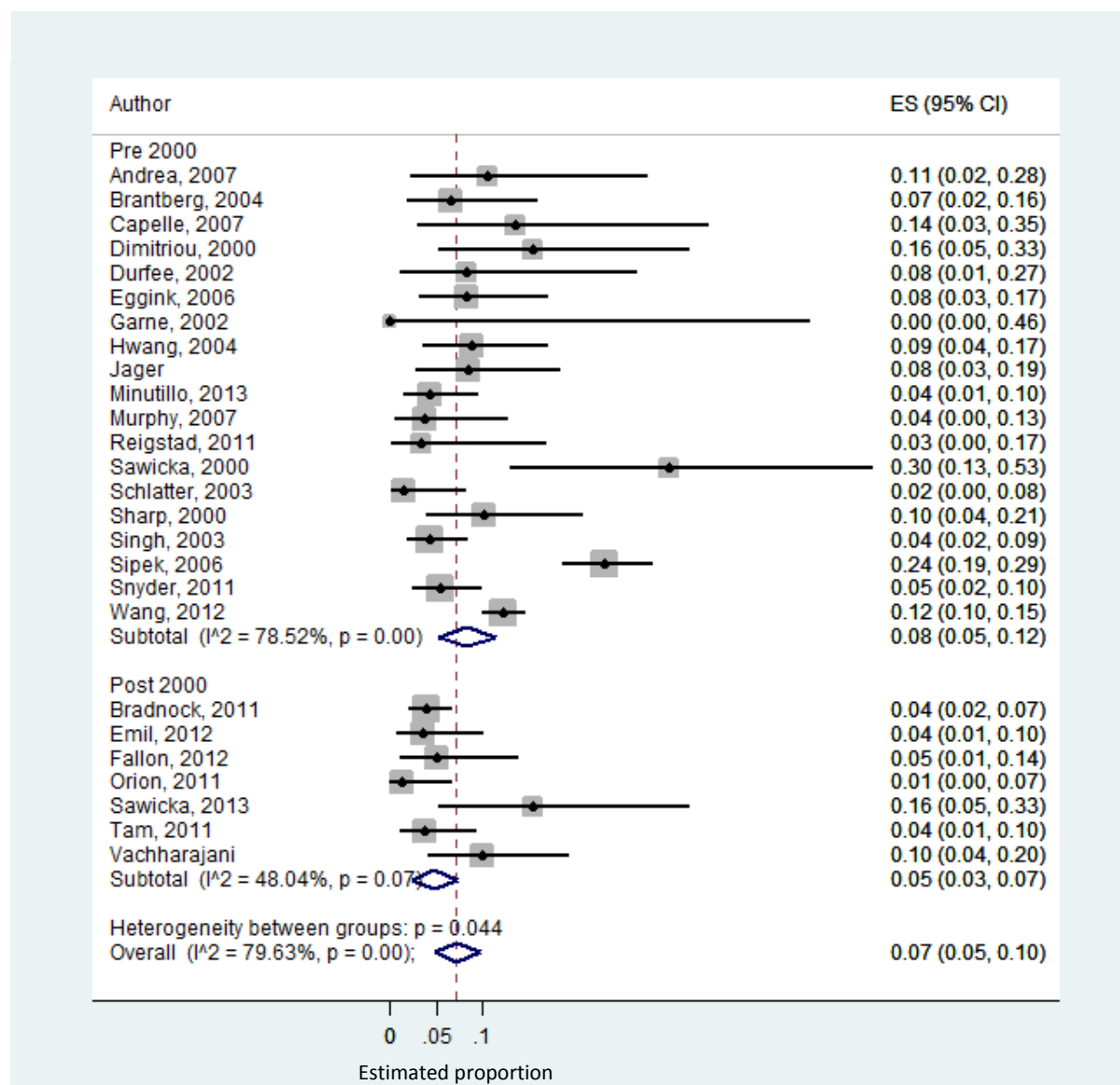
Figure 2.7. Funnel plot of studies contributing to the analysis of the difference in odds of death before 30 days in infants with simple and complex gastroschisis



2.3.2 Death within one-year of birth

Twenty-six studies contributed towards the analysis of death before one-year in the mixed group of infants, including those with simple and complex gastroschisis. The pooled estimate from the 2884 infants contributing to this analysis was that death before one-year occurred in 7% (95% CI 5-10%) of infants (Figure 2.8). These studies were, again, highly heterogeneous with an overall I^2 statistic of 79.6% ($p < 0.001$). There was some evidence that the studies including only infants born after the year 2000 had a lower pooled estimate for the risk of death (5% 95% CI 3-7% vs 8% 95%CI 5-12%) although the difference compared with pre-2000 studies was not statistically significant. Later studies were also less heterogeneous with an I^2 statistic of 48% compared to 79% in the earlier studies.

Figure 2.8. Meta-analysis of death before one year after birth for all studies reporting this outcome[†]

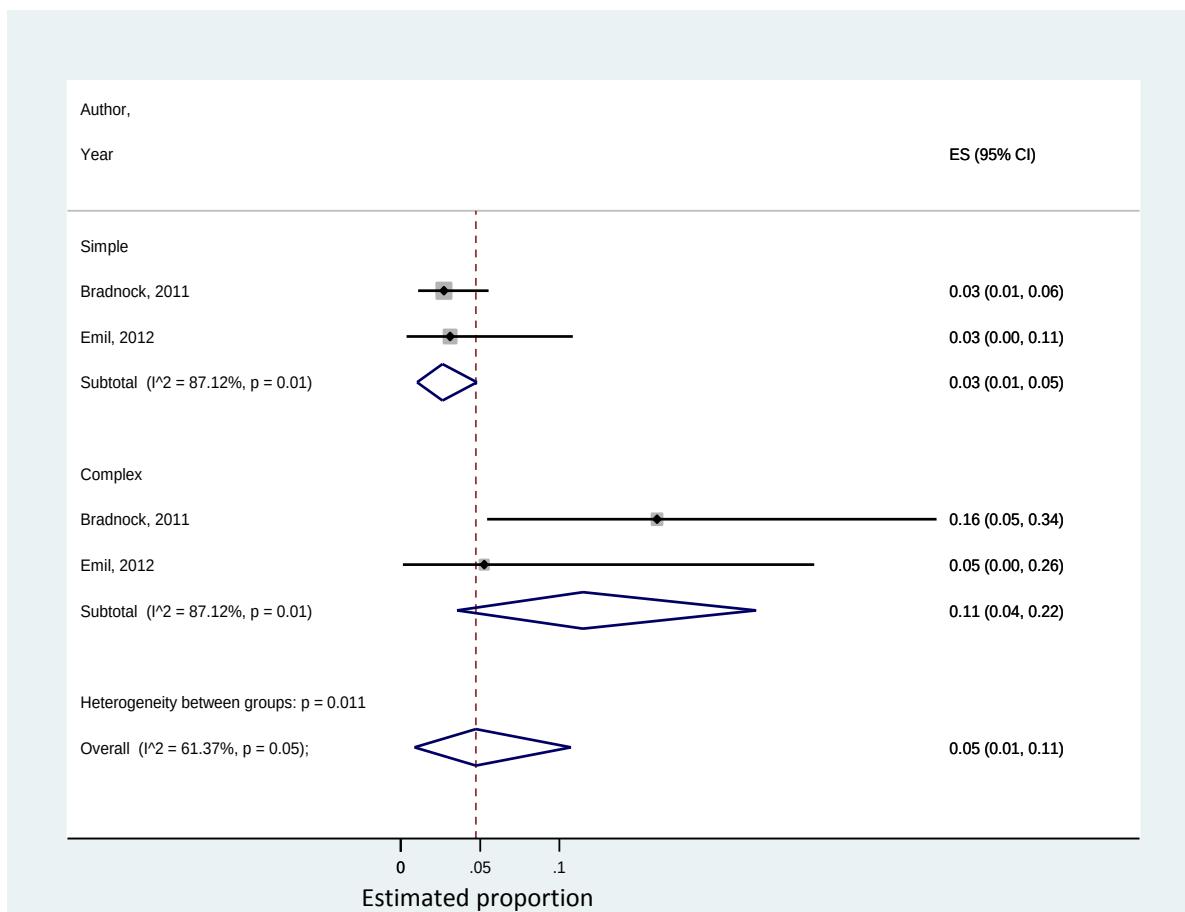


[†]Includes those with simple and complex gastroschisis ES: Estimated proportion

Two studies, involving 371 infants, enabled the assessment of death before one year in infants with simple and complex gastroschisis to be independently assessed. There were nine deaths in 321 infants with simple gastroschisis and six deaths in 50 infants with complex gastroschisis, (Figure 2.9). This shows that the pooled risk of death before one-year was 3% (95%CI 1-5%) among infants with simple gastroschisis and 11% among those with complex gastroschisis (95% CI 4-22%).

These two studies gave similar rates among those with simple and complex gastroschisis. However, due to the low prevalence of both complex gastroschisis and death before one-year as an outcome and the small numbers of infants included in this analysis these estimates are imprecise as illustrated by the very wide confidence intervals. Substantial heterogeneity between studies was again noted (I^2 61.37%, $p=0.05$).

Figure 2.9. Estimates of the risk of death before one year after birth for infants with simple and complex gastroschisis



ES – Estimated proportion

Figure 2.10 shows that there was evidence of a significant difference in the odds of death by one year in those with simple and those with complex gastroschisis ($p=0.003$). The pooled odds ratio was 0.19 (95%CI 0.06-0.57) showing that the odds of dying with simple gastroschisis were significantly lower than for complex gastroschisis.

Fig 2.10 Comparison of the odds of death before one-year after birth for infants with simple vs complex gastroschisis

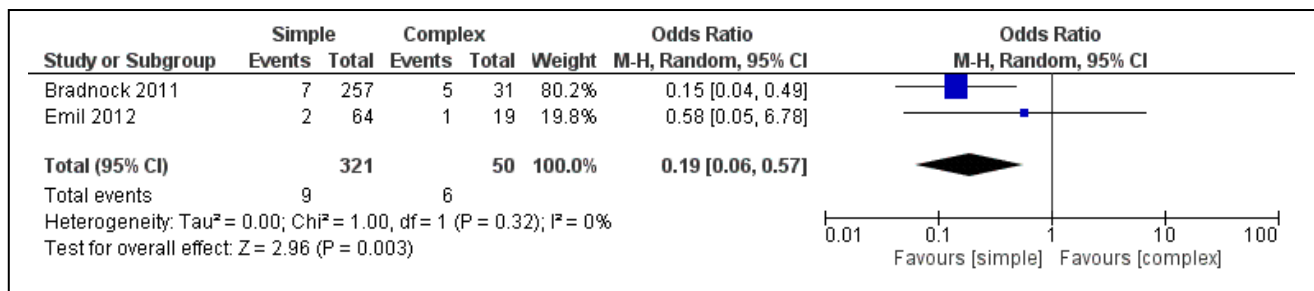
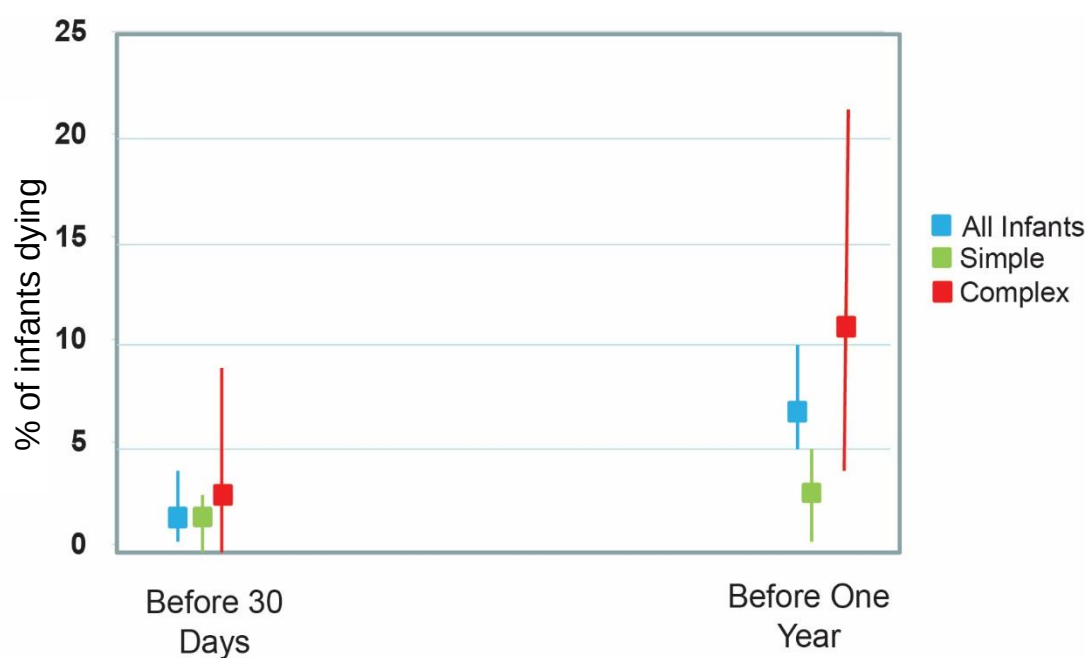


Figure 2.11 summarises the pooled estimates for mortality before one month and one year in all infants, and in those with simple and gastroschisis as separate groups.

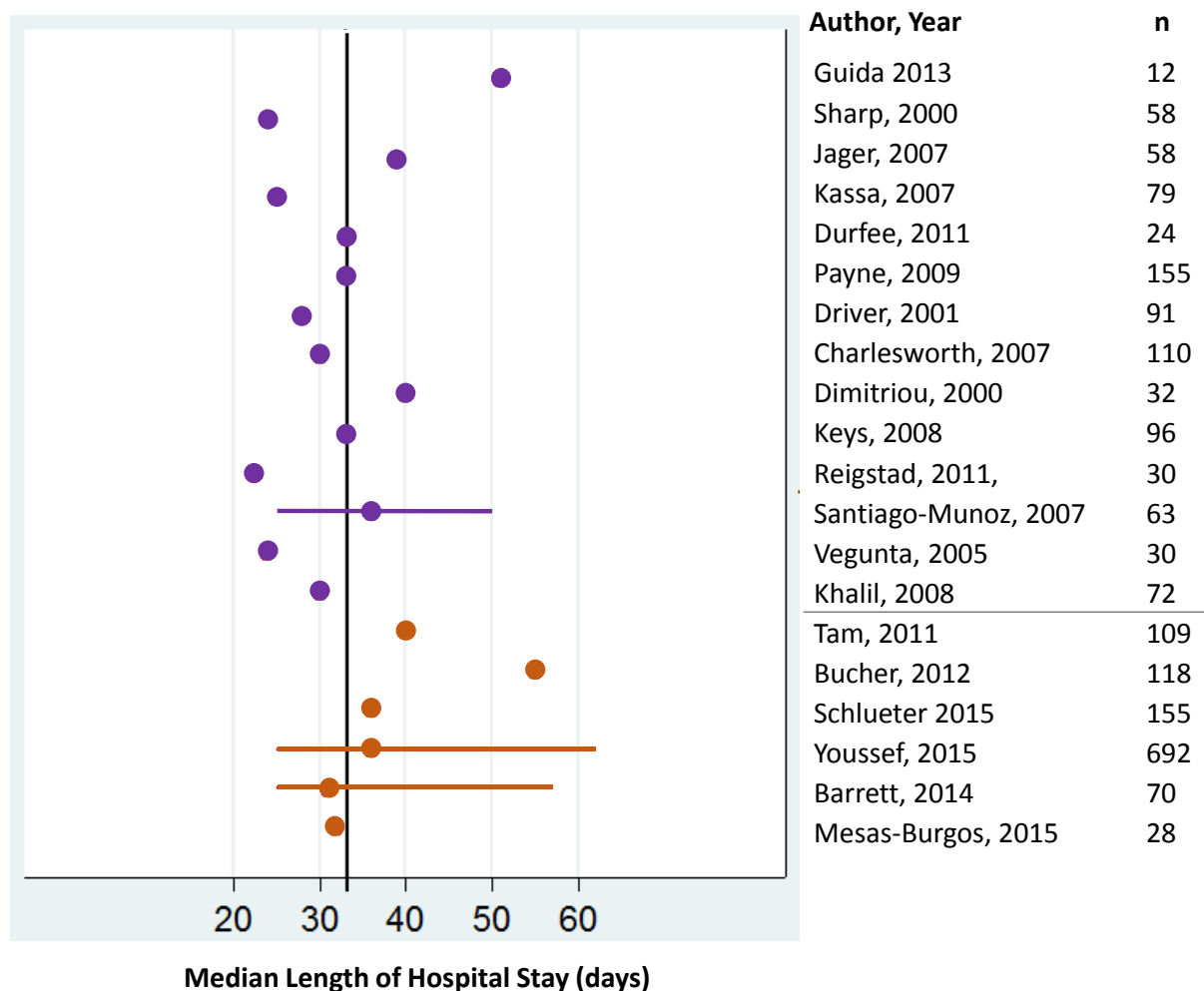
Figure 2.11. Population estimates of the risk of death in specified groups of infants with gastroschisis



2.3.3. Length of hospital stay

Twenty studies contributed to the analysis of median length of stay (LOS) representing 2072 infants (Figure 2.12). This shows that median LOS in published studies, although not assessed formally, was heterogeneous. The pooled median LOS from these studies (the median of the medians) was 33 days (IQR of medians 28.5-38.25) indicating that across these studies conducted at different time periods and different countries, discharge 'on average' occurs at around 33 days after birth.

Figure 2.12. Median length of hospital stay in infants born with gastroschisis.
(includes those with simple and complex gastroschisis).



Key:

Pooled median is shown as a vertical black line.

Studies including outcomes of infants born earlier than 2000 are shown in purple.

Studies including outcomes only of infants born after 2000 are shown in orange.

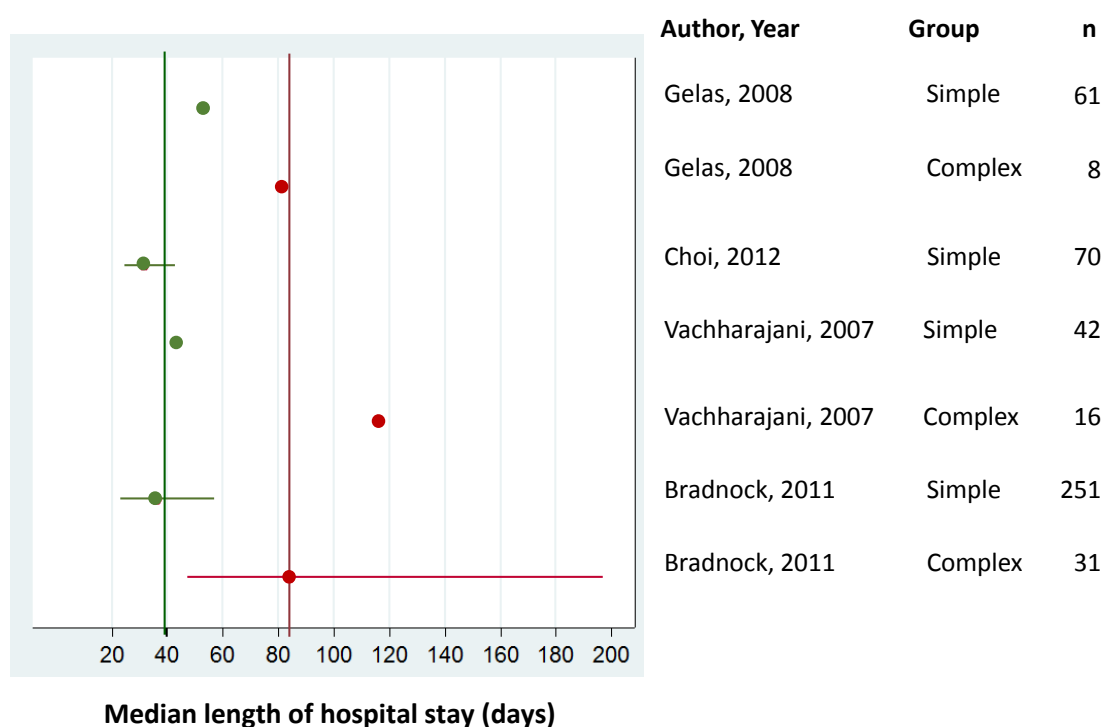
These are shown above (before 2000) and below (after 2000) the horizontal line in the right hand column

Interquartile ranges (where published) are shown as horizontal lines in the figure

A further analysis was undertaken to investigate the median LOS in those publications with infants born before and after 2000. The median of the median LOS measurements for the cohorts with infants born before 2000 was 31.5 days and for those with only infants born after 2000 it was 36 days. This difference was not statistically significant, $p = 0.10$.

Four studies separated the outcomes of simple and complex infants (Choi 2012, Gelas 2008, Vachharajani 2007 and Bradnock 2011 (Vachharajani, Dillon et al. 2007, Gelas, Gorduja et al. 2008, Bradnock, Marven et al. 2011, Choi, McBride et al. 2012). The median of the median LOSs for the 424 infants with simple gastroschisis was 39.5 days. For infants with complex gastroschisis, (55 infants in total) this was 84 days. This difference was statistically significant, $p = 0.03$.

Figure 2.13 Median length of hospital stay in infants born with simple and complex gastroschisis



Key:

Pooled median LOS in infants with simple gastroschisis is shown as a vertical dark-green line.
Pooled median LOS in infants with complex gastroschisis is shown as a vertical dark red line.

Median LOS infants born in infants with simple gastroschisis are shown in red.

Median LOS infants born in infants with complex gastroschisis are shown in green.

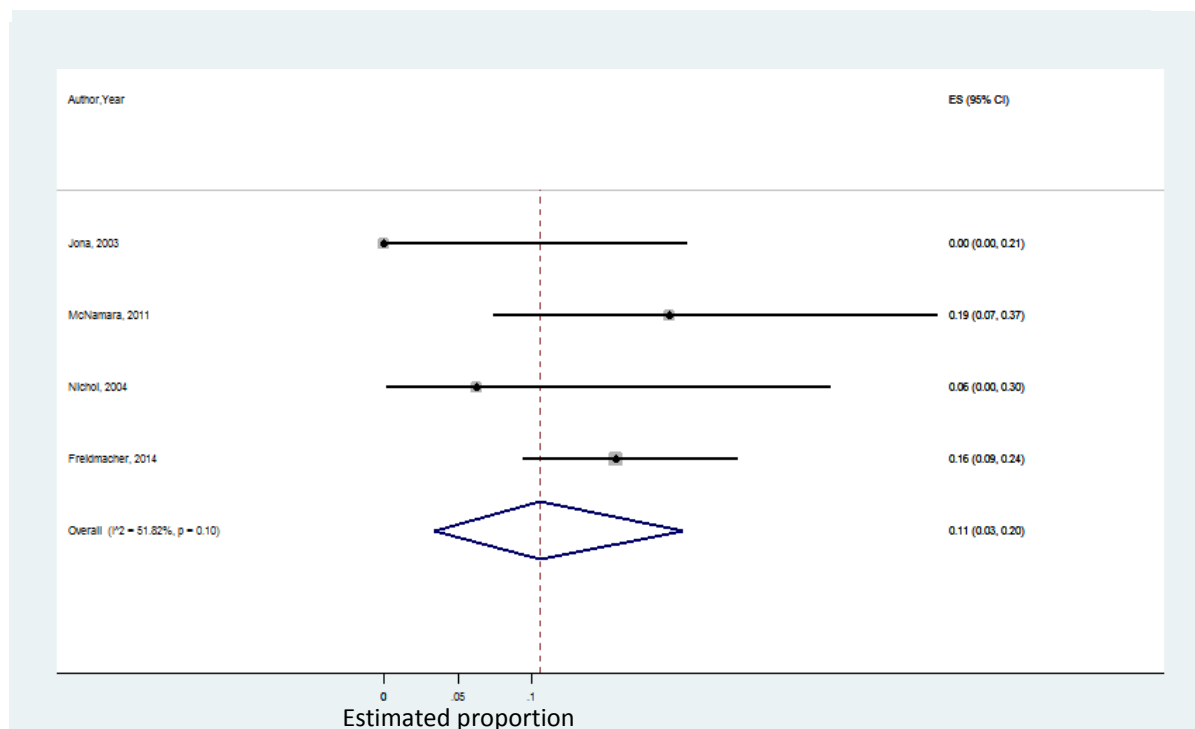
Interquartile ranges (where published) are shown as horizontal lines

2.3.4 Unplanned reoperation

Four studies were identified in which the timing of unplanned reoperation could be assessed. Two of these four did not meet the *a priori* criteria described in Table 2.2. These were Friedmacher et al, 2014 who reported reoperation before 30 days and Charlesworth et al 2014, who reported reoperation before 'four weeks' (Charlesworth, Akinola et al. 2014, Friedmacher, Hock et al. 2014). On the basis that this analysis would have had to proceed with only two studies if these were excluded, it was felt that these outcomes were similar enough to the inclusion criteria to justify being included. No other studies reported similar outcomes. The four included studies reported this outcome in 171 infants. The results of this meta-analysis are shown in Figure 2.14. This shows that the studies differed widely in the estimate of the proportion of infants with this outcome (I^2 51.8%, $p=0.10$). The pooled estimate for the number of infants undergoing early reoperation from this analysis was 11% (95% CI 5-20%).

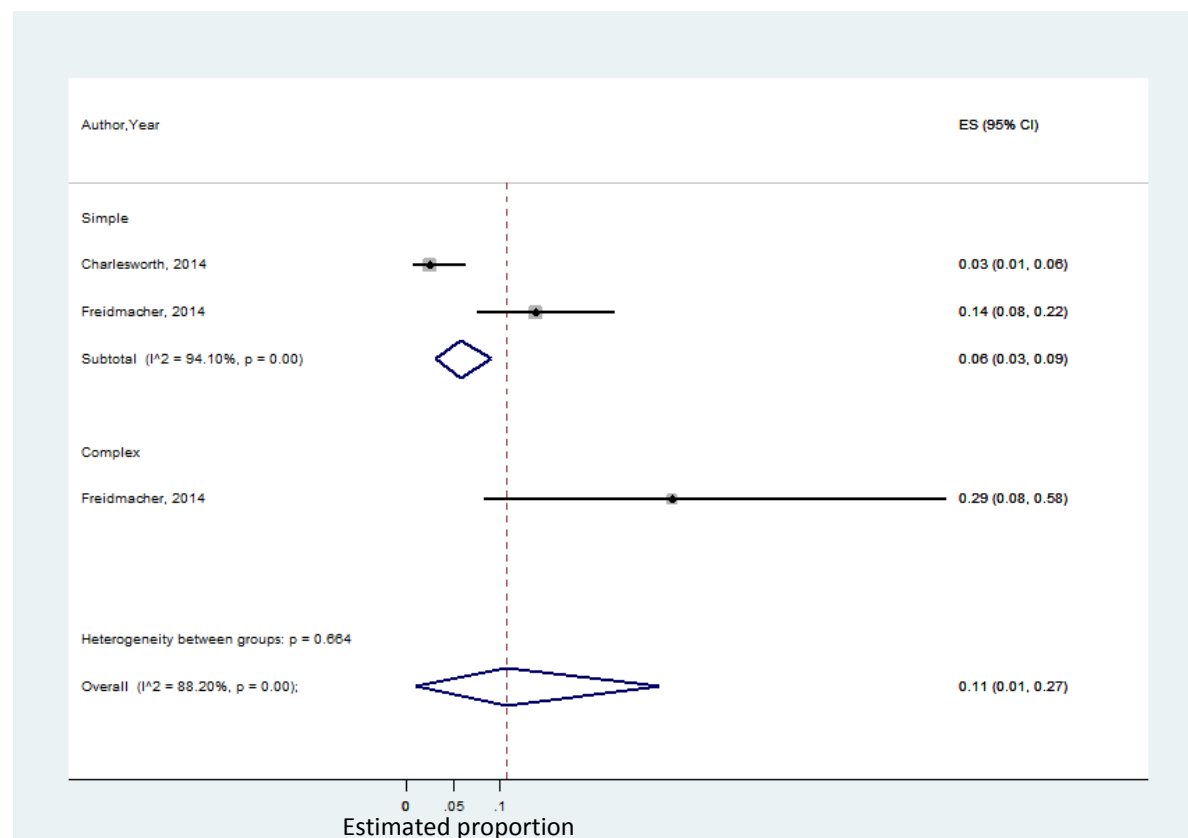
Two studies reported rates of unplanned reoperation in simple and complex gastroschisis infants separately. These were Charlesworth 2014 and Friedmacher 2014. These two studies contained information on this outcome in 250 infants with simple and 14 infants with complex gastroschisis (Friedmacher 2014 study only). The pooled estimate of the proportion of infants with simple gastroschisis requiring reoperation within 28 days was 6% (95%CI 3-9%). The proportion reported in the Friedmacher et al study in complex infants was 29% (95%CI 8-58%), (Figure 2.15).

Fig 2.14 Estimated rates of reoperation before 28 days: all infants



ES – Estimated proportion

Fig 2.15. Estimated rates of reoperation before 28 days: simple vs complex gastroschisis



ES – Estimated proportion

2.3.5. Risk of bias/ Quality of included studies

The results of the quality assessment for the included studies are given in Table 2.3. The included studies were almost all of low quality with 60 of 63 scoring five or less out of nine. Only three studies scored six out of nine, these were the BAPS-CASS and CAPSNET studies and a third population cohort study from the Czech Republic (Sipek, Gregor et al. 2006, Bradnock, Marven et al. 2011, Youssef, Laberge et al. 2015). Only the first two of these studies collected data for the specific purpose of answering research questions about management and outcomes in gastroschisis, the third used routinely collected data.

Thirty-three of the studies (52%) did not score on the adequacy of follow-up. It was frequently the case that studies did not state the length of infant follow-up or the number lost to follow-up. For this reason, the results of the pooled analysis for mortality to one-year should be interpreted with a degree of caution.

2.4 Discussion

2.4.1 Main results

This analysis has shown that within specialised units in high resource settings, few infants born with gastroschisis die in the first month after birth (2%); this rises to 7% by one-year after birth. Outcome estimates for mortality of infants with simple and complex gastroschisis were imprecise due to the small numbers of studies reporting on these two groups separately. Despite the resulting low statistical power, there was evidence that, though similar numbers of infants with simple and complex gastroschisis die soon after birth, at one year mortality diverges. These data suggest that if death is used as an outcome for quality assessment, a longer-term view must be taken, rather than focusing on the immediate post-operative period.

In common with the findings of a recent meta-analysis, infants with complex gastroschisis were found to stay in hospital significantly longer than those with simple gastroschisis (Bergholz, Boettcher et al. 2014). These results, together with the differing case fatality rates, suggest that assessing the outcomes in infants with simple and complex gastroschisis separately is a valid approach. The limited number of studies which were amalgamated to assess LOS and the use of the median of the published medians means that precise LOS estimates for the purposes of parental counselling were, however, not able to be derived.

A relatively high proportion of unplanned reoperation was noted in the first 28-30 days post-operatively in infants born with gastroschisis (11%). This figure should, however, be interpreted with caution as only a small number of studies reported this outcome, rendering the estimate imprecise.

2.4.2 Strengths of this study

This study has shown that it is possible to synthesise published data to produce population outcome estimates for gastroschisis. The inclusion and exclusion criteria for study selection ensured that the findings are relevant to paediatric surgical and neonatal units functioning within high-income countries at the present time.

These data provide, for the first time, pooled contemporary prognostic information that may be used to inform parental counselling. In particular, having an idea of the length of time that their baby is likely to spend in hospital is important to parents so that they can plan their wider lives accordingly.

Including only studies that report the outcomes of all infants and were not based on sub-populations means that these estimates are representative of the outcomes of all of the infants that would be encountered by a centre equipped to manage newborns with gastroschisis.

2.4.3 Limitations affecting quantitative synthesis

Whilst the pooled estimates of the outcomes include all infants treated in specialist centres, these analyses are nevertheless unadjusted for key covariates which may affect an individual infant's outcome. Such factors could include: prematurity, intra-uterine growth restriction and co-existing structural or chromosomal anomalies. The latter are uncommon among infants with gastroschisis although a large number of associated comorbidities have been described in the literature (Hunter and Stevenson 2008, Kamien, Zankl et al. 2010). Prematurity and its sequelae are not, however, infrequent within this population. The UK population study found that 46% of infants in the entire cohort were born at or before 37 weeks of gestation (Owen, Marven et al. 2010). This is, therefore, an important possible uncontrolled confounder. When parents are counselled it is important to note that an individual infant's course may therefore be quite different from these population estimates which represent the 'average'.

Two important features of the quantitative synthesis that may limit generalisability have been noted. These are:

- i. Heterogeneity in the included studies
- ii. Small numbers of eligible studies, in particular to assess the outcome differences between children with simple and complex gastroschisis.

2.4.3i Heterogeneity of outcomes in the included studies

Despite careful *a priori* identification of the study selection criteria for this analysis, the high level of heterogeneity between studies in almost all of the meta-analyses performed, is substantial. In many cases, this heterogeneity is likely to be a product of both the small numbers of infants in each study, as well as, for binary outcomes, the low prevalence of the adverse events assessed and thus the effects of random variation. This is of relevance when it is suggested that infrequently occurring outcomes such as early death should be scrutinised as a means of assessing an individual surgeon's or a unit's performance.

The UK population cohort study identified 393 infants with gastroschisis presenting to 29 centres in an eighteen-month period during what was termed by some as an ‘epidemic’ of gastroschisis (Wiskin, Cole et al. 2011). There were 214 infants born in England in one year. In 2015 there were 200 specialist paediatric surgery consultants in England (HSCIC 2016a). Using these data, it is possible to roughly estimate that, on average, a consultant paediatric surgeon will manage one to two infants with gastroschisis per year. The guideline produced by BAPS and the Royal College states that, *‘at appraisal, the previous year’s performance should be examined; however, to be meaningful, it will be necessary to view performance over the previous 5 years’* (RCS 2013a). Considering the low mortality in children born with gastroschisis, it would be very difficult, even over this longer period, to suggest that a rate of death, among the small number of infants treated by an individual, is unacceptably high because of the strong influence of random variation on such small sample sizes. Heterogeneity between studies reporting rare binary outcomes is also, therefore inevitable with those including small numbers of infants.

Despite these limitations, two studies by Sawicka et al (published from Poland in 2000 and 2013) are outliers with a high rate of mortality before one year after birth (Sawicka, Ploska-Urbanek et al. 2000, Sawicka, Wieprzowski et al. 2013), (Figure 2.8). Since 1989 when Poland transitioned to a freely elected parliament and a market economy, the country has seen improvements in both life expectancy and infant mortality (WHO 2016). A review undertaken in 2011 by the European Observatory on Health Systems and Policies, noted, however, that there was still a significantly lower life expectancy in Poland than ‘western’ EU states and the infant mortality rate was higher than the average rate for the 27 member states at that time (Sagan A, Panteli D, et al 2011).

The study from Sipek (2006), which contains population-based data from the Czech Republic also stands out within both analyses of mortality (Sipek, Gregor et al. 2006). The higher rates seen in this study and the studies by Sawicka may be indicative of the fact that, at the time of data collection for these studies, neonatal care in these former eastern European countries had not achieved the same standards as other high income countries.

One potential explanation for the heterogeneity noted in the assessment of length of hospital stay between studies relates to differences in the way this outcome is reported in the literature. Some authors such as Charlesworth et al (2007) and Payne et al (2009) clearly included some infants who died within their LOS analysis, with the lower limit of their LOS range at one day (Charlesworth, Njere et al. 2007, Payne, Pflieger et al. 2009). Others, such as Durfee et al (2002) stated that their LOS assessment was for survivors only (Durfee, Downard et al. 2002). Furthermore, authors rarely state whether the length of stay in infants who are transferred to other centres represents their total length of hospitalisation or merely time spent in the tertiary centre until transfer.

Heterogeneity in all outcomes is important to note as it may reflect genuine differences in populations cared for in different centres. This is a key consideration if future randomised controlled trials of interventions in gastroschisis are planned, as these differences may limit generalisability if choice of cases is not taken into account in the trial design.

2.4.3ii Low numbers of included studies

A striking feature of this analysis relates to the fact that although there was 1340 potentially eligible studies, few were able to be included in the quantitative synthesis. Two reasons underlie this:

- a. Poor quality of outcome reporting in the literature
- b. Outcomes were not reported separately in different risk groups

2.4.3ii.a Poor quality of outcome reporting in the literature

The inclusion of few studies in many of the quantitative syntheses, in particular those comparing simple and complex gastroschisis was due, in part, to deficiencies in the ways in which the outcomes were reported in the literature. This was due to a lack of standardisation in outcome reporting as well as variations in the characteristics of the populations assessed.

A common flaw in the reporting of mortality in infants with gastroschisis relates to inadequate information in published studies regarding the timing of death and the completeness of follow-up. Many of the studies, notably including the large population-cohort study from Canada (CAPSNET) and the large database studies from the USA, report only rates of death before first discharge from hospital (Abdullah, Arnold et al. 2007, Alvarez and Burd 2007, Youssef, Laberge et al. 2015). It is problematic to compare inpatient mortality as an outcome between different populations because institutional practices such as timing of transfer to smaller hospitals and delivery of home parenteral nutrition may vary between centres, meaning the length of the primary inpatient episode may also differ.

Length of hospital stay (LOS) was also inconsistently reported. As well as the differences in the populations of infants included in this assessment, many studies either reported the mean LOS or it was not clear whether the value given represented the mean or the median. It is well known that the mean is an inappropriate measure of central tendency for LOS because of the skewed distribution due to the majority of early discharges and the long-tail of very late discharges. Furthermore, in many published studies, individual length of stay values were given for specific groups of infants rather than for the population as a whole. One example of this is seen in the analysis by Owen et al (2006) who report the median length of stay separately for infants managed with and without a preformed silo and give no value for the whole group (Owen, Marven et al. 2010). These LOS values are not necessarily comparable to other populations as unmeasured factors may have led to inclusion of infants in one group rather than another.

The proportion of infants with gastroschisis that require reoperation or re-intervention within 28 days has been suggested as a performance indicator for individual surgeons (RCS 2013). This is a slightly ambiguous definition in that it does not specify whether the reoperation or re-intervention was planned or unplanned. Gastroschisis is a condition that often requires staged management, for example using a silo to assist abdominal closure (Marven and Owen 2008). For the purposes of this study, it was decided *a priori* that only studies reporting *unplanned* reoperation would be included in the meta-analysis. This outcome was not reported robustly in the literature and included studies were selected based to a certain extent on the reviewers' subjective assessment of what constituted an unplanned reoperation. As a result, few studies contributed to this analysis. Suggestions for more robust methods of reporting and assessing complications of surgery will be discussed in Section 2.6.4.

2.4.3.ii.b. Outcomes not reported separately in different risk groups

Within this study, outcome data were analysed separately for infants with simple and complex gastroschisis where this was possible (Molik, Gingalewski et al. 2001). Since this risk stratification system was proposed by Molik et al in 2001, it has been adopted by some, but not all, authors publishing outcome data. This is noticeable in the small number of studies that were able to be entered into the meta-analyses examining simple and complex infants as distinct groups.

These analyses are dominated by the UK population cohort study which adopted this system and reported the outcomes of 336 infants with simple gastroschisis and 45 with complex gastroschisis with few other studies able to be included (Owen, Marven et al. 2010). As a consequence the estimates of outcome stratified by complexity are relatively imprecise with wide confidence intervals, particularly for complex gastroschisis which is the rarer variant.

The results of this analysis do provide some evidence that there is short-term prognostic relevance in Molik's system with more infants with complex gastroschisis dying before one year and staying significantly longer in hospital. Future publication of outcomes that are stratified for infants with simple and complex gastroschisis will add to the precision of prognostic estimates and aid parental counselling. The effect of being born with simple versus complex gastroschisis on longer term outcomes is explored in Chapters Five and Six of this thesis.

2.4.4. Suggestions for improved outcome reporting and assessment

As has been discussed, robust reporting of outcomes is needed for two related purposes:

1. To allow the generation of population outcome estimates to enable comparison between different populations of infants, provide useful prognostic information and assess the efficacy of therapeutic interventions.
2. To assess the quality of care provided by an individual surgeon or surgical centre.

2.4.4i Mortality reporting

Reporting deaths within a standardised time period allows more meaningful comparisons between populations. Mortality at 30 days was chosen as an outcome in this study as this is stipulated by BAPS and the Royal College of Surgeons as one that should be assessed for surgeons caring for infants with gastroschisis (RCS 2013). The document from the Royal College does not specify whether 30 days refers to 30 days after birth or 30 post-operative days, however, as the vast majority of infants with gastroschisis are treated on day one, this can be regarded as effectively the same thing. Nevertheless, for the avoidance of error, and to allow direct comparison, a more specific definition would be preferable.

Death within 30 days of an operation is a standardised outcome measure that became an accepted benchmark for the assessment of adult post-operative mortality following the publication of the first UK National Confidential Enquiry into Perioperative Death in 1987 (NCEPOD)(Lunn and Devlin 1987, Zani, Ruttenstock et al. 2013). In the analysis reported here, studies reporting ‘neonatal mortality’ or deaths before one month of age were also included as reasonable approximations. Death in the neonatal period is a standardised outcome measure widely used in population-based perinatal assessments and by the World Health Organisation. The neonatal period refers to the first 28 days after birth if the first day is counted as day 1 and 27 days if it is counted as day 0 (WHO 2015).

Assessing mortality to 30 post-operative days allows comparisons between conditions for the purpose of a generalised assessment of surgical complications, for example for NCEPOD. Assessment of death as a post-operative complication would, however, be better captured by using the Clavien-Dindo system which provides an assessment of *all* post-operative complications including the most severe, which end in death (Dindo, Demartines et al. 2004). The strengths and limitations of this system are discussed later.

Reporting ‘death in the neonatal period’ (i.e. to 28 days after birth), would be preferable for the purposes of revalidation as well as within published studies as this provides a more holistic assessment of the quality of neonatal care and allows standardised comparisons between populations that do not depend upon the timing of the first operation.

In this study, death by one-year of age was also assessed. This outcome provides a longer perspective on mortality among infants born with gastroschisis. Some infants may have a complex course and assessment of case fatality after this longer time interval allows the inclusion of infants who survive the immediate post-operative period but die later from other complications of treatment or sequelae of other congenital problems.

There is some evidence in the published studies that the causes of early and late death differ. An example of this is seen in the UK cohort study where neonatal deaths were related to early complications of surgical management such as bowel infarction within silos and later deaths were more likely secondary to the consequences of short bowel syndrome (Bradnock, Marven et al. 2011). Thus, including later deaths allows those which may have occurred as a late result of early surgical complications to be included.

2.4.4ii. Length of hospital stay

Length of stay is known to have a skewed distribution because a few infants with complications or comorbidities may stay significantly longer than the majority who have a relatively straightforward course and infants with the most severe disease and co-morbidity not amenable to treatment tend to die very early. If this is to be reported as an outcome, authors must, therefore, report the median. Some of the responsibility for the deficiencies in the way that this outcome was reported in the literature should lie with peer-reviewers and journal editors who should encourage reporting this outcome in an appropriate manner.

In addition it is essential that authors define the population included in assessment of LOS, in particular, whether babies who died have or have not been included. In addition, the entire duration of the infant's hospitalisation in the specialist *and* the local centre should be included. This will provide a more realistic assessment for parents of the time they will spend with their infant in hospital and prevent the influence of factors such as an individual centre's bed capacity or transfer practices.

Even with these modifications, using length of stay as a marker of care quality has serious limitations. Using the median value merely provides an estimate of the 'average' time to discharge which is strongly influenced by the experience of straightforward infants who represent the majority of those treated. Although there may be differences in this time between individual institutions, the confidence intervals around the estimates of the difference are likely to be wide due to small numbers of infants affecting their precision. Alternatively it could be argued that it is not the majority of straightforward infants who are treated and discharged without event that should be of concern for the purposes of surgical performance assessment, but rather the outliers, that survive but are discharged only after a lengthy hospital stay. For parental counselling however, both an idea of the 'average' and the possible extremes are of value.

Finally, factors that may be unrelated to infant complexity or quality of hospital care may influence length of hospital stay. Parents among the advisory group that have informed the work presented in this thesis, describe significant delays in discharge related to the difficulties of setting up local care packages. Length of stay may therefore be a poor measure of the quality of hospital care, and it is an inadequate surrogate for acquired, potentially avoidable complications. The complex course of such infants could again be better captured by a system looking at adverse post-operative events such as Clavien-Dindo (Dindo, Demartines et al. 2004).

2.4.4iii Unplanned reoperation

The ambiguity within the definition of reoperation produced by BAPS and the RCS has already been described. This may lead to misinterpretation or misreporting of outcomes related to the most severe complications of surgical management (ie those requiring another theatre attendance). A more robust way of assessing this would be to use a standardised classification system of reporting post-operative complications such as Clavien-Dindo stage (Dindo, Demartines et al. 2004) (Table 2.4).

Table 2.4. The Clavien-Dindo classification of surgical complications (Dindo, Demartines et al. 2004)

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anaesthesia
IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications) requiring intensive care or intensive care unit management
IVa	Single organ dysfunction (including dialysis)
IVb	Multi organ dysfunction
Grade V	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

The use of this system would enhance reporting of post-operative complications and their degree of severity since complications are graded according to their consequence.

It is clear that in order to improve the quality of outcome reporting, robust definitions of those outcomes must first be agreed. In addition the characteristics of populations contributing to these assessments need to be defined. Table 2.5 summarises the author's suggestions as to how the outcomes stipulated by the RCS/ BAPS could be defined and standardised.

Improving the way outcomes are reported in published studies will improve the generation of population estimates, however, despite the modifications suggested above and in Table 2.5, severe limitations exist in the assessment of these outcomes as markers of an individual surgeon's performance or the quality of care provided by a given centre.

Table 2.5. Suggested modification to outcomes for revalidation in gastroschisis

Current	• Mortality 30 days
Suggested modification	• Mortality up to and including ≤ 28 days[†] after birth (all infants and those with simple and those with complex gastroschisis separately) • Mortality up to and including ≤ 365 days after birth (all infants and those with simple and those with complex gastroschisis separately) • Detailed in-house mortality review using a standardised format for all infants born with gastroschisis who die before five-years of age.
Current	• Length of stay (median)
Suggested modification	• Length of stay (median) in all infants and in infants with simple and complex gastroschisis separately. Children who die will be excluded from this assessment.
Current	• Reoperation/ Re-intervention at 28 days
Suggested modification	• Infants with a post-operative complication classified as Grade III or above using the Clavien-Dindo system of classification by 30 days after their operation[‡], (all infants and stratified by simple and complex) • Detailed in-house morbidity review using a standardised format for all infants with a post-operative complication classified as Grade III or above using the Clavien-Dindo system of classification by 30 days after their operation.

[†]Death occurring on or before day 27 after birth if the first day is counted as day 0. [‡]To allow comparison and consistency across all surgical procedures and specialities

2.4.5 Alternative methods of performance assessment

The futility of assessing rare adverse outcomes for an individual surgeon or even an individual institution has been discussed. Surgeons, therefore, need to look at different methods of investigating and learning from the events that lead to an infant's death, or indeed, an infant surviving with a severe complication, in order to improve practice. Several mechanisms are currently in place by which this occurs. There is a requirement for health practitioners to regularly review the outcomes of their clinical practice and it is standard practice for surgical departments to hold regular audit and/or morbidity and mortality meetings to review infants where complications have occurred and where children have died. It is noteworthy, however, that the 2011 NCEPOD enquiry, *'Are We There Yet?'* that reviewed organisational and clinical aspects of children's surgery identified that only 53% of centres performing children's surgery undertook such meetings in the period 2008-2010 (Mason, Wilkinson, et al. 2011). Departmental morbidity and mortality meetings provide an opportunity for timely review of infants who do not survive and those who develop complications, allow local standards of care to be investigated and provide a mechanism for quality improvement. With the contemporary culture of outcome scrutiny, and as a result of the publication of the NCEPOD report, this proportion is likely to have increased.

Another mechanism that exists in England is regional review of deaths by child death overview panels, (CDOPs). These were established in 2008 through local 'Safeguarding Children' boards and report data centrally via the Department for Education (Kurinczuk and Knight, 2013). CDOPs seek to determine whether deaths were modifiable and if lessons may be learnt that could prevent future deaths. The low numbers of gastroschisis deaths compared to the number of CDOPs, (92 in 2016) means, however, that this is unlikely to be a useful mechanism to improve practice and make an impact on a population level. In addition, paediatric surgeons are usually not members of CDOP panels.

A further means, by which the care of infants that do not survive may be analysed, is through national surveillance and confidential enquiry. Since 2012, as part of the Maternal, Newborn and Infant Clinical Outcome Review Programme, (MNI-CORP) has been collecting data on all neonatal deaths. This system will generate data on the number of infants born with gastroschisis that die in the first 28 days after birth. However, only a limited amount of data are collected that are of specific utility in analysing non-survivors with this condition due to the fact that this surveillance system collects the same data for all deaths from all causes.

The MBRRACE-UK collaboration (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK), which delivers the MNI-CORP programme also has a remit to undertake detailed review of perinatal care in selected conditions (Perinatal Confidential Enquiries). These enquiries generate learning materials that may be used to improve the care and outcomes of infants with serious morbidity. The perinatal confidential enquiry that was published in 2014 on 57 infants with congenital diaphragmatic hernia (CDH) made a number of recommendations to improve care delivered to infants with this condition (Field, Hyman Taylor et al. 2014). Within this process, a panel of experts undertook detailed case note review of 15 infants born alive with CDH who did not survive until discharge. Such a process has the ability to critically assess the quality of care provided, identifying areas where care can be improved as well as examples of good practice. It may also have the ability to detect systemic problems that could be addressed through specialty organisations such as BAPS. Perinatal Confidential Enquiry could be another modality of assessing the care of infants with gastroschisis that do not survive. This assessment would, however, be on a national rather than an individual institutional basis and the small numbers of infants with gastroschisis that die in a given year in the UK, means there may be a limited ability to detect systematic problems that may affect the care of infants with other paediatric surgical conditions.

2.5 Conclusion

Published contemporary data have been synthesised to provide population estimates for three of the outcomes currently suggested by the Royal College of Surgeons and BAPS as performance indicators in gastroschisis and one selected *a priori*. The utility of these outcomes is, however, questionable and their limitations have been discussed. The low prevalence of adverse outcomes in gastroschisis, heterogeneity between populations seen in small centres due to the influence of small numbers and uncontrolled confounders highlight the need for larger collaborative prospective observational studies such as those undertaken by BAPS-CASS and CAPSNET. The value of these and similar studies will be increased by standardisation of outcome reporting and more accurate definition of population characteristics, in particular relating to the condition of the bowel at birth. Dissemination of the findings of this study will provide a stimulus for discussion about the quality of outcome reporting of observational data in surgical conditions.

One of the motivations for the call for publication of individual surgeon outcome data by the Department of Health was to improve transparency and identify surgeons whose practice fell below acceptable standards (NHS England 2013). Only through robust assessment of care quality will this be achieved.

Chapter 3

Management and short-term outcomes among a national population cohort of infants born with exomphalos

3.1 Introduction

Chapter Two included a discussion of the importance of risk-stratification in the understanding of neonatal outcomes both when communicating information about the performance of a surgeon, department or treatment strategy and when providing parents with counselling which is appropriate to their child's possible outlook. This topic is explored further within this chapter, which describes an investigation into the incidence, management and outcomes of live born infants with exomphalos among a contemporary population cohort. This study utilised the established BAPS-CASS surveillance system to prospectively collect data on every baby born within the UK and Ireland with exomphalos that presented to paediatric surgeons within a two-year period.

Another key theme introduced in Chapters One and Two and explored further here, relates to the challenges of assessing treatment efficacy and the possible superiority of one treatment over another in rare conditions such as gastroschisis and exomphalos. The effect of this lack of evidence on the management of exomphalos both before and after birth is explored.

3.1.1. Objectives

Primary objectives

- a. To estimate the live birth prevalence of exomphalos in the UK and Ireland.
- b. To describe the current management and outcomes for infants with exomphalos born in the UK and Ireland.
- c. To assess the spectrum of co-morbidities found in these infants.

Secondary objectives

- a. To inform plans for further research into the surgical management of this condition.
- b. To provide data to inform parental counselling.

3.1.2 Research questions

The specific research questions were:

- a. What is the current live birth prevalence of exomphalos in the UK and Ireland?
 - i. What proportion of infants are antenatally diagnosed?
- b. What is the incidence of associated abnormalities in live born infants with exomphalos?
- c. How are infants with exomphalos managed in the UK and Ireland?
 - i. Is there evidence of variation with regard to:
 - Mode of delivery
 - Surgical management
- d. What factors are important in prognostication?
 - i. What impact do anatomical characteristics of the sac and its contents have on outcome?
 - ii. What is the impact of associated anomalies on outcome?
- e. What are the outcomes following different techniques of staged closure?
- f. What factors are associated with adverse outcomes such as neonatal death and sac rupture?

3.1.3 The clinical spectrum of infants diagnosed with exomphalos

Exomphalos is a structural abnormality of the abdominal wall that may be an isolated finding in a newborn infant or, as described in Chapter One, may occur alongside other structural anomalies and genetic aberrations. Genetic associations range from abnormalities in the number of chromosomes, (aneuploidy) to single gene defects. These include the well-documented association between exomphalos and a genetic error occurring on the short arm of chromosome 11 in Beckwith-Wiedemann syndrome (BWS) (Cooper, Luharia et al. 2005, Mussa, Di Candia et al. 2016). This error is thought to disrupt cellular signalling mechanisms that control cell proliferation leading to overgrowth of certain areas of the body during the time that the infant is developing in the womb (Mussa, Di Candia et al. 2016). Consequences of this overgrowth include the development of exomphalos, which occurs in approximately 50% of all infants with BWS (Elliott et al 1994). Other associated anomalies consist of: large size of the newborn (macrosomia), low blood sugar after birth (hypoglycaemia), a large tongue, ear abnormalities and in later childhood, development of solid organ tumours (Mussa, Di Candia et al. 2016). Several aneuploidies commonly associated with exomphalos are survivable *in utero* including Turner's Syndrome (45XO), Trisomy 21 (Down's Syndrome), Trisomy 18 (Edwards' Syndrome) and Trisomy 13 (Patau Syndrome). The latter two result in short life expectancy and infants born alive with these complex, multisystem syndromes are often given comfort care only.

Springett et al (2014), used UK congenital anomaly register data collected between 2005-2011, to identify 671 cases of exomphalos diagnosed both pre and postnatally. She and her co-workers noted that Edwards' syndrome was the anomaly that occurred most commonly alongside exomphalos. These authors found that 21% of all cases of exomphalos were associated with Trisomy 18, (95%CI 19-25%) (Springett, Budd et al. 2014).

In addition to identifiable chromosomal and genetic abnormalities, a number of named malformation syndromes or ‘sequences’ exist, of which exomphalos may be part. Most are thought to have a genetic aetiology and within each, characteristic structural and developmental abnormalities cluster together. Over 70 have been described in association with exomphalos (Chen 2007). Examples of those commonly encountered are outlined in Table 3.1.

Table 3.1 Examples of named syndromes or sequences associated with exomphalos

Named syndrome/ sequence	Clinical features occurring in addition to exomphalos
CHARGE Syndrome	Coloboma of the eye [†] , Heart Defects, Atresia of the Choanae*, Retardation of growth and development, Ear abnormalities and deafness
Pentalogy of Cantrell	CDH, sternal defects, heart defects and pericardial defects
OEIS Complex	Imperforate anus, cloacal exstrophy [§] , spinal defects
Limb body wall complex/ body stalk anomaly	Facial clefts, scoliosis, neural tube defects [‡] and urogenital abnormalities
Donnai Barrow Syndrome	CDH, absent corpus callosum [‡] , deafness

[†] A hole in one of the structures of the eye e.g. the iris *Abnormal narrowing of the nasal passages

[§]The bladder and bowel are fused in a single open ‘plate’ that is open on the lower abdominal wall
CDH: Congenital Diaphragmatic Hernia [‡]Failure of development of neural structures e.g. spina bifida

[‡] A midline structure connecting the two sides of the brain

Another cluster of abnormalities that may occur alongside exomphalos are thought to have an environmental aetiology. In this condition, known as amniotic band syndrome, fibrous bands within the amniotic cavity constrict areas of the growing fetus’ body. As a result they may develop, limb or digital defects, talipes equinovarus (‘clubfoot’), cleft palate, haemangioma (strawberry birthmark) or exomphalos (Cignini, Giorlandino et al. 2012).

Apart from these clustered abnormalities other, individual or multiple, structural malformations may occur alongside exomphalos that are not part of a named syndrome or sequence. The most common of these are cardiac defects. Springett et al (2014) found that 17% of infants with exomphalos had associated congenital heart defects (Springett, Budd et al. 2014). These were major defects in 5% of infants with exomphalos. Central nervous system abnormalities were noted in 14%, many of which were lethal; 12% had limb defects and 8% had defects affecting the urinary system. Springett et al identified 37% of infants or fetuses as having 'isolated' exomphalos. In these, no other structural or genetic abnormalities were detected. As their assessment included fetuses with apparently isolated exomphalos that were terminated before birth, it is possible the incidence may, in fact, be lower as cases labelled as isolated prenatally, may have had other abnormalities that would have been detected after birth had they survived (Cohen-Overbeek, Tong et al. 2010).

In order to make sense of the varied clinical spectrum of infants diagnosed with exomphalos and the prognostic implications of its many associations, clinicians and researchers such as Springett et al have tried to create meaningful diagnostic or prognostic groups. An outline of the groupings used frequently in the literature is given in Table 3.2. These groupings are broad and do not necessarily acknowledge that different infants within each category may have very different outcomes. However, their use allows the complex population of infants born with exomphalos to be grouped into categories of comorbidity that *may* have a similar prognostic outlook.

Table 3.2 Classification of categories of comorbidity in exomphalos

Group	Definition
Isolated	Exomphalos only with no other detectable structural or genetic defects. Depending on the classification used, this group may or may not contain infants that have associated gastro-intestinal problems such as intestinal atresia, (a blockage of the bowel that develops <i>in utero</i>), or malrotation, where the bowel lies in an abnormal position in the abdomen and is at risk of twisting.
Chromosomal	This group is largely composed of infants with aneuploidy. Infants with smaller genetic defects may be included in this group but varying anomalies may have a markedly different prognostic outlook.
Multiple/ Structural	The association of exomphalos with other significant structural defects such as cardiac abnormalities. Those with known malformation syndromes or sequences (Table 3.1) may or may not be included in this group, or included in the group below. This term usually refers to chromosomally normal infants.
Syndromic	Part of a specific malformation syndrome. Some of these may have an identifiable genetic basis or pattern of inheritance. BWS is a commonly occurring syndromic pattern, although this has a favourable prognostic outlook compared to other patterns of association within this category.

Within this chapter, infants with ‘isolated’ exomphalos are considered a single prognostic group, although it is acknowledged that these may have severe comorbidities directly associated with exomphalos which affect their prognosis such as pulmonary hypoplasia (Tsakayannis, Zurakowski et al. 1996) and significant viscera-abdominal disproportion. Such factors could be very likely to impact on infant outcome.

3.1.4 'Major' and 'minor' variants

The most commonly used system of risk stratification of infants born with exomphalos used in any of the published studies groups infants into those with 'exomphalos major' and those with 'exomphalos minor'. There is, however, no consensus on the characteristics of the defect that distinguish major from minor. The majority of authors have used the diameter of the abdominal wall defect to define 'exomphalos major', and values between 5 and 10 cm have been used (Morgan, Hanna et al. , van Eijck, Hoogeveen et al. 2009, Ein and Langer 2012). Others have used the term if there is liver or a proportion of the liver in the sac (Biard, Wilson et al. 2004). 'Giant' exomphalos is another term that is used, similarly, with no universally agreed definition (Ein and Langer 2012, Akinkuotu, Sheikh et al. 2015, Bauman, Stephens et al. 2016).

Some authors have suggested that when detected antenatally, infants with no extracorporeal liver are more likely to have chromosomal abnormality and therefore parents should be given a guarded prognosis (Getachew, Goldstein et al. 1992). In addition, some authors have noted that ratios of the exomphalos sac to parts of the fetal body measured on antenatal ultrasound, may have prognostic implications (Kleinrouweler, Kuijper et al. 2011, Fawley, Peterson et al. 2016). Beyond this, a clear relationship between the size of the defect and outcome has not been established.

The primary reason that authors in the surgical literature have attempted to describe infants with large and small defects separately is the fact that the surgical management of these groups is likely to be very different. As described in Chapter One, infants with significant viscero-abdominal disproportion are much more challenging from a surgical point of view and require specific 'staged' surgical strategies to return the viscera to the abdominal cavity and close the defect. When authors make reference to 'exomphalos major' and 'exomphalos minor' in live born infants, what they are attempting to communicate, is the degree of difficulty in achieving primary closure. This will, in turn, be a key determinant of infant outcome.

Within the study described in this chapter, the anatomical characteristics of the abdominal wall defect and the contents of the sac of the live born infants with exomphalos will be described. The criteria used to define 'major' and 'minor' variants in the published literature will be examined to determine whether these reflect distinct groups of infants that can be identified within the cohort. The relationship between defect characteristics and infant outcome will be described, and in particular, the features associated with the use of staged closure will be explored.

3.1.5 The fate of exomphalos pregnancies and live birth prevalence

A number of studies quote the 'incidence' of exomphalos as between one in 4000 and one in 5000 live births (Christison-Lagay, Kelleher et al. 2011). It is presumed that these estimates, refer, in fact, to the prevalence of new cases. The term birth prevalence, rather than incidence is used by convention by organisations responsible for the congenital anomaly surveillance such as the European Surveillance of Congenital Anomalies (EUROCAT) and the British and Irish Network of Congenital Anomalies Researchers (BINOCAR) in the UK. Birth prevalence is defined as '*the total number of cases of congenital anomaly (live births, stillbirths, late miscarriages and terminations of pregnancy with fetal anomaly) compared to the total number of births (live births and stillbirths)*' (Springett A 2010).

This measure includes of all of the newly diagnosed cases of exomphalos both pre and postnatally and contains those where the pregnancy did not continue until term or where the fetus was not born alive. Springett et al estimated the birth prevalence of exomphalos as 3.8 per 10,000 (95% CI, 3.6-4.1) among the areas covered by the BINOCAR registers that contributed data to their study (Springett, Budd et al. 2014).

The study described in this chapter collected data on live born infants alone and specifically only those who were managed by paediatric surgeons. It is acknowledged that looking at these cases will only provide an estimate of the live birth prevalence of exomphalos and will be affected by differing rates of termination for fetal anomaly which may vary regionally and nationally and where death occurred prior to the involvement of surgeons e.g. where comfort-only care was given.

3.1.6 Antenatal diagnosis of exomphalos

Accurate antenatal diagnosis of exomphalos allows parents to make informed decisions about further invasive testing, continuation of the pregnancy and the mode and location of delivery. In addition it enables health professionals involved in this process to counsel parents and to manage the practicalities of their choices. This abdominal wall defect is one of 11 conditions specified by the NHS Fetal Anomaly Screening Programme that should be identified on the 18-20 week anomaly scan with the expectation of the detection rate (the proportion of individuals with a positive screening result) being at least 80% (Public Health England 2015).

3.1.7 Postnatal screening for associated anomalies

The high rates of associated structural anomalies necessitate clinical vigilance and judicious use of screening postnatally. The postnatal care pathway for health professionals produced by the FASP (Appendix 7), suggests that associated abnormalities should be detected via clinical assessment, monitoring of blood glucose level and referral to genetics where dysmorphic features are present or other abnormalities are suspected. It makes no reference to the need for additional investigation to identify the presence of associated structural malformation. No UK guideline exists to outline what postnatal investigative screening should be undertaken and as a result, individual hospitals rely on local protocols where they exist. Variation in screening practices and the spectrum of associated abnormalities that are detected was assessed in the study reported here.

3.1.8 The management of infants born with exomphalos

Several areas of management were explored in this study and two were examined in particular detail. These were:

- i. Mode of delivery
- ii. Surgical management

3.1.8i. Mode of delivery

Like many aspects of the pre- and postnatal management of exomphalos, there is no consensus among practitioners about the optimum mode of delivery when exomphalos is diagnosed antenatally. The question of the safety of one mode of delivery over another arose with the advent of routine antenatal screening for fetal anomaly and improved rates of detection of exomphalos. One author, who assessed the trends in mode of delivery for these infants since the 1960s noted that; *'intrapartum rupture of an omphalocelic sac was an extremely rare event before introduction of antenatal diagnosis'* (Calisti, Manzoni et al. 1987).

Four concerns regarding the safety of vaginal delivery have been raised: local or systemic infection due to contact of the sac with vaginal flora; compromise to the blood supply of the extra-abdominal viscera; obstructed labour; and sac rupture (Paidas, Crombleholme et al. 1994, Kitchanan, Patole et al. 2000). Cases of sac rupture during both caesarean and vaginal delivery have been described in the literature (Heider, Strauss et al. 2004).

The superiority of one mode of delivery over another has never been assessed within a randomised controlled trial and no large scale observational data exist to answer this question. Where it has been addressed, studies have been limited to small retrospective case series and in most the outcomes of infants with exomphalos have been combined with those of infants with gastroschisis (Kirk and Wah 1983, Lewis, Towers et al. 1990, Moretti, Khoury et al. 1990, How, Harris et al. 2000).

The one systematic review that attempted to answer this question included infants with both types of abdominal wall defect and included some studies that excluded infants with extra-abdominal liver (Segel, Marder et al. 2001). Historically most authors have concluded, in the absence of evidence, that vaginal delivery is preferable due to the improved safety from the mother's perspective (Lurie, Sherman et al. 1999, Kitchanan, Patole et al. 2000). Most, however, go on to suggest that babies with larger exomphalos defects, using a variety of criteria to identify such cases, should be delivered by caesarean (Lurie, Sherman et al. 1999, Segal, Kang et al. 2014). More recently, a centre that favours vaginal delivery for all infants, including those with extra-corporeal liver have published their outcomes using this policy, which describe no ill effects for mother or baby (Kleinrouweler, Kuijper et al. 2011). The current UK antenatal management guideline suggests that mothers with fetuses diagnosed with 'exomphalos major' undergo planned caesarean section (National Screening Programmes 2013). The absence of consensus on what constitutes 'exomphalos major' presents a problem in operationalising this guidance (Towne, Peters et al. 1980, Ein and Langer 2012).

An objective of this study was to collect data on current practices regarding mode of delivery in the UK and Ireland and the indications for planned caesarean section in order to explore contemporary practice in the British Isles. Rates of sac rupture during delivery were estimated with a view to using these data to inform future clinical trials to answer the question of, when exomphalos is detected antenatally, which mode of delivery is safest for mother and baby?

3.1.8ii Surgical management

The two aims of the surgical management of exomphalos, namely, to return the extra-abdominal viscera to the abdominal cavity and to close the fascial defect, and the methods by which this may be achieved have been outlined in 1.1.3. Current controversy predominantly concerns those infants that are unsuitable for primary closure.

The options for 'staged-management' are: primary skin-flap closure with later ventral hernia repair, patch application, silo application, and escharotic therapy (Morgan, Hanna et al. , Pacilli, Spitz et al. 2005, Rijhwani, Davenport et al. 2005, Charlesworth, Ervine et al. 2009, Mitanchez, Walter-Nicolet et al. 2010, van Eijck, Aronson et al. 2011, Ein and Langer 2012, Lakhoo 2012). Contemporary utilisation of these methods in the UK and Ireland were assessed in this study. Within the study described in this chapter, escharotic therapy is termed 'conservative management'. Key outcomes of each mode of treatment are described, such as: surgical complications, sac rupture, infection, toxicity from topical agents, need for nutritional support and hospitalisation beyond 28 days. Information on current practice and outcomes could inform the development of future studies into the safety and efficacy of different staged closure techniques as well as the counselling of parents about management options.

3.1.9 Short-term survival of infants born with exomphalos

There are limited published data on the factors that influence survival of infants born with exomphalos. A recently published systematic review concluded that, *"Despite advances in medical and surgical therapies, giant omphaloceles are still associated with a high mortality rate"* (Bauman, Stephens et al. 2016). This study pooled the rates of death within an unspecified postnatal period in infants with large exomphalos defects. Furthermore, the quantitative synthesis included infants born in 1975 and the largest included study, containing infants born in the last 20 years in the Ivory Coast, contributed data on 173 of the 350 infants whose outcomes were combined to assess survival. This latter study, from a low income country with variable rates of antenatal care is likely to have heavily influenced the finding of this meta-analysis (Bauman, Stephens et al. 2016). It is unclear to what extent this synthesis with its methodological limitations contributes helpful information about the survival of contemporary children managed in high income settings.

The study reported here is the first population-based cohort study of infants born with exomphalos in which survival to 28 days from birth is assessed. These data will provide vital information for counselling parents on the short-term outlook of infants born with this condition.

3.2 Methods

3.2.1 Study design

A prospective, population-based cohort study was conducted, collecting short-term outcome data on infants born with exomphalos managed by paediatric surgeons in the UK and Ireland.

3.2.2 Case identification

This study utilised the methodology of the British Association of Paediatric Surgeons Congenital Anomaly Surveillance System (BAPS-CASS). The origins of this collaborative research platform are described in Chapter One. It uses a national network of reporting clinicians who are paediatric surgeons practicing within departments in the UK and Ireland. A monthly report card is sent from the National Perinatal Epidemiology Unit (NPEU) in Oxford, to a nominated clinician in each of the 28 paediatric surgical centres in the UK and Ireland. An example of the reporting card is seen in Appendix 8. Using this card, clinicians report whether they have managed any children with the condition currently under investigation within the previous month. If they had not managed any cases, they responded, using the card to indicate that they had no cases to report.

This active negative surveillance methodology has been shown to provide accurate case ascertainment when cross checked against other means of surveillance, such as reporting by obstetricians and congenital anomalies registers (Overton, Pierce et al. 2012) as well as using Hospital Episode Statistics from England (Green PA 2014).

Data were collected on new cases of exomphalos meeting the case definition presenting to participating centres over a two-year period between the 1st of March 2014 and the 29th of February 2016. At the end of the data collection period, all reporters were asked to check with their department and hospital records as to whether or not there were any cases additional to those reported using the card system.

3.2.3 Case definition

The case definition used in this study was identical to that used by EUROCAT for identifying cases of exomphalos (EUROCAT 2013). It was as follows; *any live born infant with herniation of abdominal content through the umbilical ring, the contents being covered by a membrane. This membrane may have been ruptured at the time of delivery.* Infants with gastroschisis were excluded.

3.2.4 Data collection

Where cases were reported using the card system, they were allocated an anonymous four-digit identifier and clinicians were then sent a data collection form marked with this identifier. This data collection form requested information from clinicians on presentation management and outcomes to 28 days. This was defined as the period up to 28 days following surgery or the decision for non-operative management. The data collection form is included in Appendix 9.

No personally identifiable data were collected on reported cases. Data collection forms utilised by previous studies using the BAPS-CASS system have had a standard format. The length is limited to seven pages of questions which follow a page of instructions. The contents of this form were designed by the author in order to address the research questions outlined in 3.1.2. Data were collected on the domains outlined in Table 3.3.

Completed data collection forms were posted by clinicians to a central administrating office in the NPEU in Oxford and then coded. Most answers involved marking a relevant box. Free-text answers were coded according to a coding manual.

Following coding, the data were double entered, into a customised database at the NPEU. The first entry identified possible duplicate cases using baseline data points such as the mother's year of birth, the first alphabetical part of the mother's postcode and the gestational age, gender and birth-weight of the infant. Where duplicates were identified, after checking with the reporting hospitals, the data were amalgamated into a single record. Following first entry, missing data were identified and reporting clinicians were contacted to collect this. After coding, the data were then entered again by a second administrator and any discrepancies between the first and second entries were addressed.

Where data collection forms sent to clinicians were not received by the central team within six weeks, the reporter was contacted by letter and telephone and a further form was be sent out. If there was still no response after a further four weeks, the clinician was contacted by telephone. At the end of the data collection period, the author requested all of the remaining forms be returned by centres, with regular reminders.

Table 3.3 – Areas covered on the data collection form

Domain	Areas included
Demographics	• Mother's age and ethnicity • Family history of related conditions or previous pregnancy • Gestational age, gender and birth-weight of the infant
Antenatal diagnosis and management	• Whether diagnosed antenatally • Associated anomalies detected • Invasive prenatal testing • Counselling by paediatric surgeons
Planned and actual mode of delivery	• Planned mode of delivery prior to the onset of labour • Actual mode of delivery
Timing of presentation to the tertiary centre	• Date and age at presentation to the surgical centre • Location of birth if transferred
Structural characteristics of the defect	• Size of defect at abdominal wall • Width of sac • Liver in the sac
Sac rupture	• Presence, timing and cause of rupture
Associated anomalies	• Detected clinically • Detected radiologically • Detected at surgery • Detected through genetic testing
Early medical management	• Use of antibiotics • Use of probiotics • Type, timing and route of feeds

Table 3.3 Continued – Areas covered on the data collection form

Non-operative management of the sac	• Use of tie on umbilical cord in small defects • Indications for non-operative management • Dressings and topical therapies used on the sac • Evidence of silver toxicity • Timing of epithelialisation • Use of vacuum-assisted closure • Use of elastic compression garments • Complications of non-operative management
Surgical management of the sac	• Operative technique employed • Success of technique • Silo materials • Patch materials • Need for additional procedures • Complications of operative management
Sepsis	• Episodes of infection • Infection or colonisation with an multi-resistant organism
Ventilatory support	• The need for and duration of invasive ventilation
Venous access	• The use and number of central venous lines inserted
Growth	• Weight and head circumference at discharge
Death	• Timing and cause of death
Discharge	• Timing and location of discharge from the surgical centre

3.2.5 Parent participation

Prior to commencement of this study, an advisory group composed of parents who had had a baby born with exomphalos was set up. Participants in this group were recruited by the author, largely through advertising on social media among groups of individuals who had been affected by a diagnosis of exomphalos. This group met for the first time at the start of 2014 and has met on a yearly basis since. Existing research about exomphalos is discussed with this group and an open discussion is held, identifying areas that are of importance to parents and families that should be explored within this and related studies. As such, these parents have helped to formulate and inform the research questions for the study described here. The findings of this study will, in turn, be relayed to them and disseminated through their wider networks.

3.2.6 Research ethics approval

The study was approved by the NRES Committee South Central-Oxford A (Ref: 12/SC/0416)

3.2.7 Analysis

3.2.7i Software and statistical analysis

Statistical analysis was undertaken using *Stata 13 SE*. Continuous data are presented as medians and IQR. Chi-squared and Fisher's exact test were used as appropriate, to assess differences in categorical variables, and the Mann Whitney test was used to identify differences between continuous variables.

3.2.7ii Descriptive analyses

A number of descriptive analyses were performed in order to answer the research questions outlined in 3.1.2. The demographic characteristics of the population were described and the birthweight centiles were derived using the LMS method[‡] (Cole 1990). Infants below the tenth centile for birth-weight at a given gestational age were classified as small for gestational age (SGA). Infants that were above the 90th centile were classified as large for gestational age (LGA). These calculations were done using an 'add-in' to *Microsoft Excel 2013* (Harlow Healthcare 2016).

Four categories of comorbidity were defined for infants in the cohort. Those with aneuploidy or other chromosomal defects were grouped along with those with named syndrome or sequences. For ease of reference this group is termed 'syndromic'. Infants with single or multiple structural malformations are considered in another group termed 'structural'. Infants with BWS are considered as a separate group as they have characteristic genetic or structural morbidity and are generally thought to have a favourable prognostic outlook. Infants with no other associated abnormalities other than those directly associated with the abdominal wall defect, for example intestinal malrotation, pulmonary hypoplasia or undescended testes were termed 'isolated exomphalos'. The inclusion and exclusion criteria for each group are shown in Table A.2.1 in Appendix 6.

3.2.7iv Comparative analyses

3.2.7iii.a Exploring the relationship between structural characteristics of the defect and surgical management strategy

As was described in 3.1.4, previous authors have attempted to stratify infants born with exomphalos into 'major' and 'minor' groups using a number of anatomical parameters. Of primary importance to postnatal outcome, however, is whether or not the defect can be closed primarily. As a consequence, surgical decision-making is effectively the 'gold standard' for defining an 'exomphalos major'.

[‡]The LMS method is a means of calculating deviation from normal growth centile standards devised by researchers in the UK. These deviations are then converted to growth centile for birth weight for gestational age. (Cole 1990). Reference data were 'The British 1990 growth reference for height, weight and body mass index', revised in 1998 (Cole, TJ. Freeman, JV. et al 1998)

For this reason, the question was explored in reverse: when surgeons choose staged management, what defect characteristics are present in these infants? This question was addressed to identify the characteristic(s) that best predict the use of staged closure and thus help in defining ‘exomphalos major’ for the purposes of outcome assessment, parental counselling and in the design of future surgical trials.

The anatomical characteristics of the sac were explored within the population, as were different approaches to the stratification of infants using these characteristics. The relationship of these to surgical management strategy, namely, the need for staged closure and outcome was assessed using both the standard statistical tests described above as well as receiver operating characteristic (ROC) curves for continuous variables where appropriate. Table 3.4 shows the infants that were included in this analysis and the rationale for these inclusion and exclusion criteria.

Table 3.4. Infants included in the assessment of the impact of defect size on surgical management strategy

Inclusion and exclusion criteria	Rationale
Excluded • Infants not treated surgically because they were unfit, had significant comorbidity or were palliated. Included • All other infants including those with ruptured sacs	• In these infants, surgical decision-making was not guided by defect characteristics • The presence of a ruptured sac may not necessarily dictate management choice as small defects may still be closed primarily.

3.2.7iii.b Outcome measures used in this study

The short-term outcomes assessed in this study were defined *a priori* and are defined in Table 3.5

Table 3.5 Definitions of the outcome measures used (Tables 3.15 and 3.16)

Outcome Measure	Definition
Neonatal mortality	• Infants that died before 28 days after birth
Number with outcome at 28 days (including; ventilation, enteral feeding, PN use, length of stay >28 days)	• Number of infants with the given outcome at 28 days from date zero* Excluded • Infants that died before 28 days after birth
Median of continuous outcomes	• Median of those that were not still receiving given treatment at 28 days Excluded • Infants that died before 28 days after birth
Length of stay	• Date zero to first discharge
Any infection	• Any proven or suspected infection treated with ≥ 5 days intravenous antibiotics
Wound/ skin/ sac infection	• Any proven or suspected wound, skin or sac infection treated with ≥ 5 days intravenous antibiotics
Management complication	• Complications directly associated with the modality of exomphalos management including: - Sac damage or leak in the conservative group - Wound dehiscence in the surgical group - Silo revision - Abdominal wall hernia - Wound infection (see above) - Respiratory deterioration after silo shortening
All complications	Included: • Any infection (see above) • Management complications (see above) • Complications related to being in hospital e.g: - Iatrogenic injury such as extravasation, oesophageal perforation or long-bone fracture - Multi-resistant infection Excluded: • Death • Adverse events directly attributable to comorbidity, e.g: ▪ Complications of prematurity e.g. NEC and cerebral haemorrhage ▪ Hypoglycaemia[‡] ▪ Cardiac arrest from upper airway obstruction ▪ Anastomotic leak after operation for atresia

*Date zero: date of operation if operatively managed and date of presentation if managed non-operatively

NEC: necrotising enterocolitis, an inflammatory condition of the bowel, principally affecting premature infants

[‡]Hypoglycaemia, or low blood glucose is a complication of prematurity and Beckwith-Wiedemann syndrome

3.2.7iii.c Exploring the relationship between infant characteristics and method of closure on outcome

The influence of various factors on the infant outcomes defined in Table 3.5 was assessed. Table 3.6 shows the infants that were included each of these analyses and the rationale for these inclusion and exclusion criteria.

Table 3.6 Infants included in each outcome assessment group*

Outcome assessment group	Inclusion and exclusion criteria	Rationale
By method of closure	Excluded • Infants with a ruptured sac after birth. • Infants undergoing conservative treatment on the basis of being unfit for surgery or having significant comorbidity. Included • Infants undergoing conservative treatment where this was routine practice in infants with significant viscerio-abdominal disproportion.	• Sac rupture may affect outcome independent of management technique. • These infants are likely to have different outcomes from those fit for surgery or undergoing active treatment. • These infants would have potentially been eligible for operative surgical management.
By DWR, category of comorbidity and sac rupture	Included • All Infants	• To assess the unadjusted influence of these characteristics on outcome

* See Tables 3.15 and 3.16 DWR: Defect to Weight Ratio, (defect size in cms/ weight in kg)

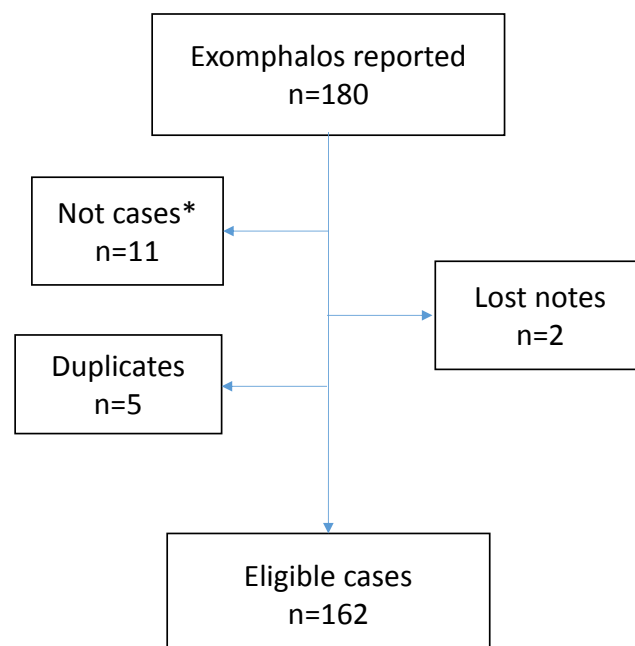
3.3 Results

3.3.1 Case reporting and data collected

One-hundred and eighty cases were reported during the study period by 28 centres. Figure 3.1 shows the process of case identification. Case notes relating to two infants were lost and were not able to be retrieved. Data collection forms were received on 100% of the remaining eligible cases.

There were 162 infants meeting the case definition who were born alive within the study period. The median number of infants reported per centre was six, (range 0-16): a median of three infants were seen by a centre per year.

Figure 3.1 Case identification and completeness of data collection



*These were reported in error and included antenatally diagnosed exomphalos that were postnatally normal and congenital anomalies located at the umbilicus such as patent vitello-intestinal duct and urachal remnants

3.3.2 Live birth prevalence of exomphalos

During the study period, 1,660,215 infants were born alive in the British Isles (Sources: Offices for National Statistics (England and Wales), Information Services Division (Scotland), Northern Ireland Statistics and Research Agency (Northern Ireland), Central Statistics Office (Ireland)). The overall live birth prevalence of exomphalos was 0.98 per 10,000 live births (95% CI 0.977-0.983).

3.3.3 Demographic characteristics of the cohort and categories of comorbidity

The demographic characteristics and categories of comorbidities are shown in Table 3.7. Forty-six infants (28%) were included in the isolated category; 72 (44%) had one or more associated structural anomalies; 29 infants had BWS (18%); and 15 (9%) had a named structural malformation syndrome or genetic abnormality other than BWS associated with their exomphalos (the 'syndromic group').

Table 3.7: Demographic characteristics of the infants in the cohort.

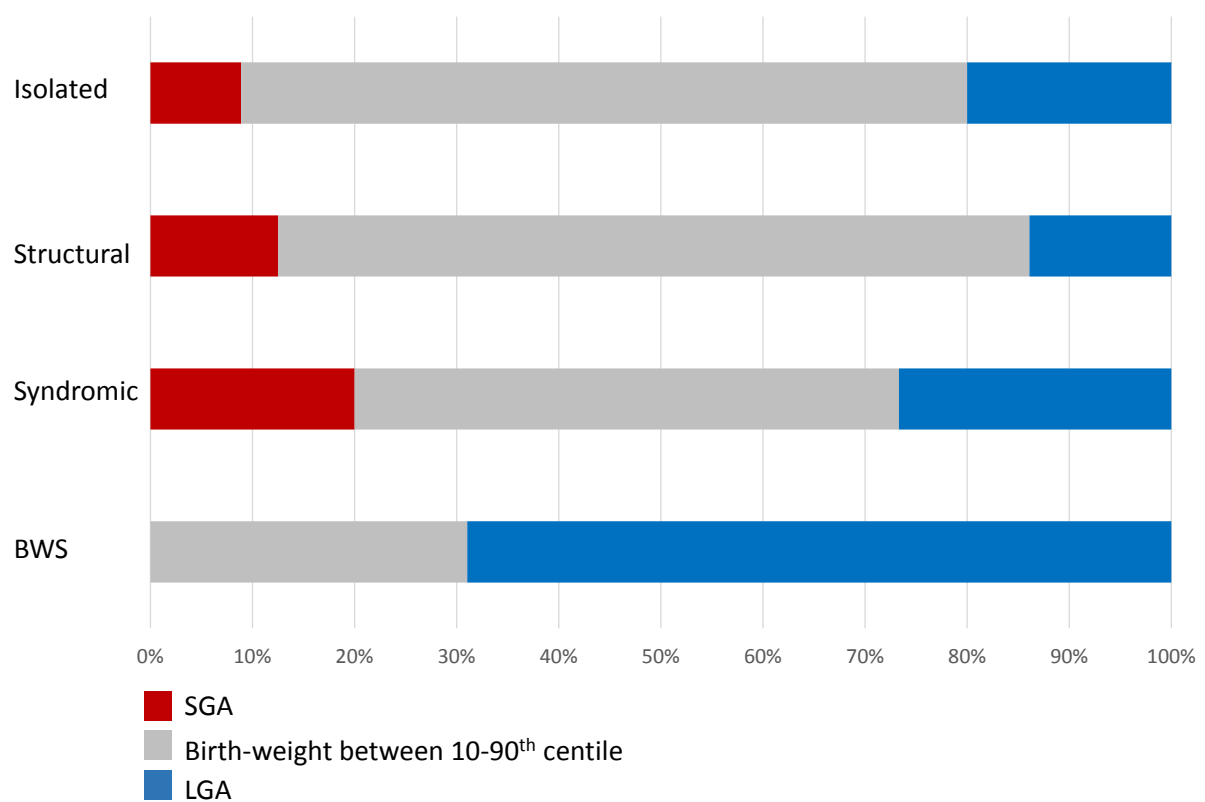
	All Infants n (%)	Isolated n (%)	Syndromic n (%)	Structural n (%)	BWS* n (%)
Number of infants (%)	162	46 (28)	15 (9)	72 (44)	29 (18)
Mother age (yrs), (median; IQR)	30 (26-35)	33 (27-36)	30 (25-37)	29 (24.5-34.5)	30 (25-33)
Maternal ethnicity (median; IQR)					
White	117 (72)	33 (72)	11 (73)	52 (72)	21 (72)
Other	45 (28)	13 (28)	4 (26)	20 (28)	8 (28)
Gestational age (wks) (median; IQR)	38 (35-38)	38 (36-39)	38 (35-38)	37 (35-38.5)	36 (34-38)
Term	102 (63)	32 (71)	9 (60)	45 (63)	10 (48)
Pre-term	59 (37)	13 (29)	6 (40)	27 (38)	19 (52)
Birthweight (g)	3058 (2420-3505)	3085 (2440-3540)	2960 (2100-3647)	2943 (2305-3315)	3340 (2480-3920)
SGA	16 (10)	4 (9)	3 (20)	9 (13)	0
LGA	43 (27)	9 (20)	4 (27)	10 (14)	20 (69)
Sex					
Male	82 (51)	19 (41)	9 (60)	39 (54)	15 (52)
Female	80 (49)	27 (60)	6 (40)	33 (46)	14 (48)
Previous child/ fetus with exomphalos, structural or genetic anomaly	3 (2)	1 (2)	1 (6)	1 (1)	0
FH of exomphalos / related conditions	7 (4)	0	0	6 (9)	1 (4)

All data presented as n (%) or Median (IQR) %s are given of those with complete data FH: Family history *BWS: Beckwith Wiedemann Syndrome

Percentages are rounded to nearest whole number and therefore may not add up to 100.

The median gestational age for the entire cohort was 38 weeks (IQR 35-38 weeks). Thirty-six percent of infants were born before term (59/161 where gestational age was known). This figure was highest in the group born with BWS, with half of these infants (52%) born before 37 weeks. Sixty-nine percent of infants born with BWS were large for gestational age (LGA) (20/29), and none were small for gestational age (SGA) (Figure 3.2).

Figure 3.2: Distribution of birthweight for gestational age among different categories of comorbidity associated with exomphalos



3.3.4 Antenatal characteristics and management

The antenatal characteristics and management of the infants in the cohort are shown in Table 3.8. Two women did not have any antenatal care. Of the remaining 160, 136 were given an antenatal diagnosis of exomphalos (85%). This proportion was not significantly different across categories of comorbidity ($p=0.5$).

Thirty-seven percent of mothers were known to have undergone invasive prenatal testing (amniocentesis or chorionic villus sampling), (59/160). These included 42% of those with an antenatal diagnosis of exomphalos (57/136). These figures may be inaccurate, however, as data on antenatal management were often lacking in the infant notes. Where the result of invasive prenatal testing was documented by the reporting clinician, 96% of all tests showed no chromosomal abnormalities (52/54). Of the eight infants in the cohort with aneuploidy or chromosomal anomalies, the diagnosis of exomphalos was known antenatally in four, and three of their mothers had invasive prenatal testing. The results of these tests confirmed that one infant had a chromosomal micro-deletion and one aneuploidy. In another infant, found postnatally to have a micro-deletion, the test result was normal.

Of the women with an antenatal diagnosis of exomphalos, where the planned mode of delivery was documented, 59/152 had a planned caesarean (39%). Of the women without an antenatal diagnosis, planned delivery was by caesarean in 3/24 (13%). When the diagnosis was known and caesarean section was the planned mode of delivery, the indication was documented for 38 mothers. Exomphalos was the sole documented indication in 29/38 (76%). Of the 29 infants born by planned caesarean, indicated only by exomphalos, 25 (86%) had the liver in the sac postnatally and the median defect size diameter, where documented, was 6cm (3.5-8cm). Where the defect size was measured 4/16 infants had a defect of less than three centimetres (25%).

Table 3.8: Antenatal characteristics and management of infants in the cohort (N=160).

	n (%)
Suspected antenatally	N=160
All	136 (85)
Median (IQR) gestation suspected, (wks)	18.5 (12-20)
Category of comorbidity	
Isolated	38 (84)
Syndromic	11 (73)
Structural	61 (86)
BWS	26 (90)
Offered invasive prenatal testing	
Known exomphalos	92/113 (81)
Unknown exomphalos	4/19 (21)
Had prenatal testing	
Known exomphalos	57/136 (42)
Unknown exomphalos	2/24 (8)
Prenatal test results	
Result documented	54 (95)
Normal	52/54 (96)
Microdeletion	1/54 (2)
Aneuploidy	1/54 (2)
Transferred after birth	
All	62/162 (38)
Known exomphalos	44/136 (32)
Planned mode of delivery	
All	
Vaginal	93/152* (61)
Caesarean	59/152* (39)
Known exomphalos	
Vaginal	72/128 (56)
Caesarean	56/128 (44)
Exomphalos unknown	
Vaginal	21/ 24 (88)
Caesarean	3/24 (13)
Indication for planned delivery	
Indication documented	38/ 59 (64)
Exomphalos only	29/38 (76)
Maternal indication	7/38 (18)
Other fetal indication	2/38 (5)
Actual mode of delivery	
Mode documented	161/162 (99)
Vaginal	69/161 (43)
Ventouse/ forceps	11/161 (7)
Pre-labour caesarean	48/161 (30)
Caesarean after labour onset	33/161 (21)

*Those where the planned mode of delivery was reported by clinicians (n=152) 108

3.3.5 Abnormalities associated with exomphalos in the cohort

Table 3.9 shows the range of genetic and structural abnormalities associated with exomphalos diagnosed postnatally; many infants had more than one structural abnormality.

Table 3.9 Congenital anomalies associated with exomphalos within the cohort

	N*	n (%)	Defect type (s)	Syndromic	Structural	BWS
Cardiac defects	130	77 (59) 70 (91)	L-R shunt			
Non PDA defects		65 (50)		5/15 (33)	47/68 (69)	13/26 (50)
Intracranial	86	13 (15)		6/11 (55)	5/41 (12)	2/17 (12)
Limb	161	11 (7) 5 (3)	Polydactyly	6/15 (40)	3/71 (4)	2/29 (7)
Thorax/ Spinal	161	4 (2) 1 (1) 2 (1)	CDH Kyphosis/ Scoliosis	1/15 (7)	1/71 (1)	2/29 (7)
Renal tract	104	14 (13)		4/10 (40)	7/46 (15)	3/21 (14)
GI tract	162	38 (23) 16 (10) 15 (9) 9 (6) 3 (2)	Malrotation VI duct remnant Intestinal atresia Other	3/15 (20)	24/72 (33)	10 (34)
Cranial/ Facial	161	15 (9) 9 (6) 3 (2)	Dysmorphic features Cleft lip/ palette	8/15 (53)	3/71 (4)	4/29 (14)
Genital tract	161	3 (2)		2/15 (13)	1/71 (1)	0

*N: Number with data on presence/ absence of abnormality e.g. for cardiac abnormalities, the number that had an echocardiogram with the result documented on the DCF

VI duct: Vitellointestinal duct Some infants had more than one GI anomaly.

Cardiac defects

The commonest abnormalities associated with exomphalos were cardiac defects. Fifty-nine percent of infants that had an echocardiogram (echo) performed, had an abnormality detected, (77/130). Data were collected on echo findings rather than their clinical significance. For this reason all abnormalities were included even though it is acknowledged that some, for example patent ductus arteriosus[†] (PDA), may not necessarily have long-term clinical implications. When infants with a PDA only were excluded, 50% of infants undergoing echo had an abnormality detected (65/130). The commonest of these were atrial septal defects, present in 41 of the 65 infants (63%), next was ventricular septal defect[‡] (VSD) (present in 18 infants (28%).

Intra-cranial lesions

Ninety-two of 146 infants with complete data were known to have had a cranial ultrasound scan (63%). In six infants, the findings were not reported. Where ultrasound findings were documented (n=86), 23 infants had abnormalities recorded (27%). Thirteen infants were found to have congenital intra-cranial abnormalities (15%). Five of these were considered to be of prognostic significance (3% of the cohort).

Renal tract anomalies

Fourteen (13%) of 104 infants that had an ultrasound of the renal tract had an anomaly detected. The commonest of these was hydronephrosis, present in six infants.

GI tract anomalies

Nine infants an intestinal atresia (6%). Vitello-intestinal (VI) duct remnants were noted in fifteen (9%) of infants and these all appeared to occur in infants with small defects. It must be noted, however, that a significant number of infants would not have had the entirety of their bowel inspected, including all of those who underwent non-operative management.

[†] **Patent ductus arteriosus**, a persistent connection between the body's main artery (carrying oxygenated blood away from the heart) and the artery to the lungs, carrying deoxygenated blood

[‡] **Ventricular septal defect**, a 'hole in the heart' resulting in a connection between the two main chambers

3.3.6 Characteristics of the abdominal wall defect at birth

In 87 infants (54%), the diameter of the defect at the level of the abdominal wall (defect diameter) was measured and this ranged from 1cm to 15cms with a median of 3cm (IQR 2-6cms). Sixty-nine infants were known to have the liver present in their exomphalos sac (43%). The presence of extracorporeal liver appeared to be related to defect diameter, (Figure 3.3). Where the diameter was not recorded, 35/75 infants had the liver in the sac (47%). This was not statistically significantly different from those in whom the defect size was measured (34/86 40%, $p=0.36$) suggesting that those infants in whom the defect size was not measured may well have similar defect characteristics to those in whom it was measured.

In infants where the defect size diameter was not recorded, clinicians were asked to record whether the infant was classified as having 'exomphalos major' or not. Where size was not measured, 38% of infants were classified as 'exomphalos major'. This was mostly, but not to be always, determined by the presence of the liver in the sac. All of the 28 infants reported as exomphalos major had the liver in the sac. Six of the 45 infants where the defect was not classified as exomphalos major had the liver in the sac (13%).

Figure 3.3 shows that the presence of the liver in the sac was related to defect size but that there were also some infants with smaller defects in which the sac contained part of the liver. Larger defects, above 7cm, always contained the liver.

Figure 3.3. The relationship between defect size and the presence of the liver in the exomphalos sac

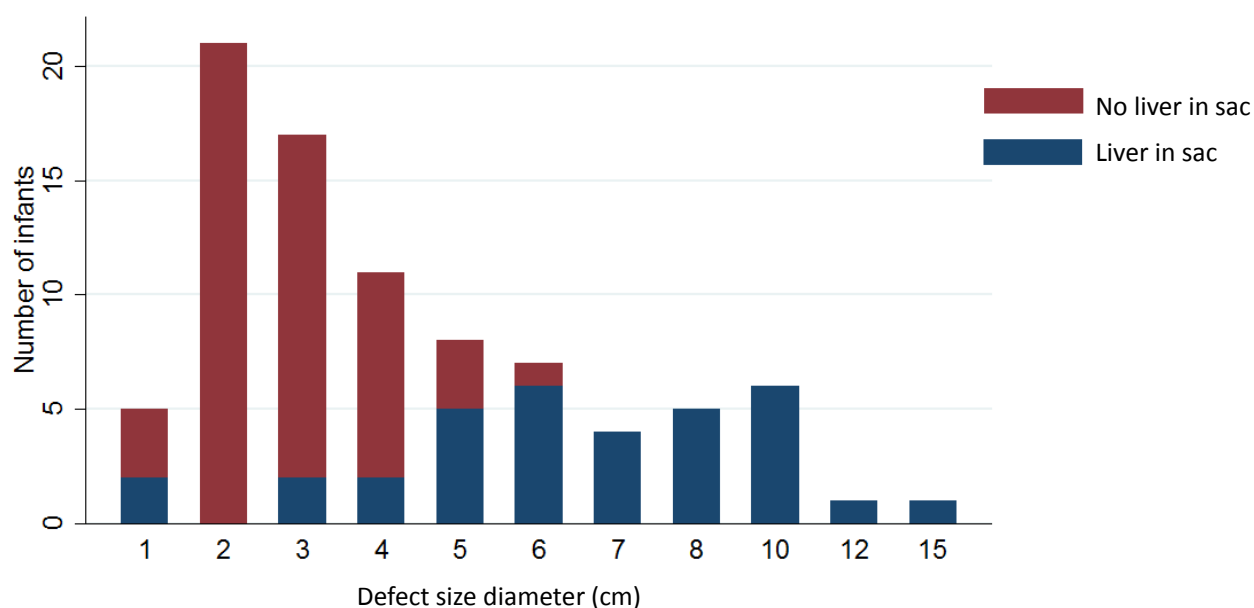


Figure 3.3 shows that defect size is a spectrum, and its distribution is skewed towards smaller defects of 3cm and below. A clear bimodal distribution at or below 5cm, or indeed any other diameter, was not seen. Informed by the distribution shown in Figure 3.3, three categories of defect size were defined (Table 3.10).

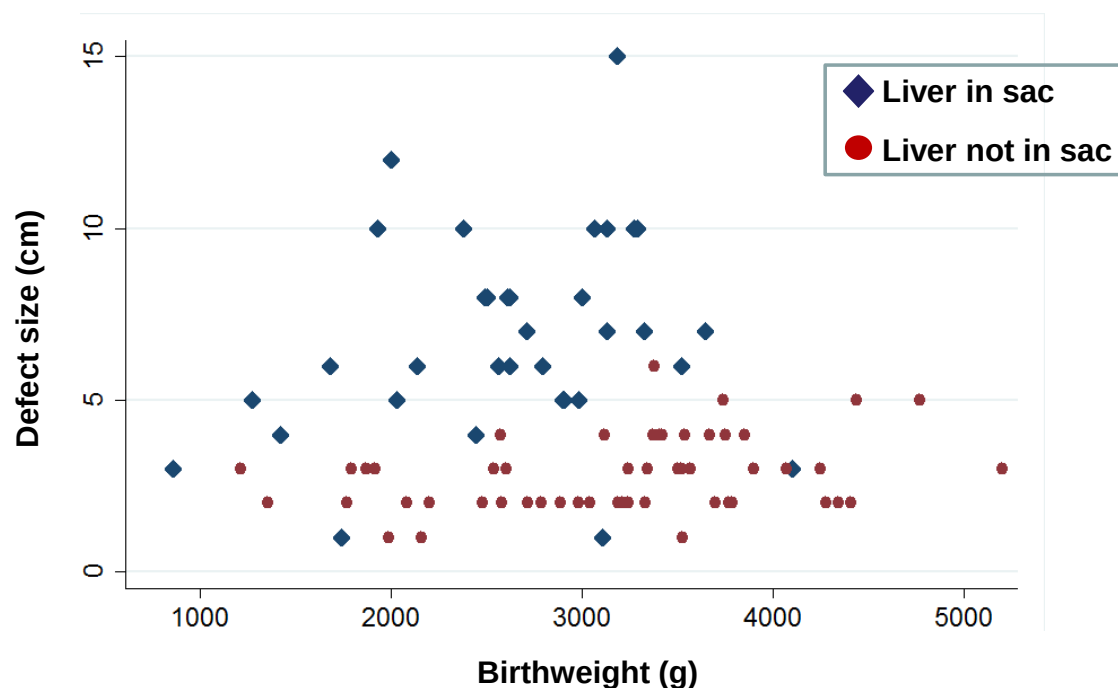
Table 3.10 The proportion of infants with liver in the exomphalos sac according to categories of defect size

	Liver in the sac n (%)
	N=86*
1-3cm	4/43 (9)
4-6cm	13/26 (50)
>=7cm	17/17 (100)

* One infant whose defect size was measured had missing information on the position of the liver

The relationship between defect diameter and the presence of the liver was explored further in relation to infant body weight. Birthweight and hence body size, varied almost ten-fold among infants in the cohort from 692-5200g meaning that the relative size of any given defect diameter would also vary. Figure 3.4 shows that the relationship between defect diameter and the presence of the liver in the exomphalos sac does indeed vary with birthweight. For example, at a diameter of 4cm, lighter infants were more likely to have the liver in the sac than heavier infants.

Figure 3.4 The relationship between defect size and extra-corporeal liver according to birthweight



The possibility of interpreting the defect diameter relative to the infant weight was explored. The diameter (cm) to weight (kg) ratio (DWR) was calculated for all infants with defect size and weight data available. DWR was able to be calculated in 86 infants (53% of the cohort). The values of the DWR ranged from 0.28 - 6.00 with a median of 1.17 (IQR 0.73-2.34).

DWR was found to be related to the presence of the liver in the exomphalos sac (Fig 3.4). When assessed by ROC analysis, the area under the curve (AUC) was 92% and the DWR cut-off that correctly classified whether the liver was in the sac for the highest proportion of children was ≥ 1.63 , correctly identifying 93%.

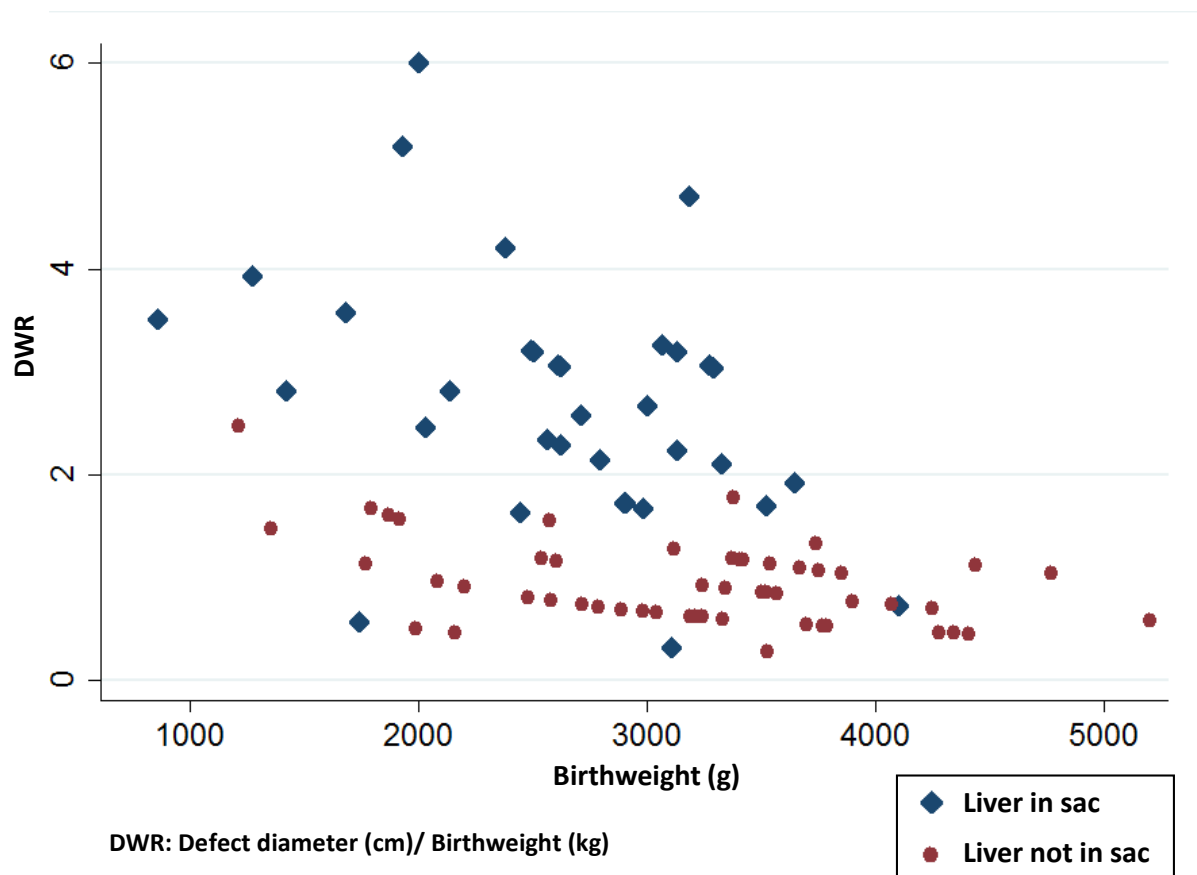


Figure 3.5 The relationship between DWR and extra-corporeal liver according to birthweight

3.3.6i Demographic associations with anatomical characteristics of the defect

One of the primary research aims was to identify prognostic factors associated with key short-term outcomes, such as neonatal survival among infants with exomphalos. Such factors included: birthweight, gestational age and associated anomalies. Possible associations between these demographic features and anatomical characteristics of the abdominal wall defect were explored to assess the degree to which the two were related (Table 3.11).

Table 3.11 Defect characteristics in different demographic groups

	Defect diameter category N=87				Liver in sac N=161		DWR N=86	
	1-3cm	4-6cm	>=7cm	p value	Liver in sac	p value	DWR	p value
All infants	44 (51)	26 (30)	17 (20)		69/161 (43)		1.17 (0.73-2.34)	
Sex								
Male	26/40 (65)	8/40 (20)	6/40 (15)	0.046	30/81 (44)	0.13	0.89 (0.63-0.90)	0.004
Female	18/47 (38)	18/47 (38)	11/47 (23)		39/80 (57)		1.68 (0.91-2.81)	
BW /GA								
SGA	2/6 (33)	2/6 (33)	2/6 (33)	0.16	11/16 (69)	0.0001	2.22 (1.48-3.2)	0.14 [†]
NGA	27/58 (47)	17/58 (29)	14/58 (24)		48/101 (48)		1.57 (0.76-2.47)	
LGA	15/22 (68)	6/22 (27)	1/22 (5)		9/43 (21)		0.82 (0.53-1.13)	0.005 [†]
Category of Comorbidity								
Isolated	13/27 (48)	10/27 (37)	4/27 (15)	0.27	18/45 (40)	0.007	1.15 (0.77-2.29)	
Syndromic	5/8 (63)	1/8 (13)	2/8 (25)		8/15 (53)		1.37 (0.79-2.59)	0.75 [*]
Structural	14/32 (44)	8/25 (25)	10/32 (31)		38/72 (53)		1.61 (0.79-3.06)	0.35 [*]
BWS	12/20 (60)	7/20 (35)	1/20 (5)		5/29 (17)		0.97 (0.61-1.45)	0.26 [*]

All values given as n (%) or median (IQR) %s rounded and may not add up to 100%. BW/GA birth weight by gestational age.

SGA, small for gestational age, NGA, normal weight for gestational age, LGA, large for gestational age. [†] comparison to NGA group ^{*}comparison to isolated group

DWR: Defect size cm/.birthweight (kg)

The relationship between infant characteristics and DWR is shown in Figures 3.6-3.8. The distribution of defect size was significantly different with the sex of the infant; male infants were more likely to have a small defect, whereas in females, defect size was more evenly spread throughout the defect size categories. Female infants had a significantly higher DWR than males ($p=0.004$).

Figure 3.6 The relationship between infant sex and DWR

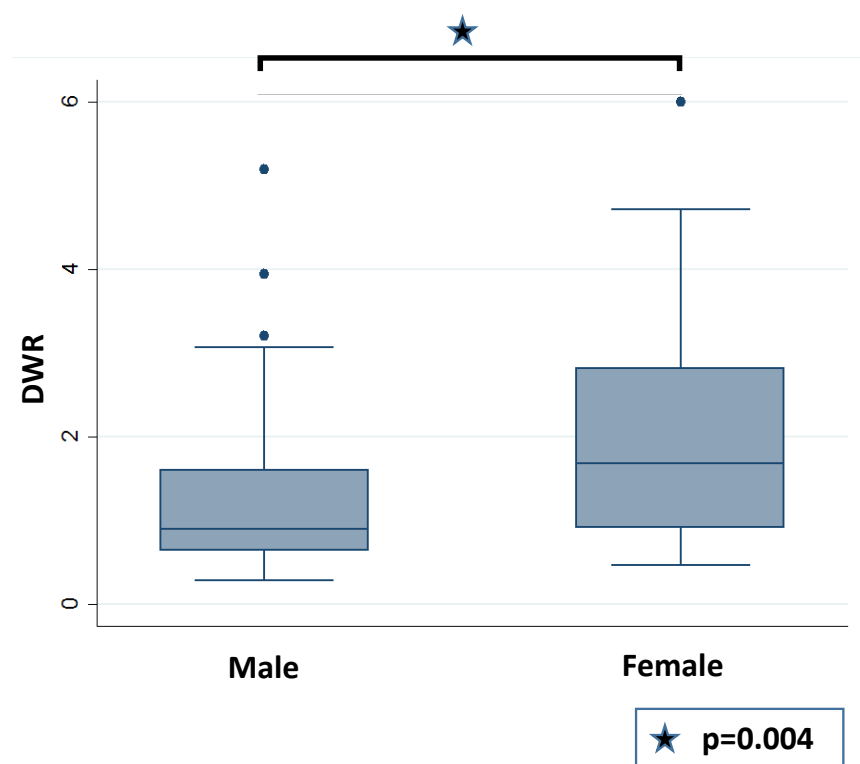


Figure 3.7 The relationship between birthweight for gestational age and DWR

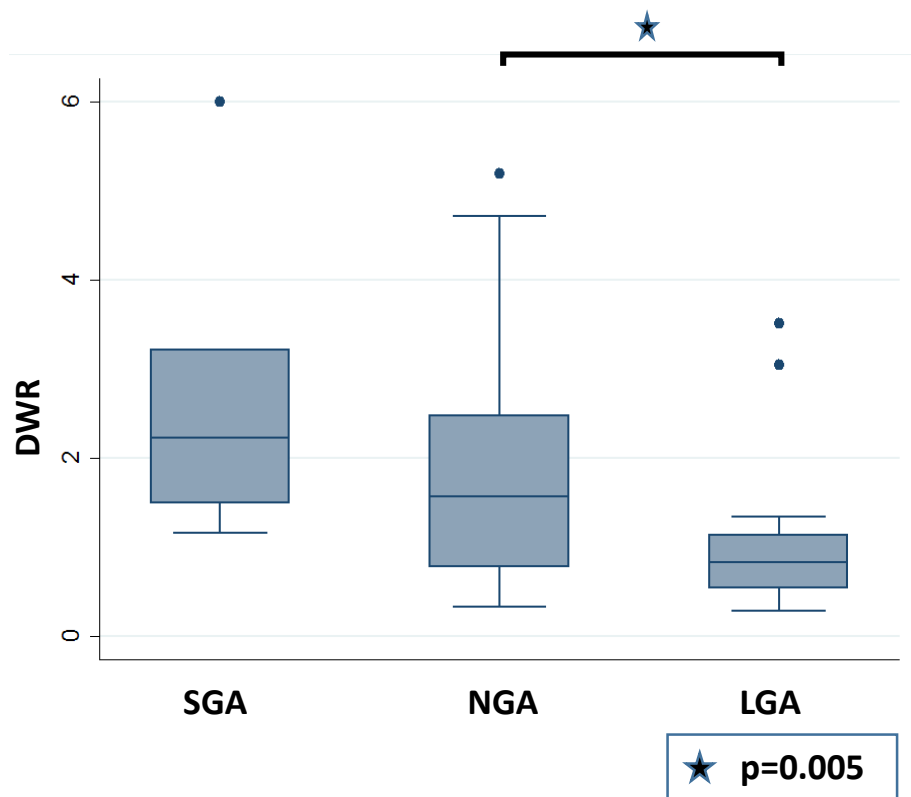
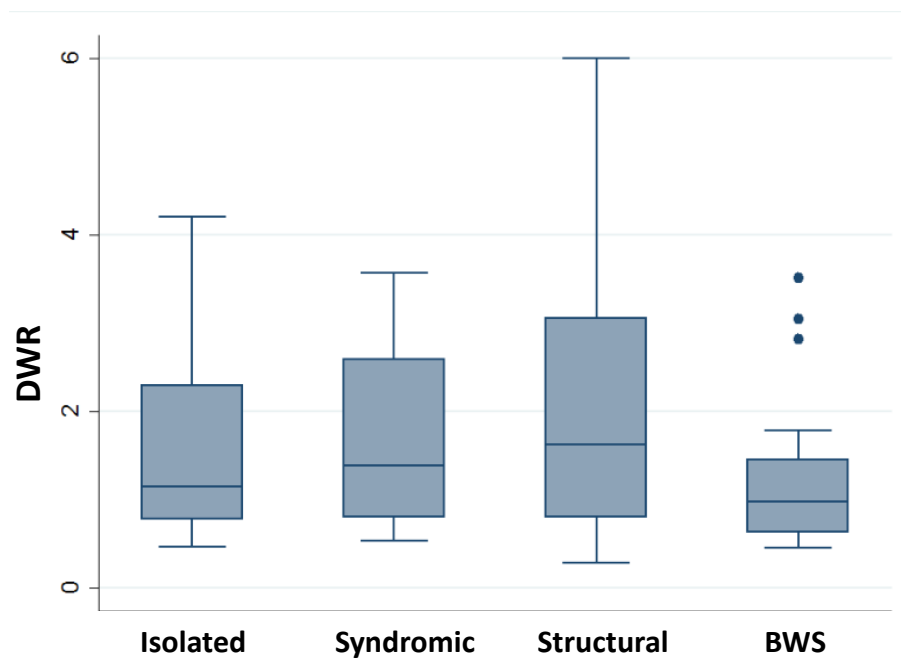


Figure 3.8 The relationship between category of comorbidity and DWR



Although there was only a very small number of infants in the SGA category (n=16), DWR was inversely related to birthweight for gestational age (Figure 3.7). Infants who were LGA had a significantly lower median DWR than those with a normal birthweight centile ($p=0.005$). It was hypothesised that this was related to smaller defects predominating in infants with BWS (Figure 3.8) who were also more likely to be macrosomic (Figure 3.2). However, a sensitivity analysis was performed, excluding infants with BWS and this difference remained statistically significant ($p=0.005$).

Figure 3.8 shows that the median DWR was lower in infants with BWS than those with isolated exomphalos, although this difference was not statistically significant ($p=0.26$). There were, however, some infants with BWS with high DWR values.

3.3.7 Exomphalos sac rupture

Fifteen infants in the cohort presented with a ruptured exomphalos sac (9%). Four of these had the liver present within the sac (27%). Defect size was measured in seven infants whose sac had ruptured. Six of these were 1-3cms in diameter (86%). Of the eight infants where the diameter was not measured, three (38%) were categorised as exomphalos major by their treating clinicians and five were not (63%). Although these numbers are small, there is little evidence that sac rupture was related to defect size among infants in the cohort.

In four infants it was not known when the sac ruptured. In the remaining 11, five ruptures occurred before delivery, five during delivery and one after delivery. Sac rupture during delivery occurred during vaginal (1/64), instrumental (2/10) and caesarean (2/77) deliveries. Three infants where there was a sac rupture during delivery had extracorporeal liver and four did not. Only one infant with sac rupture during delivery had the defect size measured. This was 5cm and the DWR was 2.46. The outcomes of infants with a ruptured sac are described in 3.3.10v.

3.3.8 Medical management requirements of infants in the cohort

3.3.8i Requirement for invasive ventilation

Ten infants, (6%) had pulmonary hypoplasia documented as an additional morbidity by reporting clinicians. Two further infants developed pneumothoraces. Fifty-four percent of all infants had invasive ventilation (n=88). Six percent of all infants who survived the neonatal period remained on invasive ventilation for longer than 28 days (n=9/140). One infant required extra-corporeal membrane oxygenation (ECMO) for severe pulmonary hypertension.

3.3.8ii Parenteral nutrition and oral feeding

Table 3.12 shows the data on the nutritional management of infants in the cohort. Fifty-three percent received parenteral nutrition (PN) during their early course (n=85). Twenty-two of 150 infants who survived the neonatal period with complete data were still receiving PN at day 28 (15%).

Table 3.12 Nutritional management of infants in the cohort

	n/N (%)	n (%) at day 28 [†]	Median (IQR) days if <28
Parenteral Nutrition			
Received PN	85/159 (53)	22/150 (15)	11 (6-15)
Enteral feed			
Commenced		125/132 (95)	2 (1-4)
Fully fed		120/129 (93)	6 (3-10)
Mode of feeding at day 28[†] N=150			
Fully oral	100 (67)		
Oral + PN	2 (1)		
Fully or partially NG	38 (25)		
PN only	2 (1)		
Gastrostomy only	2 (1)		

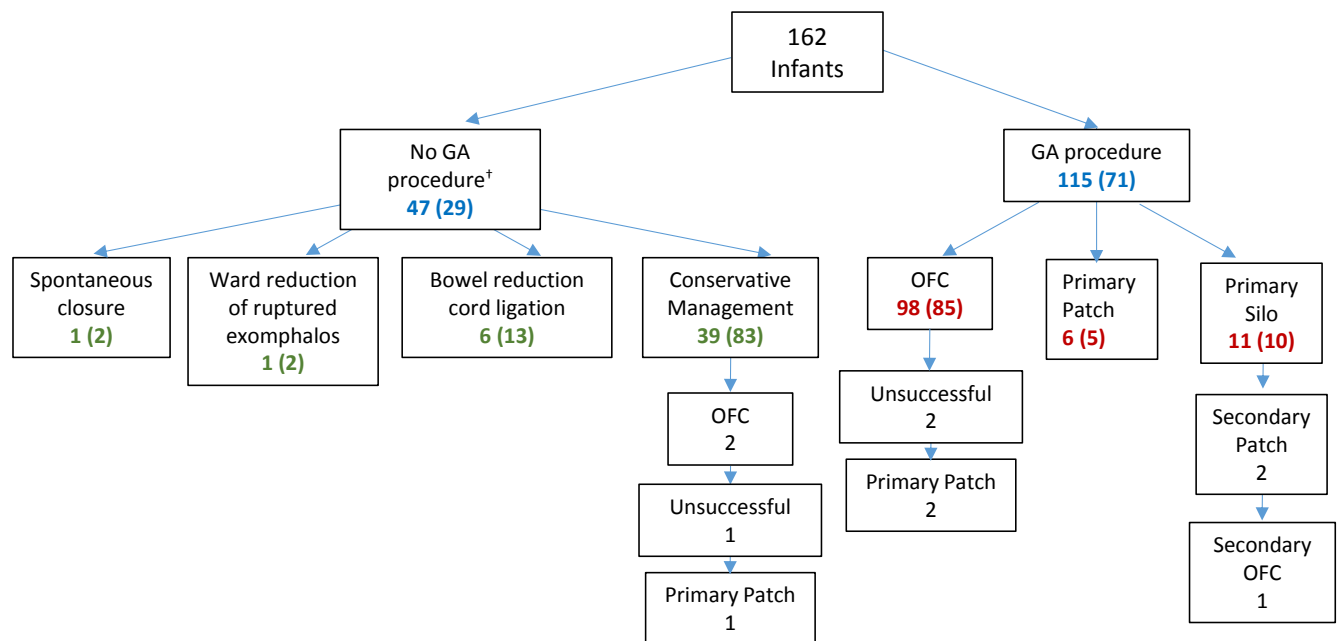
[†] Day 28 defined as 28 days after presentation for non-operative group and 28 days post-op for group undergoing surgery.

3.3.9 Surgical management

3.3.9i All infants

Figure 3.9 shows the surgical management pathways of all of the infants in the cohort.

Figure 3.9 Surgical management of all infants in the cohort



[†]No general anaesthetic procedure initially. As shown, two infants had delayed surgery

GA Procedure: Operation performed under general anaesthesia OFC: Operative fascial closure

Fifty-nine percent of all infants were managed with a successful primary operative fascial closure (OFC) (n=96). Of the 58 infants in whom primary closure was not attempted or was attempted and failed (n=2), 39 (67%) were treated with conservative management initially, 11 (19%) had a silo placed over the defect and its contents and 8 had a patch inserted to bridge the fascial defect (14%) (Table 3.13).

Table 3.13 Summary of primary management strategy for infants in the cohort

Primary method of management N=162	n (%)
Operative fascial closure	96 (59)
Conservative management	39 (24)
Silo	11 (7)
Patch [†]	8 (5)
Cord ligation	6 (4)
Other	2 (1)

[†] 2 infants with failed OFC included in patch group.

3.3.9ii. Infants with a ruptured sac

Of the 15 infants with a ruptured sac, two were managed without general anaesthesia: one had the extra-abdominal bowel reduced on the ward with the umbilical cord placed over the defect as a 'cap'. In the case of the other infant, the torn sac was sutured closed. Nine infants had a primary closure and four had a silo placed.

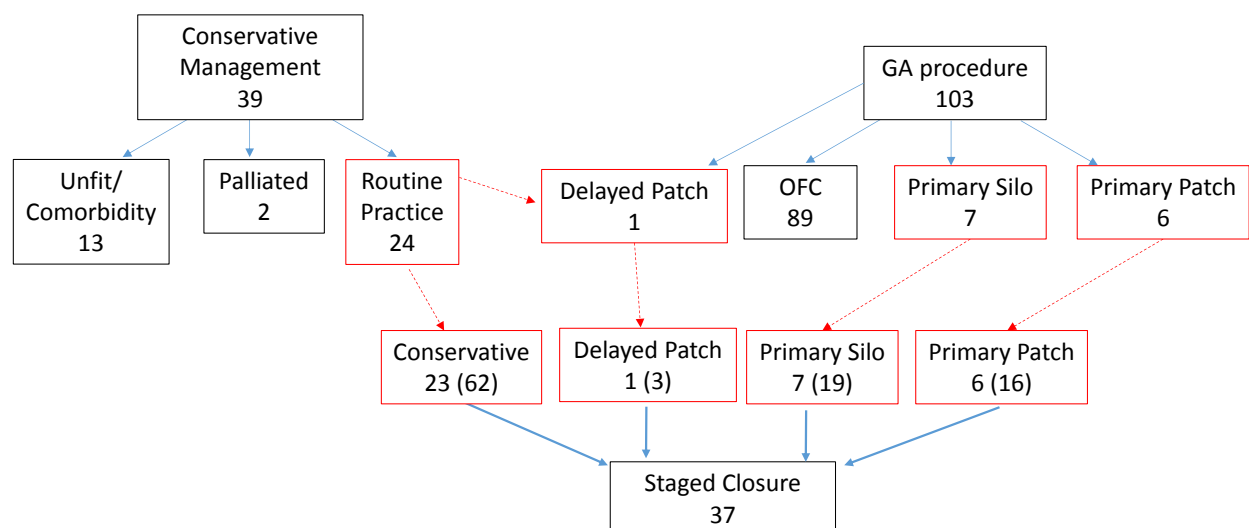
3.3.9iii Infants undergoing staged closure

One of the research questions for this study was: '*is there evidence of variation between centres with regard to surgical management?*' This was particularly with reference to infants where the abdominal wall defect was not closed primarily. In order to assess this variation, the group of infants for whom the defect could not be closed primarily and where surgeons treating them would have had a degree of choice in their surgical management strategy, was defined. Those with rupture of the sac were excluded from this assessment with the exception of the infant where the sac had only a minor tear that was sutured closed. Infants that did not undergo surgery because they were deemed unfit or where there was significant comorbidity precluding operation were also excluded.

The two infants managed with a patch after a failed primary closure, were included in the primary closure category for this analysis on an intention to treat basis.

The infants making up the group where 'choice' of staged closure was assessed are shown in red in Figure 3.10. Where infants had a defect that was not suitable for primary closure (n=37) two-thirds were treated initially with conservative management (65% n=24), 19% (n=7) were managed with a silo and 16% with a patch (n=6).

Fig 3.10 Management of infants that were not closed primarily where clinicians had a choice whether to manage operatively or non-operatively (indicated by the red boxes)



3.3.9iii.a Infants managed conservatively

When undertaking conservative management, most commonly, clinicians applied a combination of dressings and a topical therapy; this treatment was used in 47% of infants (n=17). In 17% no dressing or topical treatments were applied to the sac (n=6). Fifteen infants (44%) received a treatment containing silver, either within dressings or applied separately. Only one of these infants had a plasma silver level measured and the result of this was not known.

3.3.9iii.b Other methods of staged management

Eleven infants were managed with a primary silo, four of whom presented with a ruptured sac. Twelve infants were treated with a patch to the fascial defect within the 28 day period, either primarily or after removal of a silo. Six (46%) were made of biological material and seven (54%) were synthetic.

3.3.9iv Characteristics of infants undergoing staged closure

The characteristics of infants that were managed with staged closure were explored and compared to those managed with primary fascial closure. These are shown in Table 3.14. Infants included in this analysis and the rationale for this are described in Table 3.5. Here, unlike in Figure 3.10 the two infants with a failed primary closure are included in the staged closure group.

A ROC curve analysis was performed to assess the relationship between characteristics with a continuous distribution and the use of staged closure. The area under the curve (AUC) values for the predictive ability of these characteristics are shown in Table 3.14.

Table 3.14 Characteristics of infants undergoing primary vs staged closure.

	Primary n/N (%)	Staged n/N (%)	p value	AUC (95% CI)
Number N=139	96/139 (69)	43/139 (31)		
Sex				
Male	51/96 (53)	17/43 (40)	0.14	
Female	45/96 (47)	26/43 (60)		
Gestational age (wks)[¥]	38 (36-39)	37.5 (35-38)	0.08	
Term	65/96 (68)	29/42 (69)	0.97	
Preterm	31/96 (32)	13/42 (31)		
Birthweight (g)	3300 (2585-3745)	2795 (2380-3270)	0.0009	0.68 (0.59-0.77) [€]
Category of comorbidity				
Isolated	32/96 (33)	13/43 (30)	0.002	
Syndromic	5/96 (5)	5/43 (12)		
Structural	35/96 (36)	24/43 (56)		
BWS	24/96 (25)	1/43 (2)		
Liver in sac				
Yes	15/96 (16)	41/43 (95)	<0.0001	
No	80/96 (83)	2/43 (5)		
Defect size diameter (cm)	3 (2-4), 1-10cm	7 (5.5-8), 3-15cm	<0.001	0.94 (0.88-0.99)
1-3cm	36/53 (68)	1/24 (4)	<0.001	
4-6cm	16/53 (30)	9/24 (38)		
>=7cm	1/53 (2)	14/24 (58)		
Exomphalos major not measured[†]				
Yes	3/42 (7)	17/19 (89)	<0.001	
No	39/42 (93)	2/19 (11)		
DWR (cm/kg)	0.85 (0.6-1.2)	2.7 (2.0-3.2)	0.000	0.96 (0.92-1)
D/ W Ratio <1.64	46/52 (88)	0/23 (0)		
D/ W Ratio ≥1.64	6/52 (12)	23/23 (100)	0.000	
Defect ≥5cm				
Yes	8/53 (15)	22/24 (73)	0.000	
No	45/53 (85)	2/24 (4)		
Defect ≥5cm & Liver in Sac				
Yes	4/53 (8)	22/24 (92)	0.000	
No	49/53 (92)	2/24 (8)		
Defect ≥ 7cm				
Yes	1/53 (2)	14/24 (58)	0.000	
No	52/53 (98)	10/24 (42)		

[¥]Median/ IQR DWR: Diameter (cm)/ weight (kg) ratio AUC: Area under the curve (ROC analysis).

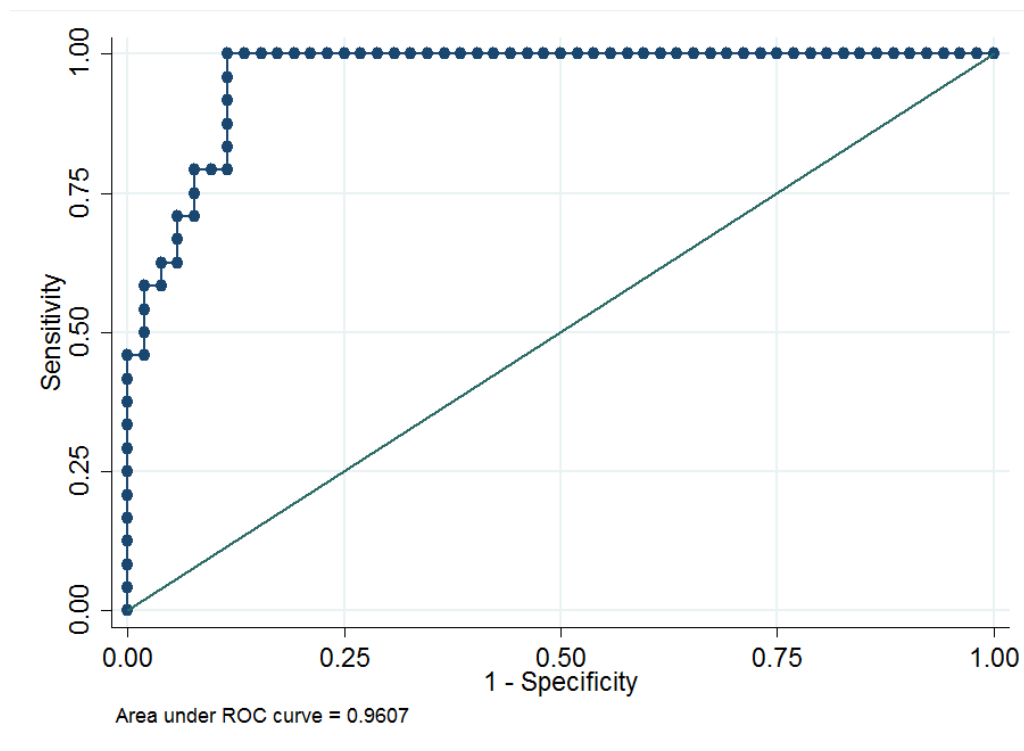
[†]Labelled exomphalos major by clinicians, defect size was not measured [€]AUC relates to 1/birthweight as weight likely to be inversely related to defect size and hence ability to close primarily (Fig 3.7)

Percentages rounded off so combinations may not always equal 100.

The analysis of the characteristics of infants undergoing primary vs staged closure included 96 infants with successful primary closure and 43 who were managed using a staged method. Infants that were able to be closed primarily had significantly heavier birthweights than those requiring staged closure ($p=0.0009$). The proportion of infants with defects able to be closed primarily differed by category of comorbidity. Seventy-one percent of infants with isolated exomphalos were able to be closed primarily compared with 96% of infants with BWS. The typical features of the defect in BWS clearly facilitated primary closure in the majority of these infants (Table 3.11).

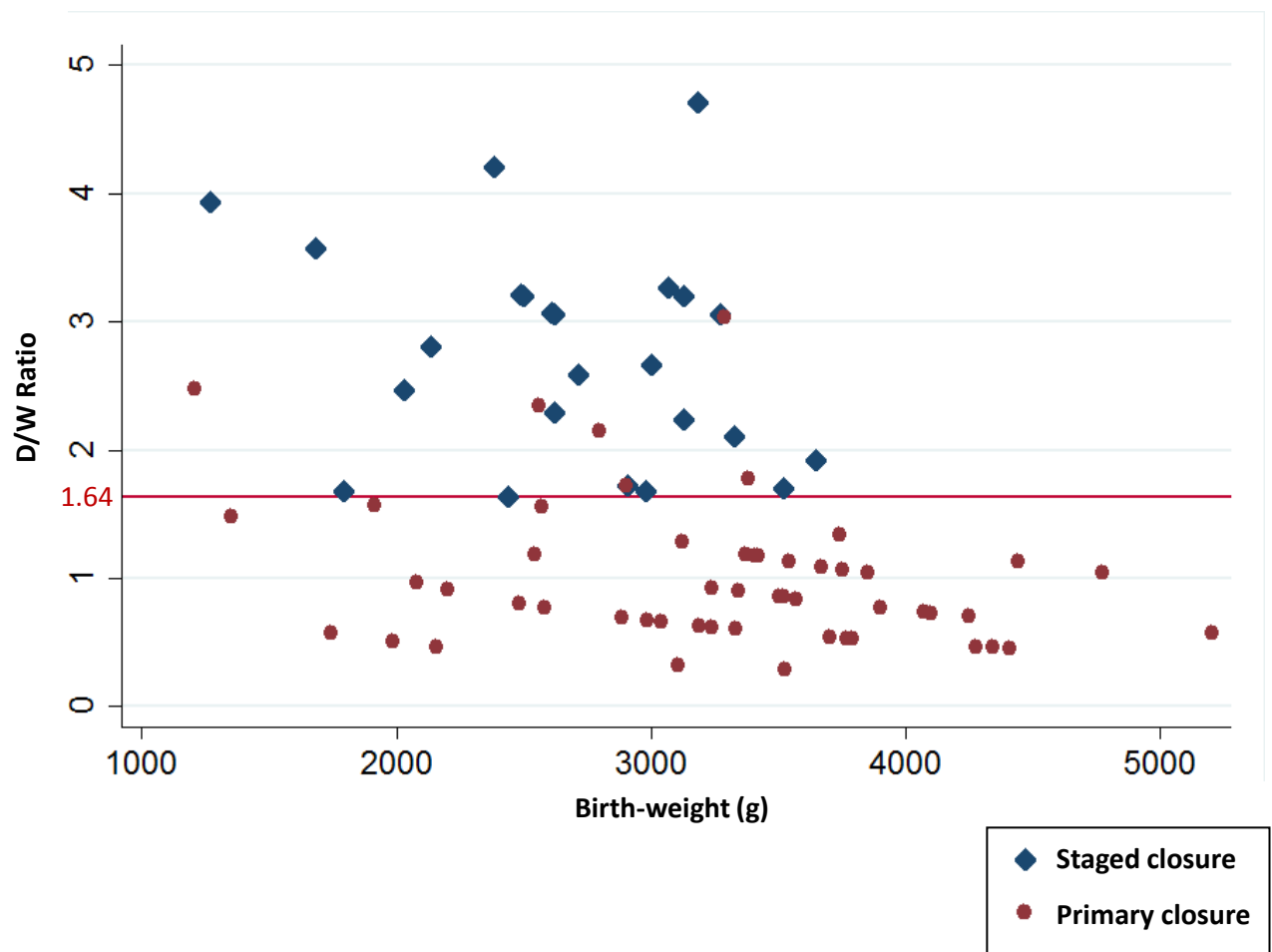
The surgeon's ability to close the defect primarily was statistically significantly related to all markers of defect size. The AUC values indicate that the best predictor of the surgeon's ability to close the defect primarily was the DWR (Figure 3.11).

Figure 3.11 ROC graph indicating the AUC for prediction of the use of staged closure by Defect/ Weight Ratio



The DWR value that predicted the use of staged closure in the largest proportion of infants (92%) was 1.64 (sensitivity 100% and specificity 88%). When this cut off is chosen in this cohort, all of the infants with a ratio of less than 1.64 were closed primarily and of those with a ratio of ≥ 1.64 , 6/29 infants (21%) had a primary closure (Figure 3.12).

Figure 3.12. The relationship between Defect/Weight Ratio and primary closure



Compared to other binary variables such as: the presence of the liver in the sac, size of defect >5cm, a defect >5cm with the liver in the sac and a defect of >7cm, the DWR cut-off of ≥ 1.64 had the best positive and negative predictive value (79% and 100% respectively).

3.3.10 Outcomes and complications

3.3.10i Complications relating to infant comorbidity

A number of adverse events affected infants in the cohort that were specifically related to comorbidities. Complications of prematurity included: five infants developing intra-ventricular haemorrhage in the brain, one with pulmonary haemorrhage, and two having suspected necrotising enterocolitis[†] and four infants with BWS had documented episodes of hypoglycaemia. Structural abnormalities led to specific severe adverse events, for example, one infant who had resection and anastomosis for a colonic atresia developed an anastomotic leak. These complications associated with specific comorbidities are not included in the subsequent analysis of outcomes.

3.3.10ii Infectious morbidity

In total, 61 infants (38%) were treated with a course of at least five days of intravenous antibiotics for a proven or suspected infection during their early management. Three infants were known to have been infected or colonised by a multi-resistant organism during their early treatment (2%). Eleven infants were treated with at least five days of antibiotics for a proven or suspected wound, skin or sac infection (7%). None of these latter infections occurred among the 15 infants with a ruptured sac but two occurred in the seven infants who had a breach in the sac that developed during conservative management.

The outcomes related to infectious morbidity in infants treated with different management techniques and with infant characteristics are shown in Tables 3.15-16.

[†]Necrotising enterocolitis (NEC) is a severe inflammatory condition affecting the bowel in newborn infants and is more common in those born prematurely

3.3.10iii Neonatal death

Seven infants (4%), died in the first 28 days after birth. All except one of these were born before term. Causes of death were varied, and pulmonary hypoplasia was cited as a contributory factor in three of the infants. Three infants received palliative care. Four of seven infants that died had the liver in the sac. Only two had the defect diameter measured, one had a DWR ≥ 1.64 and the other < 1.64 . Two of the infants that died had a ruptured sac after birth.

3.3.10iv Other early outcomes

This study specifically assessed outcomes within the first 28 days after surgery or decision for non-operative management. At the end of this time period, 34/133 infants in the cohort who survived to 28 days and had complete data were still in hospital (26%), 9/140 (6%) were still ventilated, 9/129 (7%) were not fully enterally fed and 22/150 (15%) were on PN. Some infants who were reported to have been on full feeds before 28 days were receiving PN at 28 days, this may relate to further episodes of surgery or a later need for additional nutritional support. To adequately assess these continuous outcomes, a longer-term view will be necessary. The median values for these outcomes where they are < 28 days from date zero are shown in Tables 3.15 and 3.16.

Table 3.15 Infant outcomes according to method of closure

Mode of closure	Primary	All staged [*]	p value		Conservative	Silo	Patch
N=125	87 (70)	38 (30)			23 (61)	7 (18)	8 (21)
Ventilated							
Ventilated	40/87 (46)	21/38 (55)	0.437		9/23 (39)	6/7 (86)	6/8 (75)
Days of ventilation†	2 (1-5)	5 (3-14)			10 (3-16)	9.5 (5-14)	3 (3-4)
>=28 n (%)	0/87	4/38 (11)	0.037		1/21 (5)	2/7 (29)	1/8 (13)
Full enteral feeds (FEF)							
Days until FEF	5 (3-8)	10 (5-13)			6 (4-12)	12 (5-23)	5 (3-8)
>28	5/76 (7)	1/32 (3)	0.667		0/20	1/6 (17)	0/6
Parenteral nutrition							
Received PN	37/86 (43)	25/37 (68)			13/22 (59)	5/7 (71)	7/8 (88)
PN days‡	6 (4-11)	14 (10-15)			11 (6-14)	21 (20-21)	10
<28	7/84 (8)	4/36 (11)	0.732		1/22 (4)	2/7 (43)	1/8 (13)
Length of stay (LOS)							
LOS [€]	8 (5-14)	19 (14-21)			19 (14-22)	26 (26-26)	15 (11-20)
>28	11/81 (14)	16/33 (48)	<0.001		11/22 (50)	4/5 (80)	1/6 (16)
All complications	26/87 (30)	25/38 (66)	<0.001		14/23 (61)	6/7 (86)	5/8 (63)
Management complication	10/87 (11)	11/38 (29)	0.021		4/23 (17)	4/7 (57)	3/8 (38)
Sac leak/ damage					4/22 (18)		
Any infection	23/87 (26)	21/38 (55)	0.004		12/23 (52)	5/7 (71)	4/8 (50)
Wound/ skin/ sac infection	7/87 (8)	2/38 (5)	0.721		0/23	2/7 (29)	0/8
Neonatal mortality	0/87	2/38 (5)			1/23 (4)	0/7	1/8 (13)

All data are expressed as n(%) or median (IQR) †those ventilated <28 days *Includes the infant who had a delayed OFC, %s rounded so may not add up to 100%

‡ Those on PN <28 days € Those who were discharged before 28 days.

Table 3.16 Infant outcomes according to infant characteristics

	DWR <1.64	DWR ≥1.64	p value		Isolated	Syndromic	Structural	BWS		Ruptured sac	Sac not ruptured
N‡	52	33			46	15	72	29		15 (9)	147 (91)
Ventilated	19 (37)	21 (64)	0.02		21/46 (46)	8/15 (53)	44/72 (61)	15/29 (52)		11/15 (73)	77/147 (52)
Days of ventilation†	2 (1-5)	3 (3-15)			3 (2-4)	5 (5-5)	8 (3-16)	0		4 (3-5)	3 (2-5)
>28	1/51 (2)	4/32 (13)	0.154		0/45 (0)	1/13 (8)	7/69 (10)	1/27 (4)		1/13 (8)	8/142 (6)
Full enteral feeds (FEF)											
Days until FEF	6 (3-8)	6 (5-12)			5 (2-8)	6 (3-10)	8 (5-11)	6 (5-11)		8 (5-11)	3 (3-5)
>28	3/51 (4)	3/32 (9)	0.383		2/41 (5)	0/11 (0)	7/55 (13)	0/22 (0)		1/8 (13)	8/121 (7)
Received PN	18 (34)	22 (69)			15/46 (33)	6/15 (40)	48/69 (70)	16/29 (55)		10/15 (67)	75/144 (52)
PN days ^μ	7 (5-11)	13 (6-15)			13 (7-15)	12 (8-18)	12 (6-15)	8 (4-11)		7 (6-10)	11 (6-15)
<28	3/50 (6)	6/31 (19)	0.079		2/43 (5)	1/13 (8)	17/68 (24)	2/26 (8)		6/13 (46)	16/137 (12)
Length of stay											
LOS [€]	8 (4-12)	14 (9-20)			7 (3-11)	11 (10-19)	12 (8-16)	11 (8-12.5)		14 (13-15)	10 (5-14)
>28	6/46 (13)	12/26 (46)	0.004		6/44 (14)	2/11 (18)	19/55 (35)	7/23 (30)		4/10 (40)	30/123 (24)
All complications	14/52 (27)	21/33 (64)	0.001		18/46 (39)	8/15 (53)	36/72 (50)	6 (21)		6/15 (40)	62/147 (42)
Management complication	4/52 (8)	11/33 (33)	0.004		8/46 (17)	2/15 (13)	15/72 (21)	1/29 (3)		2/15 (13)	24/147 (16)
Any infection	13/52 (25)	17/33 (52)	0.019		16/46 (35)	8/15 (53)	31/72 (57)	6/29 (21)		6/15 (40)	55/147 (37)
Wound/ skin/ sac infection	3/52 (6)	3/33 (9)	0.67		4/46 (9)	1/15 (7)	5/72 (7)	1/29 (3)		0/15	11/147 (7)
Neonatal mortality	1 (2)	1 (3)			1/46 (2)	2/15 (13)	2/71 (3)	2/29 (7)		2/15 (13)	5/146 (3)

All data are expressed as n(%) or median (IQR) ‡ not all infants had the defect diameter measured

^μThose on PN <28 days [€] Those who were discharged before 28 days.

3.3.10v Infant outcomes by surgical management technique

Table 3.15 shows the outcomes of infants by operative technique. As expected, infants undergoing staged closure had a more complex course than those undergoing primary operative fascial closure, with significantly more infants being ventilated at 28 days and more being in hospital at 28 days ($p=0.037$ and $p<0.001$ respectively). By day 28, 86% of infants undergoing primary closure were discharged, compared with 52% of infants undergoing staged closure. More infants undergoing staged closure experienced a complication, (66% vs 30%, $p<0.001$), more had a complication of management (29% vs 11%, $p=0.021$) and more had an infection requiring at least five days of antibiotics (55% vs 26% $p=0.004$). The small numbers of infants undergoing the different methods of staged closure precluded comparative analysis. Fifty-percent of infants treated initially with conservative management and 80% of infants treated with silo were still in hospital at 28 days. Only one infant who had a primary patch closure (with significant comorbidity) was an inpatient at this point.

Complications of surgical management occurred in 29% of infants managed by staged closure. For all infants managed conservatively, 7/38 (18%) were known to have experienced damage to the exomphalos sac. In three infants, these were repaired using surgical techniques. Three infants treated with a primary operative fascial closure developed an early abdominal wall hernia 3/96 (3%).

Six infants who had surgery experienced a wound dehiscence during their early management (6/116, 5%). All of these infants had liver in the sac and the two infants where the defect size was measured had A DWR ≥ 1.64 (both were treated with staged management). Three of the six infants had been treated with a patch: two primarily and one after an early silo revision. Of the 12 infants treated with an early patch, 3 (25%) had a wound dehiscence. No infant developed abdominal compartment syndrome.

3.3.10v Outcome by infant characteristics

3.3.10v.a Outcomes of infants according to DWR ≤ 1.64

There were 33 infants in the cohort with a known DWR of ≥ 1.64 (39% of those in whom it was able to be calculated). As DWR ≥ 1.64 has been shown to predict the use of staged closure, it is not surprising that the outcomes in these infants (as with those undergoing staged closure) are poorer than for infants with a ratio < 1.64 (Table 3.16). In order to further explore the impact of DWR ≥ 1.64 on outcome, the characteristics and outcomes of infants *not* undergoing staged closure was explored. OFC was attempted in seven infants (21%) with a known DWR of ≥ 1.64 and was successful in six. In the infant where OFC was attempted yet unsuccessful, surgery to the abdomen was unavoidable due to a gastrointestinal problem. This infant had a patch repair.

Details of the six infants with DWR ≥ 1.64 that underwent successful OFC are shown in Table 3.17. Two infants did not have the liver in the sac despite their relatively high DWR. In one of the infants, surgical exploration was essential due to intestinal obstruction. The infant with the largest DWR that was closed primarily (3.04) developed an early abdominal wall hernia. No other intra or post-operative complications were noted in any of the infants.

Table 3.17 Infants with a DWR > 1.64 who underwent successful OFC

BW (g)	GA (wks)	Defect diameter (cm)	DWR	Liver in Sac	Other features present*	Closure details
1210	28	3	2.48	No	None	Uncomplicated
2560	36	6	2.34	Yes	None	Uncomplicated
2795	37	6	2.15	Yes	Intestinal obstruction clinically	Correction of malrotation and relief of duodenal obstruction
2900	38	5	1.72	Yes	None	Uncomplicated
3290	34	10	3.04	Yes	None	Early abdominal wall hernia
3380	38	6	1.78	No	None	Uncomplicated

GA - gestational age (weeks), *features that may have affected surgical decision making,

3.3.10v.b Outcomes of infants according to category of comorbidity

The descriptive analysis of the outcomes of infants by category of comorbidity suggests that early outcomes were worse in infants with associated structural anomalies than those with isolated exomphalos. For example, at 28 days: 35% vs 14% of infants in each group were still in hospital, 24% vs 5% on were receiving parenteral nutrition and 0 vs 10% were being invasively ventilated.

Management complications were the most infrequent among infants with BWS, with just 3% of infants having a complication of surgical management, reflecting the defect characteristics that favour straightforward closure in the majority of infants with this condition.

3.3.10v.c Outcomes of Infants with a ruptured sac

Outcomes of the infants with a ruptured sac were similar to other infants with the exception of neonatal death; 13% of infants with a ruptured sac died in the first 28 days, (n=2). One of these died from factors that related to the cause of sac rupture, the other received comfort-care only.

3.4 Discussion

3.4.1 Main results

This study represents the first national population cohort study of the outcomes of infants born with exomphalos to have been conducted anywhere in the world. During the two-year data collection period, 162 infants with this abdominal wall defect were born alive within the UK and Ireland. As expected, the population of infants experienced a heavy burden of comorbidity with only 28% of infants being classified as having 'isolated' exomphalos.

Postnatal screening for associated anomalies was variable with the percentage of infants undergoing echocardiogram, renal tract ultrasound and cranial ultrasound noted to be 80%, 45% and 57% respectively. Abnormalities were detected on 59% of echocardiograms performed, 13% of renal ultrasounds and 15% of cranial ultrasounds. These data suggest that all infants born with exomphalos should undergo these imaging tests as part of routine post-natal management. In addition, the large number of infants with BWS seen in the cohort (n=29, 18%) and the variation in the anatomical characteristics of the defect in these infants illustrates the need to undertake vigilant blood glucose monitoring in *all* infants live born with exomphalos regardless of defect size. At least four infants with BWS were known to have experienced episodes of hypoglycaemia.

Sac rupture was not an uncommon occurrence with 9% of infants in the cohort affected. The size of defect or the presence of the liver in the sac was not related to sac rupture. The number of infants who had a sac rupture during delivery was very small (n=5), however this event did not appear to be exclusively related to defect size and occurred during all modes of delivery. The consequences of sac rupture varied, from having a minor repair to palliation and eventual death. Many infants with rupture of a small exomphalos sac had a primary closure.

A key finding of this study was the variation in management of infants with exomphalos both prenatally and postnatally. Thirty-nine percent of women with an antenatal diagnosis of exomphalos were known to have had a planned caesarean section compared to 13% whose diagnosis was made postnatally. In the majority, 76%, exomphalos was the main indication. The infants delivered by caesarean section had defects of varying sizes postnatally, suggesting that the delivery plan was not always related to concerns about defect size. Postnatally, management variation was most striking in infants whose defects were not able to be closed primarily. Most surgeons in the study opted for conservative management as a first-line treatment in these infants and 66% of infants having staged closure were managed in this way.

There was, however, a degree of 'consensus' among surgeons about the size of defect that should be attempted to be closed primarily and exploration revealed this to be related to the relative size of the defect to infant bodyweight as expressed by the defect to weight ratio (DWR). A DWR at a cut-off of ≥ 1.64 was a very good predictor of the surgical management of all the majority of infants in this cohort. The predictive value of this measurement should now be tested in a prospective study to validate the threshold of ≥ 1.64 .

3.4.2 Strengths of the study

The vast majority of all published studies on exomphalos reflect a single institution's experience over a prolonged period of time and strikingly few contain more than 100 infants. This cohort study collected data over a two-year contemporary period on all infants born with exomphalos in the population of the five constituent countries of the British Isles. The data generated therefore provide an up-to-date picture of the characteristics, management and outcomes of all infants born with exomphalos.

The BAPS-CASS system ensured a high level of case-ascertainment and with the exception of two with missing notes, the 100% return of data collection forms for all reported infants was the highest of any of the seven studies that have used this system to data (Owen et al 2010, Burge et al 2013). Detailed data collection allowed an accurate description of the comorbidities of the live born population as well as a comprehensive assessment of the differences in management strategy employed by surgeons during the study period.

Communication of the data regarding management choices and the descriptive analysis of their outcomes will generate discourse between surgeons about varying methods that are currently utilised and the possible benefits and adverse sequelae of these. In addition, for the first time, this study provides information for parents about the variation in management strategies used and will facilitate a discussion about the choices that may be available and their possible risks and benefits. Chapter Four will describe some parents' frustrations about how these discussions have previously been carried out with the existing lack of research evidence.

Due to the relatively large number of infants with exomphalos in the cohort compared to other series, an exploration of the characteristics of infants who underwent staged closure has been possible. This has allowed the development of a robust approach to outcome stratification on the basis of relative defect size that takes into account the wide variation in birth characteristics of infants in the cohort. This approach could be used in the future as a means of communication about outcomes of infants or could be used to define entry criteria into a future clinical trial. The merits of defining 'exomphalos major' as a DWR ≥ 1.64 with the liver in the sac requires further investigation in a prospective study to confirm its validity.

Neonatal mortality among infants in the cohort was low and comparable to that seen in gastroschisis (Owen et al 2010). As described in Chapter Two, reporting mortality in this set time period will contribute population-based survival data to the literature, from this relatively large number of infants in a high-income setting. These data may be used for parental counselling and if future authors report in this robust way, it will be possible to generate more accurate survival estimates using the methodology employed in Chapter Two.

3.4.3 Limitations of the study

3.4.3i Sample size

Despite the large number of infants included in this study compared with other series, the diversity of the population is such that the small numbers of infants in each category of comorbidity or management strategy group precluded detailed comparative analysis. As such, no data to guide choice of management strategy or to inform accurate prognostication could be generated.

In addition, exomphalos is a diverse condition and rare variants and associations occur, not all of which will have been observed within this population despite two-years of data collection. In particular, infants have been reported in the literature with very small exomphalos defects and their whole liver on a narrow vascular pedicle at the umbilicus (Pelizzo et al 2005). These infants usually require staged closure in order to preserve the blood supply to the liver and would be an exception to the finding of this study that all infants with a DWR <1.64 could have primary closure.

3.4.3ii Missing data

Although retrieval of missing data was thorough for infants in the cohort, some data were missing from case-notes and were not, therefore, available for analysis. Information on antenatal findings and management of infants in the cohort was particularly affected. To find these data, most clinicians relied solely on the infant's case notes where antenatal information may be sparse. More accurate information about antenatal findings, planned mode of delivery, its rationale, and sonographic features of the exomphalos sac would have been facilitated by review of the maternal notes or a contemporaneous obstetric study.

Very little data on postnatal characteristics or management were missing, however only 54% of infants had the defect size measured or estimated and recorded in the notes. All analyses relating to defect size have therefore been undertaken on only just over half of the cohort. In some infants with large defects and a liver that overlapped the edges of the defect, estimation of defect size is extremely challenging. This was particularly the case with infants with ruptured sacs where only half had the diameter recorded. The fact that a similar proportion of infants had the liver in the sac in the groups that were and were not measured suggests that it is not unreasonable to extrapolate findings from those that had the defect diameter measured to those who did not.

3.4.3iii Length of follow-up

The allocation of infants to the structural and isolated categories of comorbidity in this study posed some difficulties due to the fact that some associated structural anomalies detected may be considered to be either normal variants, or abnormalities that are transient and self-resolving e.g. hydronephrosis or atrial septal defect related to patent foramen ovale. The clinical implications of each associated abnormality will only become clear with time, as those requiring treatment or follow-up become evident.

The collection of longer-term outcome data will allow a more nuanced understanding of which are 'significant' associated abnormalities. For the present study, *all* associated structural anomalies were included in the 'structural' group (with the exception of those outlined in Appendix 6). The descriptive analysis of the outcomes of infants in the structural and isolated groups did, however suggest that even early outcomes were poorer in the structural group, indicating that these are, indeed, groups with differing outcomes.

It is clear that long term data will be necessary to fully assess the impact of infant characteristics and the choice of management strategy. For many of the infants managed by a staged technique, surgical management is on-going beyond 28 days. Later surgical procedures may carry with them a new set of adverse sequelae which could alter the profile of the complications of each staged management technique if a longer term view is taken. An understanding of survival outcomes in infants born with exomphalos will also need a longer-term view as many infants that survive the neonatal period may die later due to other congenital comorbidities, associated respiratory pathology or long-term surgical complications.

3.5 Conclusion

This population cohort study provides a comprehensive, contemporary picture of the live born population of infants with exomphalos and their short-term outcomes in the British Isles. While it is clear that a longer term view will be needed to provide a more detailed understanding of the progress and prognosis of these infants, for the majority (59%) of infants, the defect was closed primarily and they had an uncomplicated course. Eighty-nine percent of this group had no management-associated complications and 86% were discharged by one month after surgery. Similarly, of those with isolated exomphalos, 86% were discharged by one month and 83% had no complications from their management.

The data from this study provide a starting point for parental counselling both before and after birth. They describe the live born population and the varying management techniques that are used throughout the British Isles. Where evidence favouring one over the other is lacking, they will facilitate a discussion about the choices of management technique that may be employed where the defect cannot be closed primarily.

Publication of outcome data for infants with exomphalos should focus on the method of closure rather than defining infants with exomphalos as 'major' or 'minor' based only on absolute defect size. In describing the characteristics of the infants undergoing each management technique, the DWR, along with the presence of the liver in the sac provides a potentially robust way of doing this.

A collaborative research effort with paediatric surgeons in the British Isles using the BAPS-CASS, has enabled a population-based description of live born infants with exomphalos along with their early management and outcomes. For rare conditions such as abdominal wall defects, these observational data provide a starting point for answering key clinical questions. It is clear, however, that if experimental studies, such as a clinical trial comparing techniques of staged closure for infants with exomphalos, are to be designed, recruitment would need to be international, considering the small number of infants from this population cohort that would have been eligible for inclusion.

Chapter 4

Exomphalos: A qualitative study of parent experiences

4.1 Introduction

The overarching aim of the work contained in this thesis is to improve the care of children born with abdominal wall defects. In the two studies described previously, quantitative outcome data to guide management and to inform parental counselling have been generated. However, in order to provide the very best care, it is crucially important to understand, in-depth, what the experiences of this care were like. This understanding was intended to inform the rest of the work presented in this thesis by grounding it in the themes that emerged from interviewing parents who had lived experience of having a baby diagnosed with an abdominal wall defect.

Over the past 50 years there has been an increasing appreciation among health-care professionals and health-service researchers that improving the quality of care and hence outcomes for patients requires an approach that first seeks to understand their experiences (Coulter 2013). As author Angela Coulter states: *“The scientific, clinical and epidemiological knowledge base is clearly crucial for effective healthcare, but it is also important that healthcare systems respond sensitively to the needs and concerns of health service users. This cannot be done effectively without a deep knowledge of their perspective”* (Coulter 2013). This appreciation has recently accelerated and the necessity for what has been termed ‘patient-centredness’ has been formalised into both health-care policy and doctrines of good clinical and research governance (Mead and Bower 2000, NHS England 2015).

Exomphalos was chosen as an area of focus for the qualitative study of parent experiences. This congenital condition is among the most complex and challenging treated by paediatric surgeons as was observed in the study described in Chapter Three. The controversies in managing infants born with exomphalos both pre- and postnatally have been highlighted as well as the lack of robust evidence to support any one strategy over another.

Conspicuously absent from any of the published literature on exomphalos are studies which describe the lived experiences of parents of infants born with exomphalos. This work, therefore, for the first time, documents parental reflections on their experiences of care for this condition. It explores how the differing approaches to management described both in the published literature and in Chapter Three are reflected in parents' experiences and adds depth to the understanding of contemporary management of exomphalos generated within this thesis.

4.1.1 Research questions

The research questions addressed in this study are:

1. What are the experiences of parents following a diagnosis of exomphalos?
2. What can healthcare providers do to improve the experiences of parents?

4.2 Methods

This study represents a secondary analysis of a set of interviews that were undertaken as part of a larger project looking at parents' experiences of having a child who required surgical care early in life. The entire project will look at broad themes that span the variety of parent experiences of early surgery. The interviews for the larger study were carried out by Dr Lisa Hinton who is a qualitative researcher from the Health Experiences Research Group in Oxford (HERG).

The wider study has two main aims. The first of these is to generate data about parent experiences to inform health professionals and improve care. The second is to contribute parent experiences to an online resource accessible to all. This website, known as *Healthtalk* is a charitably funded enterprise that provides information for patients and their families about a variety of medical conditions (HERG 2016).

Within the larger study, seven interviews were undertaken with parents whose children had exomphalos diagnosed antenatally. It was these seven interviews that were utilised for the secondary analysis described below.

4.2.1 Parent selection and characteristics of the interviewees

Six of the seven interviews were undertaken with parents recruited through an online social media forum for individuals and families affected by a diagnosis of an abdominal wall defect. Most commonly this forum is used as a peer support network for parents of children diagnosed with gastroschisis and exomphalos. The qualitative researcher posted an advert on the group page asking for parents who were willing to be interviewed to recount their experiences. Five of these parents also attended a parent advisory group that was organised to inform the content and direction of the work described within this thesis (Section 3.2.5). The seventh set of parents was recruited through word-of mouth. Recruitment using other means such as via paediatric surgeons and specialist nurses was successful for finding parents of infants with conditions other than exomphalos willing to be participate in the wider interview study. In four of the interviews, mothers were interviewed on their own. The other three took place with both parents present. All interviewees were Caucasian and all, except one were born in the UK. Details of the interview participants are given in Table 4.1

In all cases, the diagnosis of exomphalos had been made antenatally and the abdominal wall defect was described by the parents as 'large'. All had undergone chromosomal testing antenatally that had not revealed any associated chromosomal anomalies. All had live children, having decided to continue with their pregnancy and all children having survived beyond first discharge from hospital. The ages of the children at the time of interview ranged from 16 months to 26 years and all were managed in UK hospitals.

This work represents a secondary analysis of the interviews with a subset of parents within the broader study. Secondary analysis is the use of existing data to answer a distinct research question (Thorne 1994) and here it was used to identifying areas of good practice as well as where improvements in care could be made. As a result, this was not a maximum variation sample and it was acknowledged at the outset that data saturation would not be reached.

Table 4.1. Sociodemographic details of participants

Interview	Name§	Age at Interview (years)	Relationship to child born with exomphalos	Occupation	Age of child at time of Interview	Type of defect	Recruitment method
NNS01	Sarah	34	Mother	Occupational therapist	18 months	Large, containing liver	Social media
NNS02	Hannah	39	Mother	Social worker	6 years	Large, containing liver	Social media
NNS03	Carol	46	Mother	Marketing and PR	8 years	Large, containing liver	Social media
NNS04	Ruth	37	Mother	Home-maker	8 years	Large, containing liver	Social media
NNS05	Matthew	34	Father	Salesman	8 years	Large, containing liver	Social media
NNS12	Amanda	51	Mother	Home-maker	26 years	Large, status of liver unknown	Word-of-mouth
NNS13	Stephen	55	Father	Sports coach	26 years	Large, status of liver unknown	Word-of-mouth
NNS16	Jackie	34	Mother	Unemployed	13 years	Large, containing liver	Social media
NNS17	Robert	33	Father	Unemployed	13 years	Large, containing liver	Social media
NNS19	Helen	36	Mother	Nursery Worker	16 months	Large, containing liver	Social media

§ Not original names

4.2.2 Interview technique

Interviews were conducted in the homes of participants at their invitation. They commenced with an open narrative section where parents were invited to tell the story of their experiences. This narrative section allowed parents to recount the events in their own way, highlighting aspects that were important to them, with little interruption. This technique was particularly suited to exploring an experience that began with an antenatal diagnosis and ended in the present day. The use of a narrative technique was felt to be appropriate in the context of the broad research questions of this study. By using this at the beginning of the interviews, it allowed parents to describe events that were key to their experiences in a rich and detailed way without any imposition of an external research agenda.

The narrative part was followed by a semi-structured section consisting of a series of prompts exploring issues raised in the earlier section, in previous interviews and devised *a priori* based on those issues that had arisen during review of the literature. Here, parents were asked to elaborate on areas that the researcher felt needed clarification from the narrative section. Prior to the interviews the author identified areas that would be important to cover within this latter section through literature review as described in chapters One and Two. These themes were discussed with the qualitative researcher and a prompt sheet developed. This allowed exploration of areas that were of particular relevance to this thesis, for example, parent experiences of the varying surgical techniques.

Parents were known to have all passed through a similar set of stages in the care pathway. These stages were discussed with the interviewer in order that the journey that was described could be understood within this context. These stages are illustrated in Figure 4.1 which represents a summary of the themes which emerged during analysis of the transcripts.

Interviews were audio or video recorded and where consent was given.

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graph TD
    A[Getting the Diagnosis] --> B[Fetal Medicine Appointment]
    A --> C[Unexpected - Feelings afterwards]
    A --> D[The Wait - What is was like - What info was given]
    A --> E[Lasting memory]
    B --> F[Delivery]
    B --> G[Chances of survival]
    B --> H[Termination]
    B --> I[Looking for associated problems - Preparation/ lack of preparation - Alleviation and creation of worries]
    F --> J[Neonatal Care]
    F --> K[Who is present - Invasive]
    F --> L[Separation of mother and baby]
    F --> M[Mode of delivery]
    F --> N[Postnatal care of mother]
    J --> O[Discharge]
    J --> P[Associated Problems]
    J --> Q[Surgical Management]
    J --> R[Feeding]
    O --> S[Managing Complexity]
    P --> T[Respiratory GORD+ Others]
    P --> U["(Exomphalos as part of a mutlistsyem problem)"]
    Q --> V[Rationale Experiences of care]
    V --> W[Staged closure]
    W --> X[Problems after closure]
    H --> Y[Choice]
    I --> Y
    M --> Y
    R --> Z[Disempowerment - Diminished role of parent]
    Y --> Z
    Y --> AA[Choice]
    AA --> Z
    Z --> AB[Disempowerment - Diminished role of parent]
    
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Getting the Diagnosis

- Unexpected - Feelings afterwards
- The Wait
 - What is was like
 - What info was given
- Lasting memory

Fetal Medicine Appointment

- Chances of survival
- Termination
- Looking for associated problems
 - Preparation/ lack of preparation
 - Alleviation and creation of worries

Delivery

- Who is present
 - Invasive
- Separation of mother and baby
- Mode of delivery
- Postnatal care of mother

Neonatal Care

- Associated Problems
 - Respiratory
 - GORD+
 - Others
 - (Exomphalos as part of a mutlistsyem problem)
- Surgical Management
 - Rationale
 - Experiences of care
 - Staged closure
 - Problems after closure
- Feeding

Discharge

Managing Complexity

Choice

Disempowerment

- Diminished role of parent

Deviation from a normal pregnancy

- Dealing with others
 - Friends/ family
 - Siblings
- Dealing with Uncertainty
 - Funeral planning

Sources of information and support

- Seeking and gaining information
- Peer support

Lasting Concerns

- PTSD‡
- Relationships
- Work

†Gastro-oesophageal Reflux Disease ‡Post Traumatic Stress Disorder

4.2.3 Ethical concerns and transcription

The project had approval from the NHS research ethics committee of South Central- Berkshire, ref: 12/SC/0495[†]. Audio recordings of the interviews were transcribed verbatim. Due to the use of the narrative technique, it was not possible to fully inform participants about the entire content of the interview ahead of time (Ziebland 2013). Interviewees were therefore sent copies of the transcripts of their interviews and were given the option to remove any sections they did not want included in the final transcript. Participants then signed a consent agreement for the HERG to hold the copyright for the interview content. In the results section below, pseudonyms are used and all potentially identifiable information has been removed.

4.2.4 Analysis technique

As well as answering the research questions outlined above, two other aims were key to the process of focussing the direction of this work. These were: to generate novel information about parent experiences that are specific to the pre- and postnatal management of exomphalos and to inform the quantitative aspects of the work presented in this thesis. This meant that although a number of broad themes were apparent when reviewing the transcripts, for the purposes of this secondary analysis, only certain aspects of care that related to the management of exomphalos were analysed in detail. As the author is a surgeon this process meant that the existing data were assessed from a different and specific perspective.

The transcripts were analysed thematically using techniques informed by grounded theory using *NVivo7* software to assist with data organisation (Charmaz 2006). After reading and re-reading the transcripts, the process of identification of the themes from the analysis was iterative. The process was discussed at intervals with an analysis 'buddy'. The use of a 'buddy', common in qualitative data analysis, is a means of robustly developing a coding framework through sharing and discussing ideas and interpretations with another individual.

[†]'Narratives of health and illness for Healthtalkonline 2012.' IRAS ID 112111

In this case, the author's buddy was the qualitative researcher who performed the interviews (LH). Using the interviewer was of great value in the context of this secondary analysis as LH had an in-depth understanding of the interview contents as well as her own interpretations and understanding of the participants' meanings and frames of reference.

A coding framework was devised and this was developed and finalised after discussion with LH. The final analysis plan was discussed in detail, and approved by her. Figure 4.1 illustrates a schematic explanation of all of the themes that were identified and coded from the transcripts. On this figure, the areas that were chosen for the final analysis are highlighted by the red stars. Table 4.2 illustrates the final coding framework that was used in the secondary analysis described here.

The themes included in the final coding framework were chosen as those that had key relevance to an understanding of parent experiences that were specific to exomphalos. Understanding these experiences would enhance interpretation of the findings of the national cohort study in exomphalos described in Chapter Three and could usefully inform future parental counselling and care. It was, however, appreciated at the outset that given the small subset of interviews analysed these did not represent the full range of possible experiences of care.

After identification of the final coding framework, detailed coding within each of the themes was undertaken. Coding summaries were produced and from these, the 'one sheet of paper' (OSOP) method was used to record and analyse the variety of messages from the coded data (Ziebland and McPherson 2006). This is an established technique for qualitative data analysis developed by researchers from the Health Experiences Research Group in Oxford. The OSOP summaries were discussed with LH and from these, the range of experiences contained in them were explored and described in detail.

Table 4.2. Final coding framework

Experiences of antenatal care
• Approach/ style • Counselling about survival • Reflections on preparedness for postnatal course • Counselling about termination of pregnancy • Mode of delivery
Experiences of postnatal care
• Surgical management of exomphalos - Rationale for treatment modality and parental choice - Experiences of surgical management - Experiences of staged closure • Experiences relating to associated comorbidity - Respiratory comorbidity - Sudden deteriorations/ airway problems - Tracheostomy - Ventilation - Home oxygen therapy

These data have been interpreted and analysed by the author, a trainee in paediatric surgery currently working in the UK who has her own experiences of exomphalos from the point of view of a surgeon. The author is also a mother who has experience of antenatal and postnatal care from the point of view of a patient and parent.

4.3 Results

4.3.1 Broad themes

The transcripts are rich with detail of all aspects of the parents' experiences. Figure 4.1 summarises the breadth of the themes that emerged. While the analysis that follows will predominately focus on those aspects of parents' experiences that were specific to exomphalos, it should be acknowledged that there were a number of poignant aspects of parental experiences that came across from the interviews that had broader relevance for all parents of infants that require surgery early in life. These relate in particular to the deviation from a course of a 'normal' pregnancy that is not disrupted by such an antenatal diagnosis. One mother succinctly describes this:

We grieved I think for the baby that we thought we were going to have and the baby that we were going to have

Ruth, 37

Other parents describe how despite having a large number of ultrasound scans, they were not given, until they asked for it, a scan picture of their baby's face, just having witnessed images of their baby's abdomen.

A related theme that runs through the recounted experiences is that of the disempowerment and lack of control parents feel alongside disruption to the normal role of a parent. Sarah describes how she felt when she was allowed off the postnatal-ward where she was an inpatient, to go and visit her baby for the first time.

I felt like I didn't want anybody else introducing me to my own child. And that they knew him and they'd seen him and spent time with him and I hadn't and that was really difficult. I was angry and upset the whole time I was there. It wasn't, it wasn't a good experience.

Sarah, 34

Another key theme relates to how parents seek information and support. The particular importance of peer-support is a characteristic of all of the experiences, not only the ones of parents that were recruited from the online forum.

Also resonant from parents' experiences is the profound impact that this experience has had on the rest of their lives. It is clear that the events they describe have had a lasting influence on their sense of identity, mental well-being, relationships both within and outside of the family as well as their working life and finances.

The results of the analysis of parent experiences within the coded themes outlined in Table 4.2 will now be described.

4.3.2 Experiences of antenatal care

For most parents who have a baby born with exomphalos, their journey starts at the moment, during an ultrasound scan, that the diagnosis of exomphalos is suspected. One thing that is striking about the descriptions of this moment, is the lasting clarity of this memory. Whereas some other aspects of their recollection may be hazy, most parents were able to describe the scene that occurred when they first received the diagnosis in detail. Amanda, whose son was diagnosed with exomphalos 26 years ago, describes the scene precisely;

He was very softly spoken Scottish and he just tapped my shoulder and he said "No No there's a problem with your baby" and that for me is probably the, the stand out memory .. Stephen's at the end [um] holding onto [daughter] with his arm in a sling and he said he just saw me go white, you know, so he didn't know what was going on at that stage. So that all is very, very clear in my head actually I can still see that scene really clearly.

Amanda, 51

4.3.2i Counselling style and approach

After the initial diagnosis, expectant parents were referred for an appointment at a fetal medicine department. Parents' experiences of the manner and approach of those who were counselling them varied widely. Parents valued a style that was realistic and pragmatic but communicated the uncertainties of the situation.

Where parents had been given a sense that it was very difficult to tell what the future held after birth, they seemed to experience less of an emotional disruption when later problems did occur.

Sarah, whose son had significant problems after birth, reflected on what she was told:

I think that was hard to hear, whilst I was pregnant, but it was the right thing to have kind of reinforced that you just can't tell really until the baby is born.

Sarah, 34

Some parents described experiencing a sense of profound negativity from those who were counselling them. Although, as seen in the example above, parents appreciated not being given false expectations, many felt that the joy of pregnancy was overtaken by a feeling of what a few described as 'doom and gloom'. Hannah describes this:

The consultant was very negative. [laughs] I don't know how else to put that, was very, very negative. We called him 'Doctor Death' in the end because each time we went it was just doom and gloom and it was very, very difficult.

Hannah, 39

Hannah eventually changed hospitals due to dissatisfaction with her experiences of antenatal counselling. Another mother, Jackie, whose son was born 13 years ago, describes a similar experience.

It was just so doom and gloom [he] painted this really dark picture saying that not many of these babies survive and there's always, you know, there's other congenital abnormalities for example Edwards syndrome

Jackie, 34

Some parents felt that they were given very little information about what the future held. Some felt that this was because the focus had been on getting through the pregnancy. Jackie and her husband Robert, describe how they felt that they had been given no information about what would happen after the delivery and how much of a shock the experiences were then to them. After their son was born, he was immediately taken to be attended to by the medical team. Jackie describes them putting his exomphalos sac in a bag, sucking the mucus from his mouth and passing a tube from his nose into his stomach. He was then taken away to the neonatal unit. She had not felt prepared for any of this:

We didn't know .. whereabouts he was going to go to, [if] he was going to be transferred straight over to the other hospital or, you know, if I was going to be able to see him or anything, you know. Because we wasn't told none of it, you know, I didn't know if I could hold him or, or what. We just, I just, seen this baby's head come past and then gone, you know, while they dealt with me and sorted me out. And that, that was tough.

Jackie, 34

Two other sets of parents describe how a negative focus of the health-professionals counselling them, prevented them from being given an idea of the 'full picture' of what would happen to their babies after they were born. Hannah describes her fetal medicine consultant:

He was very stern. There wasn't any warmth. He was he was very matter of fact. But, when you've just found this out and you're trying to process what it means to you, to your child, it was, it was hard. It, it needed a different approach. I needed, I needed to know the full picture and I think that, that's something I never felt at that hospital, was a well-rounded picture that, you know, some babies will live and they may have other problems.

Hannah, 39

The experience of another mother, Amanda and her husband Stephen, 26 years ago stands out as an extreme example of poor communication about the diagnosis and its implications from an obstetrician that Amanda describes as ‘cold and unfeeling’.

Amanda: *That was just such a horrible appointment ... she kept us waiting about 45 minutes. And then she called us in and before we'd even sat down she said "You'll be pleased to know it's not Downs Syndrome and it's a boy".*

Stephen: *As cold as that.*

Amanda: *And that was exactly how she, how she put it. And we were taken back because we didn't really, the sex was irrelevant at that point we didn't want to know what it, what the sex was of the baby. we didn't know that they were specifically looking for Downs so I was a bit taken back and and I said "Oh well what exactly does that mean for the baby" and she said "Well, you know, it means that it's not Downs Syndrome and, you know, it's going to have an operation when its born."*

Amanda, 51 & Stephen 59

For Amanda, this interaction stands out as one of the worst moments of her experience.

4.3.2ii Counselling about survival

A feature that is striking from the accounts of parents' experiences of antenatal counselling is the apparent variation in the information they were given about the likelihood of their children surviving. This is particularly relevant in the context of what is known about the characteristics of the parents who were interviewed for this study. All had infants with fairly similar characteristics, all having being found antenatally to have fetuses with large exomphalos defects, with normal chromosomes and no other major structural abnormalities. Chapter One, highlights the paucity of robust data on the survival of babies with exomphalos and the inconsistencies in these published data appear to have had an impact on the counselling experiences of parents.

Estimates of survival given to parents, ranged from Jackie being informed that, '*not many of these babies survive*' to the examples illustrated below.

The leaflet talked about I think eight out of ten babies having other complications and where the other complications were significant or the exomphalos was very large, it may only be that, I think it was one in ten babies survive. So [um] that's you know, when you tot up those statistics to get there it didn't look very promising at all.

Sarah, 34

This mother, Sarah, later sought a second opinion:

I was expecting him to say, eighty, ninety per cent, given that we'd been through so many tests already and it was all looking great and he said, "Forty to fifty per cent." And that was hard. I thought it was a bit better than that.

Sarah, 34

A 50% chance of survival after birth was communicated to another set of parents by a fetal medical team member who stated that this figure was based on their past experiences. Another set of parents appreciated the input they received from a surgeon they saw before their daughter was born and were given a more optimistic outlook compared to some others.

He was very, very helpful, wasn't he, and told us, well, we we were told that [um] there's there's, obviously, it's very difficult for them to give, [um] you know, figures and survival rates because each child is different but we were told that [um] she had a seventy per cent chance of survival.

Ruth, 37

4.3.2iii Counselling about termination of pregnancy

Parents experienced differences in the counselling they received about the option to terminate their pregnancy. All of the parents interviewed for this study made a decision to continue the pregnancy but all had discussed termination with their fetal medical consultant. For some, like Ruth and Matthew, it was "*broached gently*". Others describe that even after they had made and communicated this decision, there were repeated suggestions that they may wish to consider termination.

Even when I said I've made this choice, we'd made this choice, we'd thought about it [um] it was still [um] the suggestion was there to terminate [um] and it was brought up more than once to us. And [um] I found, I found that really, really challenging because I'd made my decision and I'd given my decision to them and still felt like I wasn't always supported by that.

Hannah, 39

This mother, Hannah later describes:

I always felt by this doctor that there was a pressure to terminate, that I wasn't making the right decision. Now I think some partly that was them or and maybe partly how I was interpreting. But I felt like I should have terminated in in the eyes there and that wasn't something I was prepared to do.

Helen recounts:

Every time we saw him until 25 weeks he'd say 'Quite often at this point parents chose not to continue with their pregnancy,' I don't know whether he's obliged to give us that spiel every time we went for an appointment but every time we went for an appointment that's what we'd hear. Here's your baby on the screen but some people choose not to keep her.

Stop asking. I wouldn't be here if I was going to terminate my baby

Helen, 36

Sarah comments on the difficulties of the decision-making process in a situation where information about associated comorbidity only became clearer very late in the pregnancy.

From that early scan, there wasn't really enough information. We were told we'd have to really wait twenty weeks to be more sure and to have the results of the amnio. And so the thought of maybe having to deliver the baby was very hard.

Sarah, 34

4.3.2iv Reflections on preparedness for postnatal course

A key theme when analysing parents' experiences of antenatal care arises from their processes of reflection on those experiences from their present day position. This relates to their feeling of preparedness for all of the subsequent medical problems that have affected their child with exomphalos and the impact these have had on their lives. In the example of Sarah given previously, some parents were clearly informed that there was no way of knowing what the associated problems would be before birth. Despite this, like many others, when no other problems had been detected during pregnancy, Sarah had developed a sense of optimism. Her baby's sudden deterioration in the first few days after birth, requiring a machine to support his breathing, therefore came as a shock.

It was just so out of what I imagined, you know. Before he was born, felt he'd, you know, he was in the best possible shape, everything looked like it was going as well as it could in the context of the exomphalos. But it then changed to be kind of my worst nightmare situation, basically. And they weren't sure why he was having the breathing problems. That was also very worrying.

Sarah, 34

A lack of preparedness for the infant having respiratory difficulties is common to many of the parents' experiences. Hannah states:

I had prepared myself so much for the exomphalos that I hadn't, hadn't thought about other issues. So the breathing, you know, it was, you know, there was a chance there'd be other problems but I didn't realise how much the breathing would be an issue

Hannah, 39

Carol reflected on how not being prepared for the respiratory problems her daughter had experienced was in contrast to the other aspects of her condition. She describes that her experiences of her daughter's later respiratory problems were "*worse than the original thing because it wasn't anticipated*".

It was a real massive shock [um] and also we didn't know whether there was any solution to them. Well, with the exomphalos we had always been told, you know, as long as the baby can tolerate it, we can fix this and, hopefully, he or she will go on and have quite a happy, healthy life. But with the respiratory problems it was just like, well, what's causing this, what the hell is going on? You know, it just didn't, it came from nowhere.

Carol, 46

One couple, Ruth and Matthew, describe how respiratory problems were mentioned to them antenatally but that they had been reassured that their daughter's lungs had looked normal on the scans. Their daughter was in hospital for eight months after birth and had multiple episodes of cardio-respiratory collapse secondary to tracheomalacia (a floppy windpipe). They have a slightly different perspective to some of the others who were interviewed and felt they were given as much information as they could deal with before the birth.

Matthew: *I think, at the time, that was as much as we probably needed to know about the birth.*

Ruth: *Oh, absolutely.*

Matthew, 34 & Ruth, 37

Helen felt that she had been poorly prepared by the antenatal counselling she received for the complex problems her daughter had experienced after birth. Her daughter had had normal, although limited, cardiac scans *in utero* and had been diagnosed after birth with a major congenital heart defect for which she required surgery. This surgery had led to a significant complication, which meant that at 16 months of age she could not swallow or talk. She recounts:

We never got the reality of life with Isla. Isla was gonna be fine because she didn't have a chromosome problem so she'll be okay. Nobody told us about gastro-oesophageal reflux disease or respiratory problems or heart conditions or just what life is like with a baby that doesn't sleep because she's been in hospital for the first few months of her life..

Helen, 36

4.3.2v Mode of delivery

Antenatal counselling also involved planning of the delivery. Parents received differing advice about the optimum mode of delivery. Five of the seven mothers interviewed had a caesarean section. Sarah's experience reflects that of most of these parents.

The opinion of the hospital that we were at, was that those with exomphalos major, it would be a caesarean anyway, so that was....A bit of a given.

Sarah, 34

Sarah was pleased with this choice as she stated, "*it allowed a level of sort of control and planning*".

Another mother, Carol, whose daughter was born eight years ago was offered a vaginal delivery initially, but expressed a desire for a caesarean. She describes that she searched for evidence favouring one mode over another but experienced difficulties in finding anything of value:

When I looked at the research that stuff was being based on, I could see what a small sample sometimes things were based on. [laughs] So I'd be arguing the toss slightly.

Carol, 46

Her obstetricians took a holistic view, understanding how challenging it would be for her to be with her child after the delivery if she had a caesarean.

I didn't feel that it was just like 'you're going to have a vaginal delivery and there is no discussion about this and my word is law'. It was very much a, 'well, this is what we've experienced and this is what we're seeing in other hospitals.' And, and also very valid point, which is to have a child in intensive care, having had a caesarean section is a bit of a nightmare. [laughs] So I, I totally understand, having experienced that, why the consultant thought it would be a very good idea for me to have a vaginal birth, if at all possible. Because, having had major surgery and have a child in intensive care is, and the problems of driving.

Carol, 46

Being an inpatient on the postnatal ward after having a caesarean and not being able to be with their baby was a source of distress for the mothers who had an uneventful caesarean section. They describe this as a very difficult environment to be without a new-born baby and recount their attempts to find out what was happening from busy staff members and their desire to be discharged as quickly as possible.

That first night was so painful. It was so hard. One of the things that I wished the hospital had done differently is that they put me in a unit with nine other women, who all had their babies with them, and I found it so painful. Do you know, she was safe when she was in me and there she was whisked away to another hospital to be treated and was having surgery that night and I'm in a room not being able to sleep because these babies are crying, which is great, you know, for the other mothers but for me it was so painful.

Hannah, 39

Ruth, who had a vaginal delivery, had a very different experience:

The birth was so easy, I mean I had a shower and everything and they took me down to see her before, they said she'd had a, she'd stabilised really quickly and they had a a bed at the specialist children's hospital. So I was allowed to go down and and say goodbye.

...And they'd given me a couple of photos as well, which was a really nice touch, and then they said, "Right. Well, we can we can discharge you."

Ruth, 37

Ruth was counselled differently during pregnancy. She recalls being told that “*babies don’t generally tend to do any better than by caesarean so they would try a natural birth.*” She and her husband were given a strong sense that a vaginal delivery would be a better option. He states: “*I think the theory there is also that it helps to minimise the exomphalos so it it .. pushing everything back in.*” She describes how the decision was eventually made:

They decided at thirty six weeks they said that if the defect was smaller than the head, then it would be natural. But if, if it was, if it was bigger than the head, then I would have to have a caesarean.

Ruth, 37

Amanda, who delivered her son vaginally 26 years ago stated that she was not given the option of a caesarean section and has mixed feelings about this.

Looking back now I think that’s quite risky really, you know, when they talked about maybe the membrane splitting well you think going through the birth canal might have put a pressure on him but. But no he was born normally and a caesarean was never mentioned

Amanda, 51

4.3.3 Experiences of postnatal care

4.3.3i Surgical management of exomphalos

Rationale for surgical treatment modality and parental choice

It should once again be noted that the infants of the parents interviewed for this study all had similarly large exomphalos defects. Although in many cases different methods of surgical management were discussed with parents, none of those interviewed seemed to have been involved in the decision-making as to the eventual choice of management.

One mother described her satisfaction with the way this discussion went before the birth. She describes conservative management using the term 'paint and wait'.

The hospital that Jack had his treatment at favours the paint and wait approach. So we talked a lot about whether, you know, what circumstances might they consider doing an early closure surgery but it was really apparent that Jack's exomphalos was going to be very big. So he told us, at that point, that they would use the paint and wait approach and be very conservative in the management of that, which turned out to be absolutely the right thing to do. But I felt, we felt that's what we would have preferred having read a lot about it before the appointment. So it was reassuring to feel that we were on the same page with the surgeons.

Sarah, 34

Another mother describes a definite lack of choice. She had researched conservative management on the internet and describes the impression that she had gained from other parents was that this was a, "more humane way to do it." She recalls:

I went to the hospital with this and said, "Can we do this paint and wait?" And the hospital said no, this is how, you know, we treat with SILO, this is what we do. Then I thought, oh, you know, is this not the best thing and it was, it, it was really tricky because, you know, that I thought, no, you know, ... My partner was like, you know, "they're the experts". They're going to do the right thing and it was, that was really tricky for me, was to give some of the control away I guess.

Hannah, 39

The examples above illustrate a recurrent feature of the discussion about the chosen treatment modality which relates to lack of rationale given by the surgeon for their choice. Both of these mothers state that the method was chosen because of institutional preference rather than evidence of efficacy. A rationale for the treatment choice was given to three of the parents interviewed. Two of these stated that due to concerns about infection, the preference would always be to reduce the exomphalos completely where possible. Both of these infants had conservative management after other modalities failed. Another infant had a severe associated cardiac defect and had conservative management of her exomphalos because of concerns about her ability to tolerate the abdominal surgery.

Experiences of surgical management

Two infants whose parents were interviewed for this study were managed with silos. They describe multiple procedures. These numbered 12 for the first infant who was an inpatient for three months and spent five weeks on intensive-care. The second infant had multiple interventions over the course of two weeks. In both of these cases, parents describe that each reduction caused increased respiratory distress in their baby. One father, Matthew, describes multiple episodes of desaturation, (drops in the oxygen levels in the blood) after each silo reduction. He recalls:

It basically, puts a lot of pressure on the child...[daughter] was always able to respond to it very well. She's she's very tough and yeah, she she she had a lot done to her very quickly.

Matthew, 34

Hannah, whose daughter had multiple reductions found the process distressing:

It was tricky though because the surgeries put more pressure on her. She, she'd be fine before the surgery and then she wasn't afterwards and it was hard because you'd see that, how much pressure it was putting on your child's breathing or, you know, and how, how they weren't coping with it. But it was necessary and, you know, those are the moments like was this the best course of treatment for her? Was this the way that she should have been treated here?

Hannah, 39

On reflection Hannah felt:

The SILO worked for her. But there was times when it was a lot of pressure on her lungs.

In two different infants, the surgical team attempted a 'trial of reduction' in the first 24 hours after the infants were born. Jackie and Robert's son had had compression bandages applied. They had been informed before his birth that this was one of the methods that may be attempted. After hearing that he had been unstable in the ambulance, they arrived to find that his abdomen was flat and the bandages had been applied. All looked well and they left him for a short period. During that time he rapidly deteriorated.

They'd actually put the compression bandage on too tight and his little body just couldn't take it, it just couldn't take it at all. See so everything that was originally been put back in had to come back out again and they did this on the ward, they undone the compression bandage and just released all the pressure and, and it was, it was very, it was touch and go wasn't it, I mean they'd got the resuscitation packs in his room ready.

Jackie, 34

Five days later, the surgeons attempted a closure operation with a patch. The parents were told that the operation was very challenging and in the days following this, the skin broke down and the patch came away from the muscles. Their son had closure of the abdominal wall muscles at 18 months of age.

For Carol's daughter, the surgeons attempted a 'test' of external pressure on the sac on the neonatal intensive care unit (NICU). She had seen her on NICU in the evening and she had looked well and she had breast-fed. When they went to see her the next day she recalls:

She was on ventilation and she'd nearly died during the night. Because the surgeon had decided to try and push everything back in and she went into respiratory distress and nearly died. So that was a bit of a shock.

Carol, 46

Neither Carol nor her husband was informed that this had happened. She reflected further on this:

That was probably the only point at which I felt we hadn't been involved in the, you know, because I felt it was almost like an operation. Not that any surgery was involved and she wasn't, I don't think it was done in the surgery. I think they literally just tried and pushed it in and yeah, that was not, not a good a good experience and so, basically, she was ventilated for the next nine days.

Carol, 46

Carol's daughter was eventually treated with conservative management and was allowed to bath her baby regularly which she and her daughter enjoyed.

It was such a lovely thing giving her baths because it helped with the weight, you know, her exomphalos was, you know, on me it would have been here and so when she had her baths, it took the weight off and, obviously, made her feel, you know, happy and, and it was a very nice, normal thing to do.

Carol, 46

The ability for parents to be involved with their baby's day-to-day dressing care with the conservative approach and their appreciation and empowerment as a result of this, comes across clearly from those whose infants have been managed in this way. Comments from parents include:

Carol: *I'm now one of the finest exomphalos wrappers in [name of county]*

Matthew: *I became dressing king.*

Ruth: *Well, we had the nurse. We had the home care team. They used to come.*

Matthew: *I could do it better than them anyway.*

This is in juxtaposition to other areas of their care where parents felt disempowered having lost a level of control over what had happened to their child.

Some of the parents described conservative management as a 'gentle' approach. Ruth and Matthew, whose daughter had a silo followed by a patch that became infected and caused overwhelming sepsis and was finally managed with escharotic therapy reflected:

Matthew: *I think in all, the paint and wait is certainly the least. [um]*

Ruth: *Stressful.*

Matthew: *And dangerous from the point of view of the child... there's there's no extra stress on the child so anything else that might be wrong invariably there is something. It just doesn't get exacerbated.*

Ruth, 37 & Matthew, 34

Carol reflected:

The great thing about paint and wait is, you know, it's like, it's so gradual and kind of organic, you know. It just gradually tightens up so you're not going, [raspberry sound] which then can, you know, everything has to shift about, where exactly is all going. While with paint and wait, which I'm obviously a big fan of, although I'm very biased, you know, it's just this very slow process.

Carol, 46

One of the features of conservative management is that the viscera, including in most cases, the liver, are initially covered only by the sac and after epithelisation, a thin layer of skin. Helen describes her anxiety concerning the perceived vulnerability of her daughter's abdominal organs when there were other siblings at home. Her daughter's bandages were removed before she was discharged from hospital.

So I was at home with the baby who had this exposed liver, it wasn't protected by anything it was, the bandages formed some sort of protection and they said "She doesn't need them anymore," I was absolutely terrified and it wobbled about everywhere and my toddler was loving her little sister like toddlers do and squashing and squeezing and, it was really scary.

Helen, 36

Carol describes the difficulties of putting her daughter in a car seat to take her home in this situation:

We got her in just by putting it, the straps round her bump, totally unsafe. I mean if we'd had an accident and I remember saying, surely there's a there's a way of getting, transferring baby safely from here for twenty five miles. No, nothing, there was nothing, no support at all ...it goes so against everything you're told as a parent with your new born baby or your, you know, you, you know, oh, they have to be strapped in and it was just like and I and that drive home was absolutely terrifying. It should have been great. Should have been like, [whoo] going home but we were just like, ah, what if somebody hits us? What if somebody rear ends us? You know, it was just petrifying.

Carol, 46

4.3.3ii Experiences related to associated respiratory comorbidity

As described in Chapter Three, infants with exomphalos may have a number of associated medical and surgical problems and many were touched on by parents. An example of one of these is respiratory comorbidity which is discussed below.

One of the most striking features of the parent's accounts of their children's respiratory complications associated with exomphalos are the experiences of sudden deteriorations with little warning. Some parents describe how all would appear to be well and then the child would deteriorate rapidly and require ventilatory support.

Sarah describes how this happened to her son, after she had been to see him on the surgical ward in the first days after birth.

That night, unbeknownst to my husband or I, Jack went into respiratory distress and the following morning [husband] went to the hospital, went to Jack's bed space, as it had been, and there was no baby there. And went to the reception, and kind of said, you know, "Where is he?" And they said, "Oh, it's okay. We've rung your wife and he's going to intensive care." And it turned out they hadn't actually called me. And it turned out they hadn't actually called me. They called to our home number and spoken to my parents, who were looking after our older son, so I didn't know, Dave didn't know... he was just very unwell and so they had to put him on the ventilator at that time.

Sarah, 34

This was clearly very distressing and, as Carol had noted on the first night after her daughter was born, the parents were not updated about this sudden respiratory deterioration. Examples, like these of deficiencies in communication between staff and parents are common within the interviews.

Two mothers describe witnessing their babies deteriorate whilst they were alone with them in side-rooms and the feelings of terror and helplessness they experienced.

Her cry changed. And she started to go sort of purple and then blue. The best I can describe it, she sounded like a mechanical doll. It wasn't quite right. And I just I just banged on the alarm and then they they put the crash trolley through.

Ruth, 37

There is a real sense that the experiences of many of the parents have been, as one parent described it, a "rollercoaster ride" with periods of stability punctuated by sudden dramatic deteriorations that were usually triggered by respiratory problems. A few of the infants whose parents were interviewed were diagnosed with tracheomalacia or laryngomalacia (a floppy airway or voice-box) as the cause of their deteriorations. In some cases this took a long time to be diagnosed.

Ruth and Matthew's daughter had multiple episodes of collapse, some of which lead to cardiac arrest. They describe that they felt that it took a long time for what they had observed to be taken seriously by the clinical team. It was only when it happened when doctors were present that it was eventually investigated and treated.

Once it's happened right there in front of a professional, they, obviously, they've seen it. They know exactly what happened and it is so serious that it's got to be dealt with.

Matthew, 34

Carol had a similar experience. Her daughter had multiple readmissions to hospital after discharge and she was very vulnerable when she developed respiratory infections. Carol recalled:

Somebody would sneeze in the street and she would be in hospital two days later.

Carol, 46

Carol describes struggling to make her GP and the ambulance crews understand how rapidly her daughter could deteriorate until her floppy airway was diagnosed at eighteen months of age. She describes this as a turning point in her daughter's care that made life much easier.

It was great once we actually knew that because, basically, the team immediately put a programme in place. So it was like we didn't, we no longer had to go, we didn't have to do the calls to the ambulance people going, you know, going through the whole thing. We had immediate access to the emergency respiratory wards.

Carol, 46

Being given a diagnosis and an emergency care-plan allowed Carol to have a sense of control.

This emergency access thing was brilliant. We also were given antibiotics, which we could choose to give her. [um] So I was made like the decision maker on that.

Carol, 46

In Sarah's son's case, his tracheomalacia was diagnosed very early and she and her husband were told he needed a tracheostomy. They were initially unsure and asked for more time to think about it.

They told us that was the only way, so that was the only way. But I think we just felt like we needed a little bit of time and, actually, he ended up pulling his tube out the morning that he was due to have his trachy operation and had a massive de-sat and that was another motivation to realise that, you know, his life was hanging in the balance. He really needed it

Sarah, 34

She describes what a difference it made to her son.

That was a massive, positive turning point. Immediately he had, I could see his face. He didn't have a ventilator tube up his nose or in his mouth. And we had a week on PICU[†] after he had the tracheostomy, which they do until the first tube change..It allowed us to get off PICU...Which was, absolutely the right thing.

Sarah, 34

In striking contrast to this, is Hannah's experience. She found out that clinicians were planning a tracheostomy from one of the nurses, something that distressed her greatly. She describes how, nine days after birth it was suggested by the clinicians that her daughter needed this procedure.

They explained to me why and [um] and then, in the end, we decided, this was on a Friday, we'd see what she was like on the Monday and, [um] you know, I'd obviously been there all weekend and they came again with the consent form for for us to say 'yes' to the tracheostomy and I said, "But she's had a really good weekend, you know. I don't think she needs it."

You know, the hospital staff were probably thinking, 'who does she think she is?' but that was on the Monday. On the Thursday, one of the consultants came to me and said, "Oh we've just got the results back and her lungs are fine." And I said, "Well, she came out of me screaming." He said, "Oh, I didn't realise that." And she didn't need the tracheostomy in the end.

Hannah, 39

Most of the infants required invasive ventilation during the course of their treatment. Some parents describe witnessing this as extremely distressing. Sarah described it as her "worst nightmare". Hannah recalls the time when her daughter was placed on a mode of ventilation known as high-frequency oscillation.

That was the hardest points for me. ...to see your baby visibly shake. I mean bouncing [um] and with the gel pads on their eyes and, you know, machinery everywhere and, and, and hard, in those moments, to see the end, you know. You know, can you imagine your baby without, can your baby going to school at those points? No.

Hannah, 39

[†]PICU: Paediatric Intensive Care Unit

For many of the infants, the breathing problems lasted a long time after discharge from hospital. Some were discharged on home oxygen therapy which brought its own challenges and responsibilities. Parents describe the practical and social challenges of having a child on oxygen.

She was on a wire, which was, quite interesting, it was like forty foot for both the wires so she could get free rein round the house. She was a little bit mobile at that stage.

Ruth, 37

It's like being a celebrity, having a baby on oxygen...How to attract attention in one easy lesson, just have a baby with a cannula, .. you know, a up the nose...And I used to endlessly be stopped by old ladies in the street.

Carol, 49

The high level of ongoing medical care needs for some children had a significant impact on parents' ability to sleep. Having the support of a nurse who comes two nights a week made a significant difference for Sarah:

Just the exhaustion of trying to look after him just got increasingly tough and unmanageable and, actually, to the point of being quite dangerous because, obviously, you have to be awake and alert and ready to change his tube or give him suction at any time.. So now we have nursing care two nights a week. So it means that I can sleep. ..I would never have believed that I would have somebody else in my house to look after my baby. But actually, I just, no, I couldn't do it. It wasn't safe.

Sarah, 34

Some of the parents describe the social isolation that this led to as well as examples of support that have helped this.

Ruth: *I used to have a lady come in, she'd she'd come for two hours a day, every week..*

Matthew: *She was brilliant wasn't she?*

Ruth: *Yeah and, actually, initially, I thought that I would need the help just just to have somebody to watch [daughter]. While I did the washing and, you know, few bits around the house. But, actually, I just needed somebody to have a cup of coffee with and chat to. I would be, I wouldn't leave the house at all, you know.*

Ruth, 37 & Matthew, 34

Helen describes:

Mostly it's just been living in the house for the first eight months we couldn't take her out anywhere and then that golden day when the respiratory consultant said 'Well you can maybe go to a little baby club with some other little babies.' .. our lovely health visitor organised the baby massage for Isla with only a couple of other little babies instead of the great big classes that it normally is so that was really special, that was lovely although trying to do baby massage on a baby that has a great big exomphalos there's not much baby left [laughter] to do massage on, but she enjoyed it and it was positive touch and it was yeah it was a really good way of getting Isla used to having, having nice things happen to her.

Helen, 36

4.4 Discussion

This study sought to understand the experiences of parents following a diagnosis of exomphalos and use this information to identify ways in which these experiences could be improved for future parents. Extreme variations in parent experiences were apparent even from this relatively small number of interviews. These relate to counselling and management choices throughout many aspects of care and range from the 'tone' of the antenatal counselling, to the choice of mode of delivery and surgical management strategy. The variations in management are particularly notable when it is remembered that the sample of parents included in this study shared many similar characteristics antenatally.

The results illustrate the variations in management and counselling that arise in a rare condition with a sparse evidence base. It is clear from parents' experiences that the lack of accurate information about survival, management and outcomes in infants diagnosed with exomphalos in the published literature means that clinicians rely on experiential 'evidence' and institutional practices that are chosen without clear evidence of efficacy. This was the case for discussion both with fetal medical consultants and obstetricians as well as with surgeons.

4.4.1 Antenatal counselling

Information given to parents before the birth of their child varied widely. Many were given rather a bleak outlook on the future and termination was frequently suggested as an option even when parents had stressed that they wished to continue with their pregnancy. This bleak picture appeared to have been given in some cases without accurate provision of a holistic idea of what the future may hold.

This negative tone is interesting considering that authors in the past have tried to emphasise that for babies born with exomphalos and no other chromosomal or major structural abnormalities, the outlook is not so bleak. Twenty years ago, Fisher et al published data from the South East Thames Congenital Malformation Registry and noted that live-born infants with exomphalos and no other associated abnormalities had much better chances of survival than previously published data had suggested (Fisher, Attah et al. 1996). Even 20 years ago, a 79% survival to one-year after birth in these infants was noted and the authors called for those involved in antenatal counselling to be better informed of the outlook for infants diagnosed with exomphalos with no other associated abnormalities (Fisher, Attah et al. 1996). They state: *“Appreciation of this improved outcome for isolated exomphalos is important for all those involved in the care of such infants and the parents of the infant. Although in ideal circumstances the neonatologist and neonatal surgeon will have been involved in the antenatal care, in many instances this does not happen and the antenatal team may be unaware of the good outcome for live-born infants without additional anomalies.”*

Even accepting this as a small sample, the experiences of parents whose children were born in recent years with large exomphalos defects suggest that a fairly bleak outlook is still being communicated antenatally. The study described in Chapter Three suggests that there is a significant burden of comorbidity in the population but that the majority of children had good short term outcomes.

Only 4% died in the neonatal period; this is similar to the proportion of gastroschisis infants that died in the previously published population cohort study from the UK (Owen, Marven et al. 2010). It is clear though that a longer-term assessment of their outcomes, will, however be essential.

Some parents describe a lack of preparation for the ‘whole picture’ of what life would be like for them and their baby with exomphalos. One area for which parents appeared to be particularly poorly prepared was the associated respiratory problems which their children experienced after birth and in some cases were still experiencing.

Respiratory problems associated with exomphalos have been well-described by several authors (Thompson, Greenough et al. 1993, Tsakayannis, Zurakowski et al. 1996, Zaccara, Iacobelli et al. 2003). It appeared from the parents’ experiences that those undertaking antenatal counselling lacked an appreciation of this and many failed to mention respiratory sequelae to parents before birth. This led to many distressing, frightening and confusing postnatal experiences for patients characterised by the “*What the hell is going on?*” comment by one mother.

4.4.2 Mode of delivery

Approaches to managing the birth of the exomphalos baby and the information given to parents about the ‘best’ mode of delivery differed between centres. Variation in practice was also in evidence in the population cohort study described in Chapter Three. The lack of robust evidence to demonstrate the benefits of one modality over another has been discussed, and it is clear from those interviewed that their eventual choice was heavily influenced by obstetrician preference. One aspect that was evident was the distress that mothers experienced at being separated from their baby, often in a geographically distinct location, whilst on the post-natal ward.

Where mothers had had an operative delivery they were further restricted physically, by being an inpatient for a longer period, during what is a very critical period in the infant's care and not being able to drive once discharged home. This provides an example of where there is a lack of evidence to guide management choice and having an understanding of lived-experience of that choice may help with parental counselling and decision-making.

4.4.3 Surgical management

None of the parents were given a choice about the surgical closure strategy for their child's exomphalos. In some cases, different modalities of treatment were discussed with parents but institutions appeared to have established views on the superiority of one management technique over another based on their own experience although it was also clear that many of the babies experienced complications as a result of these decisions. This once again reflects the lack of robust evidence to guide the management of exomphalos. Within this small, relatively homogenous group of children, a number of different strategies were employed.

4.4.4 Limitations and reflexivity

It is acknowledged that this small collection of parent interviews is unlikely to represent the full range of experiences of all parents who have an infant diagnosed with exomphalos. This subset was largely recruited from a group of individuals for whom exomphalos is a significant part of their lives. That is, those who actively engage in and, in some cases, oversee, an online support network for families affected by abdominal wall defects. Five of the seven attended a parent advisory group meeting. It is possible, therefore, that these individuals may have had 'extreme' experiences that do not represent those of the majority of infants or their parents. The profound impact that these experiences had on parents may have led them to want to talk about them and 'spread the word'.

A feature of the narrative technique is that it allows parents to relate a version of events that emphasises some aspects and deemphasises or censors other. As qualitative researcher Johanna Shapiro states: *“All stories necessarily contain elements of authenticity and inauthenticity, are always partly trustworthy and partly untrustworthy, to some degree unavoidably self-representations and performances”*(Shapiro 2011).

None of this, however, detracts from the validity of what these parents describe. Although, as Ziebland describes, the results *“give(s) little insight into the distribution and frequency of particular perspectives or characteristics of the population”* (Ziebland 2013), they do illustrate the variation in parent experiences. The results particularly illustrate the extreme variations in counselling and management that parents and patients experience in a rare condition with little robust evidence for guidance. It is apparent that two infants with a similar set of problems diagnosed and managed at the present time in two different hospitals in the UK may receive very different information and treatment; something that was observed in the study described in Chapter Three. In addition, parents appear to be given little choice. Even with this small subset of parents, these messages were clear.

It should be noted that there are important parent experiences that have not been included in this dataset that should be acknowledged. The subset does not include any parent whose infant was diagnosed with a genetic or associated structural defect antenatally. Neither does it include any parent who proceeded to a termination of pregnancy or who experienced a fetal death *in utero*. All of the infants have survived and therefore no parent described experiences of the death of a child with exomphalos. All of these are relatively common experiences among parents whose baby has an exomphalos and therefore their absence, although justified by the need to deal with specific, focussed research questions, is significant.

The analysis of the qualitative data described within this chapter has been performed by a trainee in paediatric surgery who is currently practicing in the UK. Infants with a large exomphalos defect are infrequently seen and yet the author has already experienced different approaches to management of these infants by different surgeons. Experiences of surgical care have been represented here to demonstrate variation in approach rather to illustrate the superiority of one over another. Any personal prejudices of the author regarding surgical techniques should not, therefore have influenced the analysis.

The author is, in addition a mother, who has experienced antenatal care as a patient and post-natal care as a parent. This may have added a level of empathy with the interviewed parents and to the interpretation of their recounted experiences. When reviewing the interview data, a comparison of the experiences of others to one's own experience is inevitable. The author clearly has opinions about the standards of care she would expect. By working with LH who performed the interviews and acted as analysis 'buddy', the authenticity and validity of the representation of the stories in the analysis has been independently verified.

4.4.5 Clinical implications

The following sections describe the author's suggestions on how practice may be improved based on the preceding analysis of parent experiences; boxes 4.1- 3 summarise these.

4.4.5i Implications for antenatal counselling

Parents favoured a holistic, frank and gentle approach in antenatal counselling as well as one that communicated the uncertainties of the situation. Where this had occurred, or parents felt that staff had understood the level of information they needed, their overall level of satisfaction with their care appeared high. This was the case for Ruth and Matthew, who felt they were given all of the information they could handle and for Sarah who felt she had been given a frank and honest picture of her baby's outlook.

Parents appreciated being involved in management decisions regarding planned therapy for their child's exomphalos after birth or the mother's mode of delivery. This was in contrast to examples where the parents were offered little choice in the management strategy such as in the case of Hannah who was told that her daughter was going to be managed with a silo with little rationale for this choice. There has been a recent drive within the health-service to involve patients in decision making and this is a mandatory feature of good clinical practice embodied by the mantra "*no decision about me without me*" (Department of Health 2012).

Counselling of parents should include an emphasis from health-professionals that, even when no additional anomalies are detected on ultrasound scan, significant abnormalities may be present and further complications may ensue. Their 'rule-in' rather than 'rule-out' nature should be stressed. Many parents felt unprepared for the associated medical sequelae that their children developed. This was particularly the case with respiratory comorbidity. Informing parents about these possible problems before birth may help them prepare in some way for the "*roller-coaster ride*" that, for many, ensues.

Antenatal counselling should be tailored to the individual family's feelings about the amount of information they wish to receive in any one session. In many cases it needed to be richer in detail about what postnatal life would be like and the range of implications for the family and their wider lives. If necessary, multiple appointments could be made, over which information could be delivered slowly or repeated. This could involve a specialist midwife or neonatal nurse as some parents felt that these individuals were both accessible and understood their information needs.

While some parents, like Ruth and Matthew, found the clinicians they dealt with antenatally very helpful and professional, there is clearly room for improvement in the approach of some clinicians, that parents described as “*stern*” and “*cold*” to parents going through such experiences. Those counselling parents may wish to remain emotionally detached from the very difficult decisions that they have to discuss with parents, it is, however clear that the tone and atmosphere of the counselling remains with parents indefinitely. Where this is negative, it gives parents the impression of a lack of empathy as well as creating a divide between parents and health professionals so that parents appear to feel that they are ‘battling’ on behalf of their child, even before they are born. This is something that may stay with them throughout all their subsequent interactions with health professionals.

Parental experiences of antenatal counselling could be improved by providing regular training for health professionals that focus on humanising communication skills. This would help to instil a sense of empathy and gentleness. The professionals’ approach should be to collaborate with and empower parents in their decision-making rather than being dictatorial or combative.

4.4.5ii Implications for postnatal care

While all parents were appreciative of the treatment their children received and praised hospital staff from cleaners to consultants, some parents found that care was disjointed and communication poor. There were a number of examples of parents not being informed of marked clinical deterioration in their children or about the management choices that were planned for them. A large survey assessing the experiences of parents whose children had spent time on NICU had similar findings, noting deficiencies in parent-staff communication that paralleled those noted by parents in this study (Wigert, Dellenmark et al. 2013). Parents appreciated regular contact with the same surgical consultant who took overall responsibility for all aspects of care.

Good inter-disciplinary working was also appreciated, when health professionals from different specialities involved in their child's care were regularly updated and teams worked together.

In addition, parents valued occasions where health-professionals demonstrated that they were aware of the wider picture of their family life and provided support that improved their sense of isolation after discharge like Helen's respiratory consultant and health-visitor who facilitated and organised a baby massage class that she could attend. This was not, however, always the case, as in the example of Carol who was left to work out how to get her daughter home safely in a car seat with little support from the hospital. As one parent who attended an advisory group that informed this work, succinctly put it, "*Think family*".

It is clear from the interview data that peer support is vital to parents and provides a sense of community as well as a sounding board for parents who may find it difficult to discuss the problems that they and their child are experiencing with friends and family. Researchers who have looked at other severe medical conditions affecting children have previously identified the importance of parental peer support (Paterson, Brewer et al. 2013, Rossman, Greene et al. 2015) and finding out from other parents "*about daily life issues, such as functioning in school, quality of life and practical details that might be of importance for the child's future life*" (Bratt, Jarvholm et al. 2015). Health-professionals should be aware of this and facilitate links to other families both locally and via the internet.

The key messages for health professionals are summarised in Boxes 4.1-4.3.

Box 4.1: Summary of key messages for teaching and learning for all health professionals

Messages for all professionals

- Be human and show empathy. Professionals should be wary that they can come across as cold and unfeeling, creating divisions between themselves and parents that are hard to break down.
- Listen to parents views and respect them, even where they differ from one's own. Parents are experts in their own children.
- Involve parents in all decision-making, provide them with accurate, up-to-date information to assist this and where this is not available, be frank and honest about this.
- Consider and communicate *all* of the implications of a given management course, for example, a mother being an inpatient and not being able to drive after a caesarean delivery or the length of time an infant will be in hospital if a given surgical treatment is chosen
- Endeavour to understand the wider family life of the parents and how their inpatient stay may affect their other children, finances, personal relationships and working life
 - Provide access to psychological support as well as social services that may be able to assist them
 - Understand the importance of peer support and direct parents to where this is available through local connections as well as social media

Box 4.2: Summary of key messages for teaching and learning of health professionals providing antenatal care

Messages for professionals providing antenatal care

- Understand how much information parents want at any given time and offer repeated opportunities to provide this in small quantities or repeat information where necessary.
- Normalise the pregnancy as much as possible, share joy and provide scan images of the baby's face.
- Provide parents with a holistic view of life after the birth of their infant, emphasise uncertainty and the impacts on their wider lives. Discuss long-term sequelae such as respiratory and gastrointestinal problems.
- Allow parents to make their own choices based on all of the information you have given them.
 - When they have made a choice, for example, about continuing with the pregnancy, support them in this as well as providing them with the option to change their mind in a sensitive manner.
 - When they request a surgical management choice that is not offered in a given centre, facilitate a discussion about how that can be achieved.

Box 4.3: Summary of key messages for teaching and learning of health professionals providing postnatal care

Messages for professionals providing postnatal care

- Parents appreciate time with their infant before they are transferred to another hospital, this should be provided wherever possible
 - Photograph mementos of newborn infants are strongly appreciated by parents who will be separated from their baby
- Postnatal ward staff should be aware of the emotional distress mothers feel when separated from their newborns
 - Side-rooms should be provided where possible to avoid regular contact with other mothers and their babies
 - It is essential for mothers to be kept up to date with what is happening to their newborn infant when they are separated
- Empower parents to be actively involved in their child's care, for example, assisting with dressing changes, this provides them with a sense of increased control and ameliorates the degradation in their parental role that most feel.
- Parents appreciate regular input with the same team with clear consultant leadership and regular contact with that consultant.
- Clear and regular communication between teams caring for the same infant is essential. Where this is lacking, it leads parents to lose trust in the institution as a whole.
- Plan discharge carefully to pre-empt and avoid social isolation, ensure safe transfer home and that services are in place to support the medical and psychosocial needs of the family.
- Where children have fragile respiratory reserve, having an emergency care plan and therefore a route to rapidly access acute care is of significant value to parents.

4.5 Conclusion

The study reported in this chapter reflects the experiences of parents of children diagnosed with exomphalos using an entirely different methodology to that used in the studies described in chapters Two and Three. The rich data obtained from only a small subset of parents has led to a number of key messages for health professionals that will enhance understanding of how to improve care for these families, a key goal of this work. Crucially, the analysis has highlighted the importance of giving consideration to the personal and emotional aspects of care within the post-graduate training of individuals who will be involved families similar to those interviewed, both pre- and postnatally. One author suggested in 1988 that educators should make, *“patient and their families’ narrative of the illness experience more central in the educational process”* (Kleinman 1988). It could be argued that the profound messages from parents within these interviews could be used to train and better inform health-professionals about the depth and reach of parent experiences. The resources created from them for the *Healthtalk* website could be used to for this purpose.

The parent experiences described here, illustrate what Angela Coulter refers to as the, *“unfortunate paradox at the centre of modern medical care”* (Coulter 2013). She claims: *“As modern medical knowledge has advanced, offering considerable benefits in terms of more effective treatments, so healthcare delivery has become progressively more complex, fragmented and difficult to manage.”* She argues that this has, *“distracted attention from the human experience of being ill and the search for cures has overshadowed the important business of caring for people.”*

There is increasing quantitative evidence of the high levels of maternal psychological distress that an antenatal diagnosis of a congenital anomaly causes (Brisch, Munz et al. 2003, Brosig, Whitstone et al. 2007, Kaasen, Helbig et al. 2010). Levels of distress appear to be correlated to the severity of the malformation (Brosig, Whitstone et al. 2007, Aite, Zaccara et al. 2009) and with diagnostic and prognostic ambiguity, (Aite, Zaccara et al. 2009, Kaasen, Helbig et al. 2010) all of which were present for this group of parents. Some authors have found that forewarning about congenital anomalies ameliorates stress after delivery (Hoehn, Wernovsky et al. 2004). Others have found that prenatal diagnosis increases postnatal distress (Skari, Malt et al. 2006).

Evidence of the adverse effects of maternal stress on pregnancy outcome are emerging (Brunton 2013, Glover 2014, Glover 2015) as well as the profound and lasting impact on parents of having a child undergo intensive treatment in hospital (Chen, Jeruss et al. 2007, Aftyka, Rybojad et al. 2014, Kubota, Yamakawa et al. 2016). Listening to, attending to and improving the experiences of parents may help to ameliorate the effects of this trauma and potentially lessen or prevent later medical, psychological and social impacts on the parents and wider family.

Finally, it is very clear that more comprehensive data on the outcomes of infants born with exomphalos are needed to better inform those who are managing these infants both pre- and postnatally. The data generated by the national cohort study described in the preceding chapter will help to address this information gap. This will help to guide management choices and encourage discussions about alternative options to further involve parents in decision-making and care, an approach that has been demonstrated to improve satisfaction and outcomes (Coulter 2013).

Chapter 5

Gastroschisis: parent and child reported long-term outcomes in a population cohort

5.1 Introduction

The study described in Chapter Two of this thesis has generated data that will be of value in counselling parents of infants diagnosed with gastroschisis about their short-term outlook. There is, however, a lack of robust long-term data about what happens to these children after the first year of life. The aim of the study described in this chapter, along with that described in Chapter Six, is to fill this gap by evaluating childhood outcomes among a population-based cohort of children born with gastroschisis. The experiences of parents described in the preceding qualitative study have highlighted the need for both short and long term prognostic information to support parents and health professionals in making treatment choices and preparing for future care.

No robust assessment of long-term outcome in children born with gastroschisis would, therefore, be complete without including the parental and child perspective on 'how they are doing'. The study described in this chapter explored a methodology for investigating childhood outcomes in gastroschisis incorporating these viewpoints. The aim was to enable assessment of aspects of their well-being that can only be evaluated in this way, such as: health related quality of life or the parent and the child's views on the appearance of their abdomen. In addition, parents have an important role in providing information about their children's physical health and medical history that may not be easily obtained from hospital records.

5.1.1 Research questions

The specific research questions that this study was designed to address are:

- Are any factors e.g. mode of delivery, gestation, birthweight, type of anomaly, condition of infant at diagnosis, associated anomalies, method of closure associated with a poor outcome including morbidity, developmental impairment, poor health-related quality of life (HrQOL) for children born with abdominal wall defects?
- What is the burden of on-going morbidity at older ages in children born with abdominal wall defects?
- What are the parent and child-perceived cosmetic outcomes of surgery for gastroschisis and what has been the impact of these on the child's life?
- What has been the impact of having a child born with gastroschisis on the family in terms of their internal and external relationships, working life and self-perception?
- Do the educational outcomes and burden of special educational needs within this cohort of children differ from those of the general population?

5.1.2 The BAPS-CASS gastroschisis cohort

Between the 1st of October 2006 and 31st of March 2008, newborn infants with gastroschisis were anonymously reported to BAPS-CASS, using similar methods to those described in Chapter Three, creating a national population cohort. Outcomes to one year of age in this cohort have been published (Owen, Marven et al. 2010, Bradnock, Marven et al. 2011). The case-definition of gastroschisis for the original studies was: infants with a congenital malformation characterised by visceral herniation through an abdominal wall defect lateral to an intact umbilical cord and not covered by a membrane. Those with aplasia or hypoplasia of abdominal muscles, skin-covered umbilical hernia or exomphalos were excluded.

Three-hundred and ninety-three infants were confirmed as new cases that presented to paediatric surgeons during the eighteen-month data collection period. These included 336 infants with simple gastroschisis (85.5%), 45 infants with complex gastroschisis (11.5%) and 12 infants in which the type of gastroschisis was not confirmed (3.0%). These were reported from 28 paediatric surgical centres in the UK and Ireland. Forty-six percent (182 infants) were born before 37 weeks gestation. Fifty-one percent were managed with a primary fascial closure, 36% had closure with the assistance of a preformed silo, seven percent had: a closure at the bed-side without sutures, four percent, a custom silo, and one percent a patch applied to the fascial edges (1%). The few remaining infants were described as 'other' primary closures and included infants in who required more extensive surgical exploration due to associated bowel problems.

The short-term outcome results received global interest from the paediatric surgical community as they suggested more favourable outcomes in infants treated with primary fascial closure compared with those managed with a preformed silo. Infants managed with a pre-formed silo took longer to reach full enteral feeds and had an increased risk of intestinal failure. In addition, two infants from the cohort with simple gastroschisis died as a result of intestinal ischaemia that occurred within a preformed silo (Bradnock, Marven et al. 2011). Peter Nichol, a Chief of Paediatric Surgery from Wisconsin in the USA who wrote the editorial for the one-year outcome paper suggested that the differences noted between these treatment groups warranted further investigation. He stated that; *"It is important, given all the potential variables, that such a study is comprehensive and longitudinal"* (Nichol 2011). The aim of the studies described within this chapter and Chapter Six (which investigates outcomes reported by clinicians) was to provide just such a comprehensive and longitudinal assessment using population-based data and to provide a robust assessment of long-term treatment efficacy as described by the IDEAL collaboration (Cook, McCulloch et al. 2013) with the children in the cohort who by this stage were aged seven to nine years of age.

5.1.3 What is known about long-term outcomes in gastroschisis?

As described in Chapter Two, the majority of reports on outcomes in gastroschisis are limited to events that occur during the first hospital admission. A number of authors have, however, tried to examine what happens to these children over a longer period of time. In the process of designing this study, a literature review was undertaken in order to identify common long-term outcome domains explored within published studies in children born with gastroschisis. The results of this are shown in Appendix 10. In addition, areas that have been neglected by other investigators to date were identified. These domains were used to inform formulation of the research questions of this parent and child reported outcome study. Table 5.1 summarises the key areas explored in the studies outlined in Appendix 10 as well as the tools that other authors have used to assess them.

Table 5.1. Domains used to assess long-term outcomes in children born with gastroschisis.

Outcome domain	Assessment tools used in published studies
1. Growth	• Height and weight (usually converted to z-score[†]) • Body Mass Index (BMI) - Comparison to population norms
2. Neurodevelopment • Neurosensory • Motor • Expressive language • Education and Learning • Presence of ADHD	• Detailed ophthalmology and audiology assessment • Physiotherapist/ Cerebral palsy assessment - Gross Motor General Classification System • Parental questions about motor milestones • Bayley II and III • CAT/CLAMS • PRUNAPE • Need for educational support/ special school • Non-standard parental questions • Bayley III • WISC-IV and WPPSI-III • Multidisciplinary assessment

[†] see 5.2.6ii Bayley II and III: Bayley scales of infant and toddler development (2nd and 3rd edition)

CAT/CLAMS: Capute Scale Clinical Adaptive Test/Clinical Auditory Milestone Scale

PRUNAPE: Psychomotor development in primary care WISC-IV: Wechsler Intelligence Scale for Children-IV

WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence ADHD: Attention Deficit Hyperactivity Disorder

Table 5.1 Continued. Domains used to assess long-term outcomes in children born with gastroschisis.

Outcome Domain	Assessment tools used in published studies
3. Behaviour	• Strengths and Difficulties Questionnaire (parent version)
1. Gastrointestinal symptomatology • Abdominal pain • Abnormal stool pattern • GORD Symptoms	• Non-standard parental/ gastroschisis adult questions • Functional status II questionnaire (Rome criteria) • Bristol stool chart • Functional status II questionnaire (Rome criteria) • Medications for GORD • Non-standard gastroschisis adult questions
1. Cosmesis	• Non-standard parental/ gastroschisis adult questions
2. Psychosocial	• ‘Mental Health’ Assessment • Parenting Relationship Questionnaire (PRQ) • Parent interview • Non-standard parental/ gastroschisis adult questions • Beck’s Depression Inventory • Rosenberg’s Self Esteem Scale • Cohen’s Test for Life Management
3. Quality of Life	• Non-standard parental/ gastroschisis adult questions • KIDSCREEN-52 • SF-36

GORD: Gastro-Oesophageal Reflux Disease

5.1.4 Educational outcomes of children born with gastroschisis

The long-term impact of early events on an individual’s educational attainment has recently been brought into sharp focus. There is clear evidence of a negative impact on educational performance for every additional week of gestation that an individual is born before term (Quigley, Poulsen et al. 2012). In addition, it is likely that physiological instability, severe infection or hypoxia in the neonatal period may have additional detrimental effects (Wood, Marlow et al. 2000, McNally, Bennett et al. 2006, Pike, Brocklehurst et al. 2012).

Following concerning data from animal models about the impact of certain modalities of general anaesthesia on the developing brain, evidence has begun to be sought about whether the same is true in humans, and if so, what factors exacerbate or ameliorate these effects (Jevtovic-Todorovic, Hartman et al. 2003, Paule, Li et al. 2011, Jevtovic-Todorovic, Absalom et al. 2013, Davidson, Becke et al. 2015, Davidson, Disma et al. 2016).

Long-term educational impacts of early management choices and adverse events in children born with gastroschisis have never been systematically assessed. One of the key debates about the management of gastroschisis among the paediatric surgical community concerns the methods of bowel reduction and defect closure. Those who advocate 'ward-based' reduction or early application of a pre-formed silo 'at the bedside' have cited the lack of a requirement for general anaesthesia as a potential benefit. For these reasons, this study explored whether it would be possible, with parental consent, to obtain educational data from schools, about infants born with gastroschisis within the population cohort. The aim was to be able to compare these to adjusted population norms and explore the relationship with factors such as gestational age at delivery, the use of general anaesthesia and episodes of sepsis.

5.2 Methods

5.2.1 Study design

The methods used to assess the long-term outcomes of children born with gastroschisis in the published studies described in the tables in Appendix 10 fit into two broad categories: face-to-face assessment or structured questions administered from a distance, using either a postal questionnaire or telephone interview. As the BAPS-CASS cohort of children had been managed by 28 different surgical centres spread throughout the UK and Ireland, the logistical and financial burdens of arranging face-to-face review for all of the surviving children were too great to be practically feasible. For this reason, a postal questionnaire was designed to gather data from parents and children in this study. This is a methodology commonly employed where large cohorts of children are followed up, for example in neonatal clinical trials (Marlow, Greenough et al. 2006, Brocklehurst, Farrell et al. 2011).

A questionnaire was designed to be answered by the main care-givers for the child. Although this would most often be the parents, this may not always be the case. For simplicity however, within this chapter, this is referred to as the 'Parent Questionnaire'. Another, shorter, questionnaire was designed that could be completed by the children themselves.

5.2.2 Research ethics approval

This study received ethics approval from the London Research Ethics Committee ref: 14/LO/1919 and was adopted onto the National Institute for Health Research (NIHR) Clinical Research Network portfolio (IRAS ref: 155257). The central ethics approval covered the conduct and coordination of the study by the NPEU. Local Research and Development approvals were sought and obtained from all participating centres for these institutions to act as 'Participant Identification Centres' (PIC) sites. These approvals were based on the acknowledgement that no research activity was conducted by nominated local clinicians other than patient identification on behalf of the NPEU.

5.2.3 Case identification

The Republic of Ireland was not included in the follow-up study. All of the children known to be alive at one-year from the 27 UK centres were eligible to be included. During the original cohort study, the study lead for each centre was asked to keep copies of their original data collection forms. In addition, reporting clinicians were requested to make a note of identifiers, such as the date of birth and the hospital number, alongside the four-digit anonymous identifier on the retained section of the blue reporting cards shown in Appendix 8. The intention was that these would be kept within departments in a dedicated BAPS-CASS folder for future reference.

In this follow-up study, local BAPS-CASS leads were sent data-sheets that provided a list of the infants known to have been reported from the original cohort represented by their anonymous four-digit BAPS-CASS identifier. Basic information collected in the earlier studies such as gender and birth-weight were additionally added to assist re-identification (Appendix 11). If the infant was known to have died before one year, this was clearly recorded on the data-sheet and no further action was required for these children. The intention was that BAPS-CASS leads would use these data-sheets to aid re-identification of the infants from the original cohort if the original reporting card data had been lost. If children were found to have died at any point, they were not included in this study.

5.2.4 Confirmation of life status and current contact details

After identification of the children from the original cohort, local clinicians were asked to add the current address details to pre-prepared, sealed packages produced by the author at the National Perinatal Epidemiology Unit. These packages were marked with anonymous identifiers for the clinicians to match to the current contact details.

It was felt that the paediatric surgical centres' in-house record systems were an unreliable means of assessing whether the children were still alive and identifying their current contact details. The children may have died or moved house since they were first treated and the surgical centre may be unaware of this, as it was often not their local hospital. In England the *NHS Spine* was used by clinical leads to identify whether the children were still alive and to trace their current contact address. The *NHS Spine* has within it, a directory called the 'Summary Care Record' which contains current demographic and clinical information for all individuals receiving healthcare in England. This is updated whenever the individual comes into contact with any health-care provider including their GP. Local leads for this study were provided with instructions outlining how to trace the current contact details and vital status of the children using the *NHS Spine*. In Scotland, regional health authorities keep the most up-to-date contact information on all individuals living within that region. In addition they keep a 'death file' of all children within the area that are known to have died. After agreement from the health authorities, they were contacted by centres and provided information on the vital status and contact addresses directly to the centres. In Wales, administrative staff had access to GP databases to identify contact details for the children. In Northern Ireland, the NI ECR (Northern Ireland Electronic Care Record) was used for these purposes.

5.2.5 The structure of the packs

The packs sent to parents contained the items listed below.

1. An invitation letter to parents (Appendix 12)
2. A parent information leaflet (Appendix 13)
3. A *Freepost* envelope
4. A sealed pack containing the questionnaires

The invitation letter and the parent information leaflet were reviewed by the parent advisory group that were involved with the design and development of this study (see 5.2.6). Their contents and layout were found to be acceptable to parents. In addition the text of these documents was analysed using the Flesch-Kincaid grade level and Flesch reading ease assessment tools (Kincaid JP 1975). The invitation letter had readability scores of 6.9 and 78.7 and the leaflet, scores of 6.6 and 72.9 as measured by the Flesch-Kincaid grade level and reading ease respectively. The grade level, corresponded to children of age 11-12 years. The reading ease is a measure that indicates on a scale of 0-100, the difficulty of comprehending a document, with a score of 100 indicating an extremely simple document and a score of 0, a very complex document.

The invitation letter which was sent out by the surgical centre informed parents that researchers at the NPEU had asked them, (their paediatric surgeon) to invite them to participate in the study and that the researchers did not possess any identifiable personal information about them. The letter and leaflet explained the aims of the study and the reasons for undertaking it. Areas covered in the questionnaires were outlined. The questionnaires were placed in a sealed envelope marked by a sticker that read: *"This envelope contains the questionnaires, please open only if you wish to, after you have read the other information enclosed"*. If parents did not want to open the questionnaire envelope, they were asked to return it, unopened, in the *Freepost* envelope.

The sealed envelope contained the following:

- i. A parent consent form (Appendix 14)
- ii. A questionnaire for parents to complete (Appendix 15)
- iii. A child assent form (Appendix 16)
- iv. A questionnaire for children to complete (Appendix 17)
- v. A tape measure
- vi. A change of address card

The consent form, which the parents were requested to return with the questionnaires, contained an option for them to provide the NPEU with their contact details so that the findings of this study could be relayed back to them. These contact details and the front page of the questionnaire, where they recorded their names, were stored separately from the questionnaires. Parents were asked to contact the BAPS-CASS office at the NPEU if they preferred to complete the questionnaire over the phone. If they opted for this, an interpreting service was also offered. Children were requested to complete an assent form to indicate that the details of the study had been explained to them and that they were willing to take part.

5.2.6 Design of the questionnaires

The content of the questionnaires was designed to answer the research questions outlined in 5.1.1. The outcome domains assessed in this study are outlined in Table 5.2 as well as the tools chosen to assess them. The choice of these domains was informed by the literature review described in 5.1.3. What follows in 5.2i-iv is a description of how these outcome areas and their included domains were defined in this study as well as the process of selecting the tools with which to assess them.

Table 5.2. Outcome domains included in the questionnaires[‡]

Domain	Specific areas assessed	Tools used
Development	• Motor • Vision • Hearing	Questions used in previous neonatal follow-up studies
Physical Health	• Nutrition • Cow's milk protein intolerance • Gastrointestinal symptomatology • Growth • Use of medications • Recent health-care service utilisation	- Bespoke questions <i>Paediatric Gastrointestinal Symptoms- Rome III Version</i> (QPGS-RIII) - GORD questions* - Normative UK data[¥] - Bespoke questions
General well-being	• Family Impact • Health-related quality of life (HrQOL) • Perception of abdominal appearance	- Bespoke questions <i>CHU-9D</i> (Child and parent versions) - KIDSCREEN-52^δ - Bespoke questions

[‡] Children's questionnaires contained HrQOL tools only

[¥]See 5.2.6ii.c

^δChildren's questionnaire only

* See 5.2.6ii.b

5.2.6i Neurodevelopment

The tables in Appendix 10 and Table 5.1 outline a number of neurodevelopmental concerns that have been raised in previously published long-term outcome studies of children born with gastroschisis. Neurosensory impairment and in particular, hearing problems have been highlighted as a possible problem for some children with gastroschisis as they grow up (Lunzer, Menardi et al. 2001, van Manen, Hendson et al. 2013). In the published studies shown in these tables, hearing, vision and motor function have been assessed by formal audiology, ophthalmology, physiotherapy and developmental paediatric assessment at multi-disciplinary follow-up.

A number of neonatal follow-up studies including large-scale clinical trials have assessed similar outcomes using questionnaires. Some authors have previously suggested that a questionnaire is an acceptable means of assessing functional outcomes such as vision and cognitive ability, particularly for large cohorts (O'Connor, Stephenson et al. 2004). The questions on motor development, vision and hearing included in the questionnaire were informed by those used in two neonatal trials run from the NPEU (Brocklehurst, Farrell et al. 2011, Darlow, Marschner et al. 2014). These in turn had been loosely based on areas of the Multi-Attribute Health Status Assessment or Health Utility Index (HUI) (Feeny, Furlong et al. 2002). The responses to these questions will be compared to known population norms identified from literature review.

5.2.6ii Physical health

5.2.6ii.a Nutrition

There have recently been concerns about a possible high incidence of cows-milk protein intolerance or allergy in children born with gastroschisis (Burge, Drewett et al. 2015). In some cases this may be extreme, leading to anaphylactic reactions. This was an area where it was felt that the tertiary hospital records lack accurate data and so a question was included in the questionnaire to collect data from parents on this. The responses would be compared to those in the data collection form completed by clinicians from the hospital records.

5.2.6ii.b Gastrointestinal symptomatology

1. *Abdominal pain and abnormal bowel habit*

A tool was sought to describe childhood gastrointestinal (GI) symptomatology that could distinguish increased frequency of abdominal discomfort and abnormal bowel habit from those of the normal population of children in the UK. Few validated tools were found to exist and none were specific to children born with gastroschisis. Existing tools have been designed for assessment of symptomatology in 'structurally normal' children. The most widely used of these is the Questionnaire on Paediatric Gastrointestinal Symptoms, Rome III Version (QPGS-RIII) (Walker LS 2006, Baber, Anderson et al. 2008). This questionnaire was developed by the Rome Foundation, an international, not-for profit organisation composed of interested experts that seeks to describe and investigate so-called 'functional gastrointestinal disorders' (FGIDs). FGIDs are defined by the foundation as; *'disorders of the digestive system in which symptoms cannot be explained by the presence of structural or tissue abnormality, based on clinical symptoms'* (Rome Foundation 2014). Although the children born with gastroschisis are not 'structurally normal', the QPGS-RIII was utilised in this study to describe patterns of symptomatology in children with gastroschisis using a standard measure that has been evaluated in populations of 'normal' children rather than to diagnose FGIDs *per se*. The Rome questionnaires have been used in a number of research studies including two follow-up studies of children born with gastroschisis (South, Marshall et al. 2008, Saps and Bonilla 2011, Guida, Pini-Prato et al. 2013, Saps, Nichols-Vinueza et al. 2014).

The QPRS-RIII contains questions that aim to diagnose the following ten FGID symptom patterns: functional dyspepsia, irritable bowel syndrome, abdominal migraine, functional abdominal pain, functional abdominal pain syndrome, functional constipation, non-retentive faecal incontinence, aerophagia, cyclic vomiting syndrome, and adolescent rumination syndrome. Not all of these patterns of symptoms were relevant to children born with gastroschisis according to the literature review described in 5.1.3.

Questions pertaining to a diagnosis of abdominal migraine, aerophagia, and adolescent rumination syndrome were removed from the questionnaire with the permission of the Rome Foundation.

2. *Gastro-oesophageal reflux*

Specialist paediatric gastroenterological organisations place a strong emphasis on symptomatology in making the diagnosis of GORD. A widely-used current guideline for the diagnosis and management of GORD in children states that; '*in older children and adolescents, as in adult patients, history and physical examination may be sufficient to diagnose [GORD] if the symptoms are typical*' (Vandenplas, Rudolph et al. 2009).

A number of tools have been developed to assess GORD symptoms in children although only one of these has been evaluated against a physiological measure of GORD, (pH monitoring) (Stordal, Johannesdottir et al. 2005, Vandenplas, Rudolph et al. 2009). The corresponding author of this study was contacted for the details of the questionnaire but they did not respond.

A recent systematic review looking at questionnaires for the assessment of GORD identified eight that were designed for use in infants and children and these were further evaluated (Bolier, Kessing et al. 2015). Four of these were potentially relevant to the age group in the current study and one was designed as a diagnostic tool. This was the *Pediatric Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire* (PGSQ) (Kleinman, Nelson et al. 2011). This tool was developed in association with the pharmaceutical industry, possibly with a view to using it in trials of GORD medication. Permission was not forthcoming from the first author to use this tool for the present study despite repeated requests.

The tool that was used in the gastroschisis parent questionnaire was a short set of questions that had been used to identify the prevalence of GORD symptoms in a population of children without chronic medical problems or acute illness attending paediatric clinics in the USA (Nelson, Chen et al. 2000). These questions had been selected from adult questionnaires and the psychometric properties of the tool had not been formally evaluated nor had it been tested against other diagnostic measures. The large initial study where it was initially evaluated did, however, contain data on the prevalence of symptoms among the population that tested it. Permission to use these questions was obtained from the first author of the paper.

5.2.6ii.c Growth

The studies shown in the tables in Appendix 10 suggest that growth in infants with gastroschisis is initially slow but that then improves and normal percentiles are attained later in childhood (Swartz, Harrison et al. 1986, Giudici, Bokser et al. 2016). The study in Australia by Harris et al suggested that later in childhood, these children may have a higher prevalence of obesity than the normal population (Harris, Minutillo et al. 2014).

Unless they had chronic sequelae from their gastroschisis surgery such as short-bowel syndrome, the children from the BAPS-CASS cohort would not have had their height or weight measured in the tertiary hospital for many years. Their parents were therefore asked to provide an up-to-date weight for the children and to measure their height. A tape-measure and instructions were provided in the pack to assist with the latter. These data would then be compared to population norms and z-scores generated using UK height and weight standards (Cole 1990). Z-scores indicate the degree of deviation from the mean height or weight children for boys and girls at each age which can then be converted into centiles derived from normative UK data (Cole, TJ. Freeman JV 1998).

Height and weight data were also used to calculate Body Mass Index (BMI). Cut-offs have been derived to classify BMI in children into five grades that correspond to those used in adults at 18 years of age. These range from -3 (thinness grade 3) to 2 (obese) (Cole, Bellizzi et al. 2000, Cole, Flegal et al. 2007).

5.2.6ii.d Use of medications and recent health-care utilisation

The burden of current symptomatology in the children was assessed further by asking their parents to document their children's current use of medications and use of health-services in the preceding six-months.

5.2.6iii General well-being

5.2.6iii.a Family impact

The significant impact that having a child born with an abdominal wall defect had on the wider lives of the parents interviewed was clear from listening to their experiences as described in Chapter Four. Only one small study was identified from the literature review that had looked at this in families affected by gastroschisis. Lunzer and co-workers had interviewed parents at home or in the hospital setting (Lunzer, Menardi et al. 2001). These authors found that having a child born with gastroschisis had affected decisions and feelings about future pregnancies for most parents.

The '*Impact on the Family Scale*' was designed to assess the family impact of childhood illness (Stein and Riessman 1980, Stein and Jessop 2003). After reviewing this tool and studies that had employed it, it was clear that this is only relevant to those families where the child had a chronic condition with on-going current medical problems. This would not be the case for most of the families in the cohort as their children would have been completely well for the vast majority of their lives.

Therefore, rather than use the tool, a set of questions were devised that covered similar domains to the *Impact on the Family Scale*. These explored the impact that having a child born with gastroschisis had on the parents': work, relationships with their friends and partner, childcare choices, leisure time and any other children. In addition, parents were asked about whether it had affected their mood and feelings about themselves, whether they felt 'stronger as a person'. This last question was intended to leave the respondent with a feeling of positivity as some of the other areas may have been quite upsetting to answer.

All of the questions were designed to be answered with a three-point Likert scale: 'not at all', 'only a little' and 'quite a lot'. Separate questions differentiated an impact in the past from one in the present day. Parents were also able to record anything about impact on the family in a free text section for analysis using the qualitative methods described in 5.2.7.

5.2.6iii.b Perception of abdominal appearance

A number of previous studies have noted that children and adults born with gastroschisis have concerns about the appearance of their abdominal wall in the longer-term (Davies and Stringer 1997, Koivusalo, Lindahl et al. 2002). A review of the literature to identify a tool for parents or children to report their feelings about their scarring did not reveal a suitable tool to use. Table 5.3 contains a summary of the available tools that this search revealed as well as the reasons why they were not felt appropriate to use in this population.

Table 5.3. Available tools to assess cosmetic appearance after surgery

Tool	Use and ♦ Limitations
The Derriford Scale (Klassen, Jenkinson et al. 1998)	• Designed for self-report by adults after cosmetic surgery ♦ Focusses on one <i>visible</i> feature of appearance ♦ Not suitable for children e.g. <i>'My feature makes me feel unattractive'</i>
Vancouver Scar Scale (VSS) (Sullivan, Smith et al. 1990)	• Clinician reported scale, used in evaluation of linear surgical scars and scarring after burns surgery • Four parameters measured: pigmentation, vascularity, pliability and height ♦ Clinician reported, does not cover key aspects such as feelings about their scar and the impact it has had on the life of individuals
Patient and Observer Scar Assessment Scale (POSAS) (Draaijers, Tempelman et al. 2004)	• Includes clinician (vascularisation, pigmentation, thickness, relief and pliability) and patient-reported aspects, (symptoms, opinions on scar appearance) ♦ Clinician reported aspect is fundamental ♦ Patient's opinions limited to scar appearance or symptoms e.g. <i>'Is the scar irregular'</i> rather than life-impact of scar
Wound Evaluation Scale (WES) (Hollander, Singer et al. 1995)	• Clinician reported scale devised to assess repaired lacerations ♦ Clinician reported, objective measure, unsuitable for gastroschisis-associated scarring
Manchester Scar Scale (MSS) (Beausang, Floyd et al. 1998)	• Clinician reported scale to assess post-operative scarring. Parameters include colour, contour, distortion and texture. ♦ Clinician reported, objective measure
Patient Scar Assessment Questionnaire (PSAQ) (Durani, McGrouther et al. 2009)	• Patient reported measure developed to aid assessment of therapies devised to treat scarring. Contains domains covering scar appearance and patient satisfaction. • Satisfaction domain limited to feelings about appearance, discomfort, and self-consciousness. Limited assessment of life impact of scarring. ♦ Validated in adults (self-report), not in children or report by proxy ♦ Refers to 'a scar' – children with gastroschisis may have a scar but most have only a surgically created umbilicus

The most appropriate of these tools appeared to be the PSAQ although this has not been validated for use by children or for report by proxy. Most importantly, this questionnaire did not seem to be appropriate to most children born with gastroschisis as their cosmetic outcomes relate not only to a scar but primarily to the appearance of their umbilicus and how closely it resembles that of a child without gastroschisis.

As no appropriate tool could be found, bespoke questions were devised to assess whether the appearance of the child's umbilical area or abdominal wall scars has caused the parent or the child any anxiety in the past, as well as any concern for the future. There were separate questions where the parents could report their own and their child's perspectives. The aim was to explore whether these were different, with the limitation that the child's perspective would be entered by proxy.

In keeping with the suggestion by other authors that simply referring to 'satisfaction' with scar appearance does not often generate meaningful responses, the feelings of the parent and child about their umbilicus and scars were addressed in a more nuanced manner (Wong, Forrest et al. 2013). It was assessed whether the child has experienced any social embarrassment or peer discrimination as a result of their abdominal appearance. Questions such as, *'Do you ever worry about people seeing your child's tummy, for example, when they are changing, swimming or at the beach?'* addressed the impact of the scarring on their daily lives. There were free-text areas in this part of the questionnaire where parents could add any additional information about their feelings concerning the appearance of their child's abdomen.

Parents were additionally asked whether the child currently or previously had had an umbilical hernia. This was also explored in the clinical outcomes study but it was acknowledged that if children had developed a hernia after discharge from the tertiary centre, this may not be recorded in the patient records.

5.2.6iii.c Health-Related Quality of Life (HrQOL)

There is a growing appreciation that, *'children experience effects of illness and treatment beyond physiologic outcomes'* (Matza, Swensen et al. 2004) and that *'biomedical parameters such as morbidity and mortality are by themselves insufficient to capture the impact of health care interventions on the lives of survivors and their families'* (Saigal and Tyson 2008). In order to quantify and robustly assess the impact of a previous treatment or current condition on an individual's current level of *'social, physical and emotional functioning'* compared with that of their peers (Bradlyn and Pollock 1996), a number of constructs covered by the non-specific term 'Health-Related Quality of Life' (HrQOL) can be assessed (Morris 2009).

Many now consider HrQOL as an, *'integral outcome variable in medical care, clinical research and even clinical trials'* (Saigal and Tyson 2008). In this study, in order to adequately evaluate long-term outcomes after treatment for gastroschisis and identify if there were differences between groups with different early characteristics or management, an assessment of the children's current HrQOL was felt to be essential.

A large number of tools have been developed to assess HrQOL in childhood, either by self or proxy report. Authors have debated and assessed whether proxy reported HrQOL (from asking parents) differs significantly from when this outcome is reported by children themselves. A recent systematic review found differences in self and parent-reported QOL in the majority of studies that included both measures and suggested that *'both parent and child perspectives are essential to understanding the impact of a condition on a child's QOL'* (Jardine, Glinianaia et al. 2014).

In the study reported here, children were asked to complete two tools, the KIDSCREEN-52 and CHU-9D questionnaires (Ravens-Sieberer, Auquier et al. 2007, Stevens 2010). These two tools comprised the entire contents of the child questionnaire. Care-givers were also asked to complete the CHU-9D. As it was acknowledged that the adults would be likely to sit with and assist their children completing the child questionnaire, it could be therefore be assessed whether child and proxy reported HrQOL as measured by the CHU-9D differed.

Both of these tools were chosen because the existence of normative population data for individuals in the UK. This is not true of most other measures of HrQOL in childhood which have been developed and tested in other populations internationally. These tools differ slightly in the constructs they measure. KIDSCREEN-52 covers a number of domains which are largely focussed on well-being. CHU-9D is concerned with 'health-status' and was developed in children aged seven-eleven years in Sheffield, UK (Stevens 2010). This tool comprises a preference-based tool which means that the data generated can be used to perform a cost-utility analysis between children from different sub-groups such as simple and complex gastroschisis and by mode of treatment. It is a very quick and simple set of questions for children and their parents to complete which refer to the immediate past, asking how children are/ were 'today' or 'last night'. It was thought that these factors may improve response rates, particularly as the care-giver questionnaire was already lengthy.

The KIDSCREEN-52 questionnaire was developed through a large-scale cross-sectional study funded by the European Commission (Ravens-Sieberer, Herdman et al. 2013). It has been tested and validated in UK children from eight years of age. Although it was acknowledged that some of the children in the cohort would be between seven and eight years of age, it was felt that they would be close enough in age to the target population to be able to complete it.

This tool was chosen in addition to the CHU-9D as it generates a more nuanced picture of children's health-related quality of life, breaking this down into the domains of physical and psychological well-being, moods and emotions, self-perception, autonomy, parent relations and home life, social support and peers, the school environment, bullying and financial resources. This instrument has been used to assess well-being in children with other chronic conditions such as cerebral palsy and other congenital anomalies such as congenital diaphragmatic hernia (Dickinson, Parkinson et al. 2007, Michel, Baumstarck et al. 2013). The sections on self-perception and bullying were of particular interest in this cohort due to their abdominal appearance. Due to the length of the KIDSCREEN-52, this tool was only included in the child's questionnaire.

5.2.6iv Education and schooling

Parents were asked when their children started full-time schooling, whether they received any special needs support in school and whether they had a health-care plan in place. The latter was added following a suggestion by a parent who reviewed the questionnaire during a cognitive interview (see 5.2.7). Permission to contact the child's teacher was requested. Parents were asked to gain permission from the teacher to pass on their contact details and these were recorded on a detachable portion of the questionnaire to be stored separately.

In England, children undergo standardised educational assessment from six years of age (Department of Education 2013). This study explored whether parents would be happy for data from their assessments, as well as an assessment of the child's behaviour by their teacher using a recognised tool (the *Strengths and Difficulties Questionnaire*, SDQ) to be used as part of a holistic long-term assessment of their progress to date (Goodman 1997).

5.2.6v Socio-demographic data

Data were collected about the respondent's age, schooling, employment, first-language, ethnicity, physical health and household members.

5.2.7 Patient and parent involvement, questionnaire testing and review

The research questions and design of this study were informed through consultation and collaboration with a parental advisory group consisting of families of children born with abdominal wall defects. Both the parent and the child questionnaires were reviewed by members of the parent group who found them to be acceptable. In addition to this process, parents of two different children with abdominal wall defects who were of a similar age to those children of the cohort study, looked at the questionnaires in depth. Cognitive interviews about their design and content were conducted via telephone. These telephone interviews highlighted areas that should be included in the questionnaire. In addition, the parents indicated that their children would be happy to complete the child questionnaire but that they would more than likely sit with them as they completed it to help them with any aspects that they did not fully understand. One mother noted that questions that refer specifically to the 'belly button' should be avoided as many children may not have an identifiable point that they would refer to. The wording was changed, to refer to the 'belly button area'.

5.2.8 Data entry and analysis

Data were double-entered into a customised database at the NPEU and discrepancies identified and resolved. Socio-demographic characteristics of the population that responded were described. Similar data collected during the first cohort study were used to assess characteristics of respondents and non-respondents to the follow-up study to assess the presence and extent of responder bias.

Stata 13 SE was used for statistical analysis unless otherwise stated. Descriptive information is presented as frequencies or proportions with 95% confidence intervals. Continuous data are presented as median and interquartile range unless otherwise stated. Categorical data were compared using χ^2 or Fishers Exact test and the Mann-Whitney test was used for comparison of continuous data.

Free text questionnaire responses were analysed using qualitative analysis informed by the principles of grounded theory (Charmaz 2006).

Scores for the KIDSCREEN and CHU-9D questionnaires were generated using analytical syntax for *SPSS* provided by the organisations that administer these questionnaires. These scores were compared to population-based data using Student's t-test. The adult and child scores for the CHU-9D were compared using the same method.

5.3 Results

5.3.1 Centre participation and response rate

Local permission was granted for all of the 27 paediatric surgical units in the United Kingdom to act as participant identification centres. This took seven months to achieve from the time of REC approval. The 28th centre from the original cohort study was a neonatal unit only and children were followed up in another centre which was included as a PIC site. Three-hundred and eight live children were identified and their parents were sent packs. The table in Appendix 18 shows the number of children from the original cohort that were identified in each participating centre and the number that were found to have died whose parents were not therefore contacted. The number of respondents and returned packs is shown. Five packs were returned to sender with no other address to re-send them to. A total of 46 packs were returned by care-givers.

A total of 43 parent questionnaires and 40 child questionnaires were returned having been completed. The response rate was therefore 15%. Three packs were returned blank indicating that 1% of parents communicated that they did not wish to participate.

5.3.2 Characteristics of respondents

Forty-three care-giver questionnaires were completed. These were all sent by post with the exception of one that was completed over the telephone. Table 5.4 shows the characteristics of the respondents compared to the rest of the eligible original cohort. Children that had died were excluded from this comparison. The only significant differences noted between the respondents and non-respondents was that parents where the mother was slightly older were more likely to respond ($p=0.04$) and the distribution of methods of closure differed between respondents and the rest of the eligible cohort. More care-givers of infants managed initially with operative fascial closure (OFC) responded than those managed with pre-formed silo (PFS) $p=0.04$. This was due to the fact that two of the larger centres which had used PFS in many of their children from the original cohort, did not send packs out for this follow-up study in a time frame that allowed the responses to be analysed.

Despite the very low response rate in view of the very minimal differences between respondents and non-respondents, the decision was made to analyse the data which had been provided by the parents who responded.

Table 5.4 Characteristics of those who responded to the questionnaire compared with the rest of the eligible cohort[‡].

Characteristic	Completed Questionnaire n (%)	No Questionnaire Completed n (%)	p value [‡]
	N=43 (12)	N=315 (88)	
Ethnicity of mother[§]:			
White	37 (88)	274 (91)	0.54
Non-white	5 (12)	27 (9)	
Sex of child:			
Male	25 (58)	140 (45)	0.1
Female	18 (42)	174 (55)	
Maternal Age (yrs)[†]			
Median (IQR)	30 (28-35)	29 (27-32)	0.04*
Children's Age (yrs)[‡]			
Median (IQR)	8 (8-9)	8 (8-8)	0.51
Birthweight (g)			
≥ 2500	21 (49)	128 (41)	0.33
< 2500	22 (51)	184 (59)	
Gestational Age (wks)			
< 37	20 (47)	141 (45)	0.85
≥ 37	23 (53)	172 (55)	
Type of Gastroschisis			
Simple	38 (88)	271 (86)	0.91
Complex	4 (9)	36 (11)	
Unknown	1 (2)	8 (3)	
Type of Closure -All			
Operative Fascial Closure	26 (61)	128 (41)	0.21
Pre-Formed Silo	12 (28)	118 (37)	
Custom Silo	3 (7)	29 (9)	
Ward	1 (2)	13 (4)	
Primary Patch	0	9 (3)	
Other Primary	0	15 (4)	
Other Staged	0	1 (0)	
Unknown Closure	1 (2)	2 (1)	
Type of Closure OFC vs PFS			
Operative Fascial Closure	26 (60)	128 (41)	0.04*
Pre-Formed Silo	12 (28)	118 (37)	
Other	5 (12)	69 (22)	
Received PN			
< 28 days	28 (68)	177 (60)	0.29
≥ 28 days	13 (32)	119 (40)	
Intestinal Failure Associated Liver Disease (IFALD)*			
Yes	4 (12)	12 (5)	0.09
No	28 (88)	226 (95)	

[‡]Infants who died were not eligible for inclusion [†]Current maternal age (calculated from original data)

[‡]Age at sending questionnaire or 1/1/16 if not sent

[§] Ethnic group of infant recorded on first data collection form.

* As recorded by clinicians on the first data collection form

5.3.2i Parent questionnaire - characteristics of respondents

The characteristics of the care-givers who responded are shown in Table 5.5.

Table 5.5. Self-reported socio-demographic characteristics of those who responded to the questionnaire

Characteristic	n (%) N=43
Relationship to child:	
Mother only	38 (88)
Father only	3 (7)
Mother and Father	1
Other (Legal Guardian, extended family)	1
Ethnicity[‡]:	
White	41 (98)
Non-White	1 (2)
Age:	
Median (IQR)	32 (29-36)
Age at leaving full-time education:	
16 years or less	18 (42)
17-18 years	16 (37)
19 years or over	7 (16)
Still in full time education	2 (5)
Live with spouse or partner	28 (65)
Same partner N=41	
With same partner	22 (54)
Not with same partner, on own	9 (22)
Not with same partner, new partner	10 (24)
Other pregnancies	
Number having other pregnancies	23 (56)
Had a baby since	19 (44)
Long-standing physical problem	
Yes	5 (12)
Affecting day-to-day activities	4 (9)
Long-standing mental health problem/ learning disability	
Yes	3 (7)
Affecting day-to-day activities	1 (2)

Some data items missing, therefore not all cells add up to the original N

% rounded to whole numbers therefore may not add up to 100

[‡]Care-givers self-reported ethnicity, hence different from infant's ethnicity (Table 5.4)

5.3.3 Parent questionnaire responses

5.3.3i. Neurodevelopment

One of the children was not able to walk by two years-of-age. This child had had a very complex course and had received a combined liver and bowel transplant a few years prior to data collection. All children were now able to fully mobilise.

Eleven children wore glasses (26%). Five (14%) were described by care-givers as having some difficulty seeing (with glasses if they were worn). The reasons given for this were varied but unknown in the majority. Five children (12%), were described by the respondents as having some problems with hearing. None needed a hearing aid. Four of these were attributed to recurrent ear infections or 'glue' ear.

5.3.3ii. Physical health

5.3.3ii.a Feeding and nutrition

Thirteen respondents (30%) said that they had been told that their child could not take milk that was made from cow's milk. This answer did not appear to identify those with a genuine intolerance, however, as the reasons given ranged from respondents stating that the children were initially breast-fed to some reporting that they needed a period on parenteral nutrition (PN) in early life. One child was currently receiving non-oral feeds, via a tube, directly into their stomach (a gastrostomy).

5.3.3ii.b. Abdominal symptomatology

The QPGS-RIII tool assesses abdominal symptomatology in the preceding two months. The child with a gastrostomy who had had a liver and small bowel transplant was excluded from the analysis of the QPGS-RIII data. It was felt that this child could potentially have symptomatology related to their transplant rather than due only to the previous history of gastroschisis. The results of the QPGS-RIII are summarised in Tables 5.6-5.8.

Abdominal pain was frequently reported among the children. Eighteen (44%) had regular upper abdominal pain in the last two months and 23 (56%) had lower abdominal pain. This is in contrast to a sample of normal children from the community in Chicago, USA who were assessed using the QPGS-RIII where 8% were found to have regular abdominal pain (Saps, Adams et al. 2012).

In most cases, respondents reported that pain was infrequent, mild and that episodes were short-lived. Three children had upper abdominal pain 'several times a week'. There were a few children who had more severe pain and some who had it 'most of the day'. For most of the symptomatic children, pain was a long-standing problem, present for over a year. This was the case in 61% of those with upper abdominal pain and 77% of those with lower abdominal pain. Nine children had missed school or stopped activities because of abdominal pain (21%). In addition to pain, 11 children (26%) had regular feelings of bloating in the upper abdomen.

Three children met the Rome III diagnostic criteria for irritable bowel syndrome (7%). Although they cannot be classified as having this due to their diagnosis of previous gastroschisis, meeting these criteria could be seen as a marker of frequent adverse symptomatology in these children. Nine children met the criteria for functional constipation (21%). Three children had been on laxatives in the last six months. One had been admitted to hospital with constipation in the preceding year.

Table 5.6. Symptoms of abdominal pain in children born with gastroschisis as reported by care-givers using the QPGS-RIII

	Had pain	Frequency		Severity		Duration of episodes		Duration of symptoms		Relieved by stooling		Missed school	
Recent upper abdo. pain	N=41 18 (44)	N=18		N=18		N=18		N=18		N=17		N=18	
		1-3 x month	15 (83)	A little	9 (50)	<1hr	11 (61)	<=1m	3 (17)	Never	2 (12)	Never	8 (44)
		Once/ week	0	Some	8 (44)	1-2hrs	4 (22)	2m	2 (11)	Occasionally	3 (18)	Occasionally	5 (28)
		Several x/week	3 (17)	A lot	1 (6)	2-3hrs	0	3m	1 (6)	Sometimes	5 (29)	Sometimes	4 (22)
		Daily	0	Great deal	0	Most day	3 (17)	4-11m	1 (6)	Most of time	5 (29)	Most of time	1 (6)
						All time	0	>1yr	11 (61)	Always	2 (12)	Always	0
Recent lower abdo. pain	N=41 23 (56)	N=23		N=22		N=22		N=22		N=20		N=21	
		1-3 x month	21 (91)	A little	16 (73)	<1hr	11 (50)	<=1m	1 (5)	Never	2 (10)	Never	15 (71)
		Once/ week	0	Some	5 (23)	1-2hrs	6 (27)	2m	2 (9)	Occasionally	1 (5)	Occasionally	2 (10)
		Several x/week	2 (9)	A lot	1 (5)	2-3hrs	4 (18)	3m	1 (5)	Sometimes	11 (55)	Sometimes	4 (19)
		Daily	0	Great deal	0	Most day	1 (5)	4-11m	1 (5)	Most of time	2 (10)	Most of time	0
						All time	0	>1yr	17 (77)	Always	4 (20)	Always	0

Table 5.7. Symptoms relating to bowel habit in children born with gastroschisis as reported by care-givers using the QPGS-RIII

	Frequency		Consistency		If hard, how long hard for		Holding manoeuvres	
Recent bowel motions	N=41		N=39		N=11		N=42	
	2 times week/ less	1 (2)	Very Hard	0	<1m	5 (45)	Never	27 (64)
	3-6 x week	9 (22)	Hard	6 (15)	1m	0	1-3x month	7 (17)
	Once/ day	27 (66)	Not too hard/ not too soft	22 (56)	2m	0	Once/ week	4 (10)
	2-3 times/ day	3 (7)	Very soft/ mushy	2 (5)	>=3m	6 (55)	Several times/ week	4 (10)
	More than 3 x /day	1 (2)	Watery	0			Every day	0
			Variable	9 (23)				

Table 5.8. Soiling in children born with gastroschisis as reported by care-givers using the QPGS-RIII

	How often	How much	How long soiling for
	N=42	N=17	N=15
Recent soiling	Never 24 (57)	Staining Only 12 (71)	<1m 3 (20)
	<1m 9 (21)	Large < Whole Poo 5 (29)	2m 0
	1-3 x m 2 (5)	Whole Poo 0	3m 1 (7)
	Once/ week 1 (2)		>=3m 1 (7)
	Several x / week 5 (12)		4-11m 1 (7)
	Every Day 1 (2)		>1yr 9 (60)

Table 5.9. Symptoms of GORD in children born with gastroschisis as reported by care-giver

	n / N (%)	n (%) Reported in Nelson et al (2000) N=566	p value
Thrown up/ been sick	1/40 (3)	23 (4) [¥]	1.00
Felt like throwing up/ felt nauseous	6/41 (15)	42 (7.5) [¥]	0.13
Burning pain in chest	3/40 (8)	10 (1.8)	0.05*
Stomach ache	16/42 (38)	135 (23.9)	0.06
Stomach ache above belly button	12/41 (29)	41 (7.2)	<0.001*
Sour taste in mouth	7/41 (17)	13 (2.3)	<0.001*
Pain on swallowing food/ drink	2/41 (5)	11 (2) [¥]	0.22

[¥] Estimated from graphs in (Nelson, Chen et al. 2000)

Nine children soiled their underwear more than once a month (21%) and in five of these, this was occasionally with a large amount of stool.

The questions assessing gastro-oesophageal reflux referred to symptoms in the last week (Table 5.9). In this table they are compared to the responses of the parents of 566 children between three and nine years-of-age attending paediatric clinics in the USA (Nelson, Chen et al. 2000). Symptoms of GORD were not uncommon amongst the children of respondents to the questionnaire, with seven children (17%) having nausea and seven having a sour taste like vomit in their mouth in the preceding week. None of the children had recently been on medication for GORD. Although the number of respondents was small, the frequency of some of the GORD symptoms was significantly increased compared with those children in the study by Nelson et al (2000).

When asked at the end of the questionnaire if they had, 'any further concerns about their child' in a free-text answer; eleven respondents (26%) mentioned worry about gastrointestinal symptoms. Three mentioned constipation and two of these had painful defecation:

"Constipation will be a forever problem for her and not nice seeing her in pain trying for a poo"

Two respondents mentioned that their child's tummy was bloated a lot of the time and two that frequent pain was a problem. Three mentioned that their child ate very little and had to be prompted to eat.

"He does not seem to put on weight much, he is within his growth and weight chart but looks thin. And he eats little and often as his stomach (belly button) area hurts and is tight"

One described that their child had frequent vomiting.

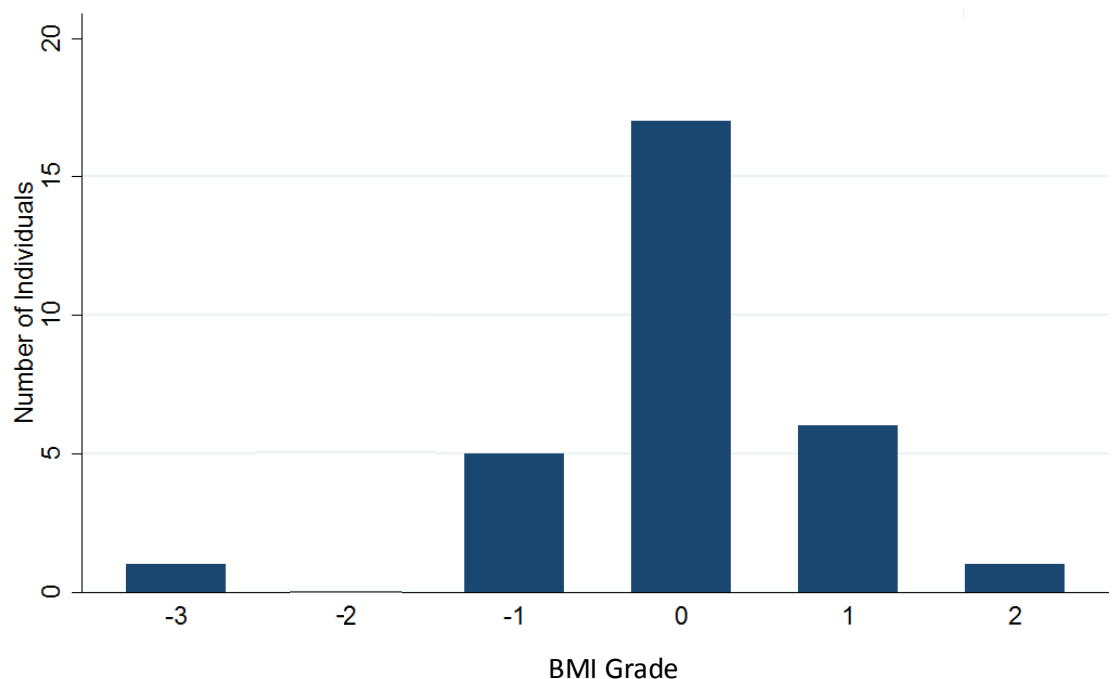
"Quite a sensitive stomach sometimes but then is sick and everything OK"

In summary, among respondents to the questionnaire, ongoing gastrointestinal symptomatology was not uncommon in childhood. Frequent pain was noted in approximately half of the children and this had prevented many of them attending school or doing normal activities. Constipation was also a common problem in many children and some required laxatives in the longer term. GORD symptoms also appeared to be troublesome in some of the children.

5.3.3ii.c Growth

Thirty-five respondents recorded their child's height and weight. These were converted into z-scores and the children's BMI grades were calculated using international standards (Cole 1990, Cole, Bellizzi et al. 2000, Cole, Flegal et al. 2007) (Figure 5.1.). The median height centile for the children was 55 (IQR 24-71). The median weight centile was 44 (IQR 19-86). Seventeen children (58%) had a normal BMI, five children had a lower than normal BMI (one had a BMI of thinness Grade 3). Seven children (23%) had a higher than normal BMI (overweight or obese).

Figure 5.1. The distribution of BMI grades among respondents



Key

- 3 Thinness Grade 3
- 2 Thinness Grade 2
- 1 Thinness Grade 1
- 0 Normal Weight
- 1 Overweight
- 2 Obesity

5.3.3ii.d Health service use

Eight children were on long-term medication (19%). Four children had been admitted to hospital in the last 12 months (9%), three of these admissions were related to gastrointestinal symptoms.

Seven children (16%) had seen a community paediatrician in the last six months. Two children (5%) were being assessed for attention deficit hyperactivity disorder (ADHD).

5.3.3iii Psychosocial outcomes

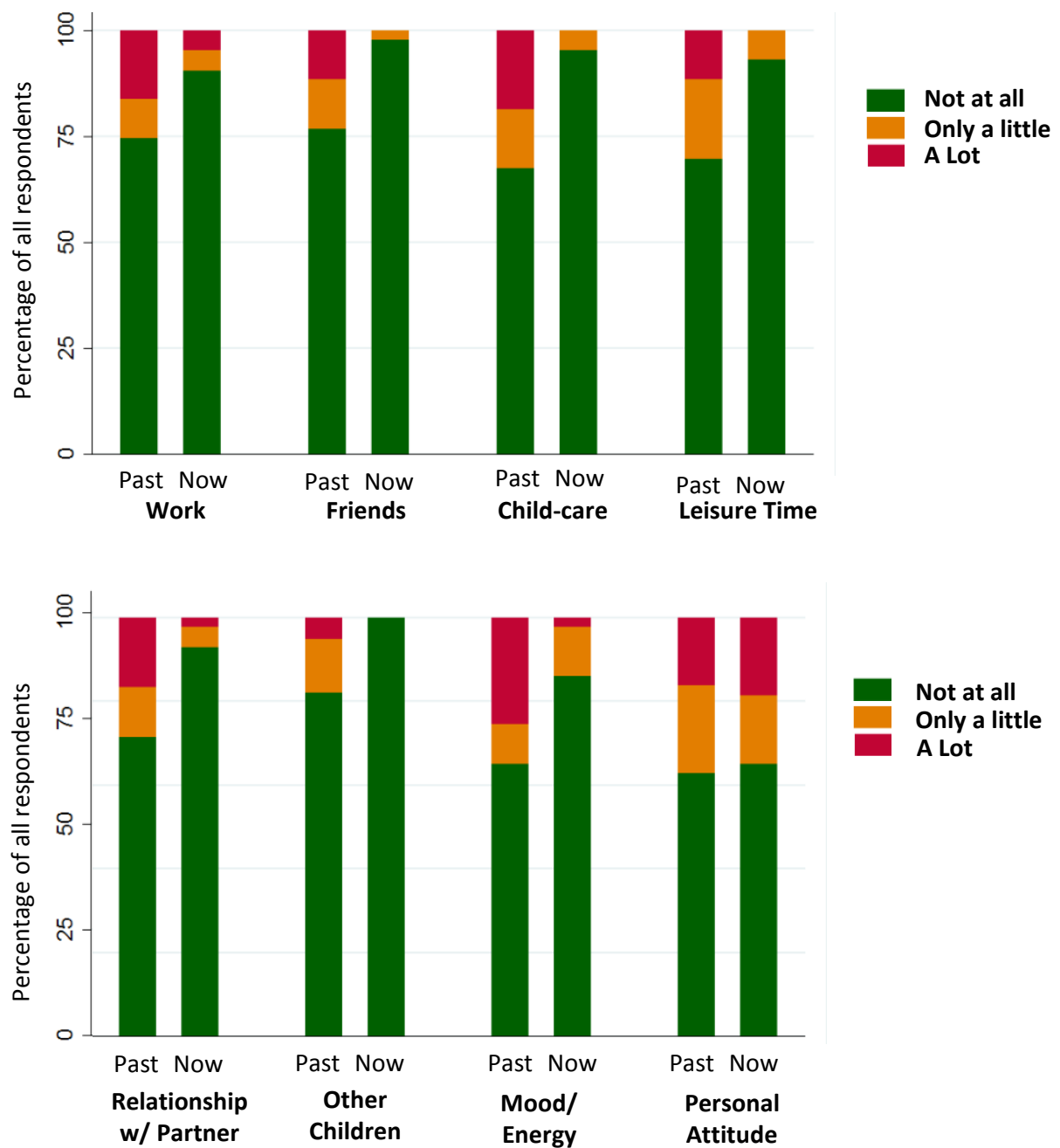
5.3.3iii.a Family impact

Care-givers were asked to rate the impact that having a child born with gastroschisis has had on the domains described in 5.2.5iii.a. The results are shown in Figure 5.2.

Most care-givers did not feel that having a child born with gastroschisis had affected any of the domains included in the assessment, either currently or in the past. Where an impact was felt, in every domain, the impact appeared to lessen with time, with fewer responding that they were affected in recent times. No respondents noted a current impact on their other children and only one, on their relationships with their friends.

15 people (35%) responded that having a baby born with gastroschisis had, in the past, affected the way they felt about themselves in a positive way. This was very similar to the number that felt this currently, 14 individuals (33%). In contrast to this the domain where the largest number of respondents had felt an adverse impact was on their mood and energy levels in the past. Fourteen (33%) individuals noted a negative impact on these and for 10 (24%), this was 'quite a lot'. Five respondents (11%) still felt this effect currently.

Figure 5.2. Responses to questions on impact of having a child born with gastroschisis on the domains shown



A free-text question was included regarding the impact that having a child with gastroschisis had had on the care-givers and their family. Eighteen parents wrote something in this section. Many of the parents who responded, reported that their child had had a short stay in hospital and had had no problems since discharge.

One parent wrote:

'Aside from the initial few weeks of treatment, annual check-ups for the first few years and the scar - gastroschisis has had no effect on us as a family, and my child is exactly like any other child. There is nothing she can't do.'

Some of the responses echoed those of the parents whose interviews are reported in Chapter Four.

Common themes included a sense of social isolation, both before and after their child was discharged home. Two examples of this are shown below.

'Life was put on hold when he was first born due to the stay in intensive/special care, isolated from the world.'

'I only attended one baby group with my child as some of the other mothers were very rude and judgmental of me and my child almost like they thought I had done something to cause him to be born with gastroschisis.'

A profound impression was gained of what a frightening and stressful experience the pregnancy and stay in hospital had been for some parents as well as the impact of this on them and their relationship. Examples of parents' responses are shown below

'It was a terrifying time. The doctors didn't think my child would make it and we almost lost him a few times.'

'I will always fear I am going to lose my child. Her transplant gives her a complicated life as she's at risk of infections. She is my whole world. It breaks my heart.'

'Father of my child wasn't ready for the problems and separated when he was 8 months old.'

'I feel at the time my baby was born, it put a lot of pressure on my relationship with my partner. I feel it also caused me to have severe post-natal depression, which meant that did not bond with my baby for a long time. In recent years I have overcome this.'

Some parents mentioned the positive effect that the experience had had on their personal attitude.

Examples include the following statements.

'Made me stronger as a person and my child and I are very close'

'My son was discharged from outpatient care at two years of age rather than anticipated five-six years and this had a very positive effect on my wellbeing and confidence.'

5.3.3iii.b Cosmetic appearance

The answers to the questions about the appearance of their child's umbilical area from care-givers are shown in Table 5.10. Responses have been analysed by method of primary closure for the two most common methods: operative fascial closure (OFC) and pre-formed silo (PFS).

None of the respondents felt that their child's umbilicus looked normal. More parents whose children had been managed by PFS thought that their child's umbilicus looked 'abnormal' than those managed by OFC although this was not statistically significant. Twelve children (30%) had had an umbilical hernia at some point. Only three children had had an operative repair of an umbilical hernia (12%). More children managed with PFS had had an umbilical hernia than those with OFC. This difference was not statistically significant.

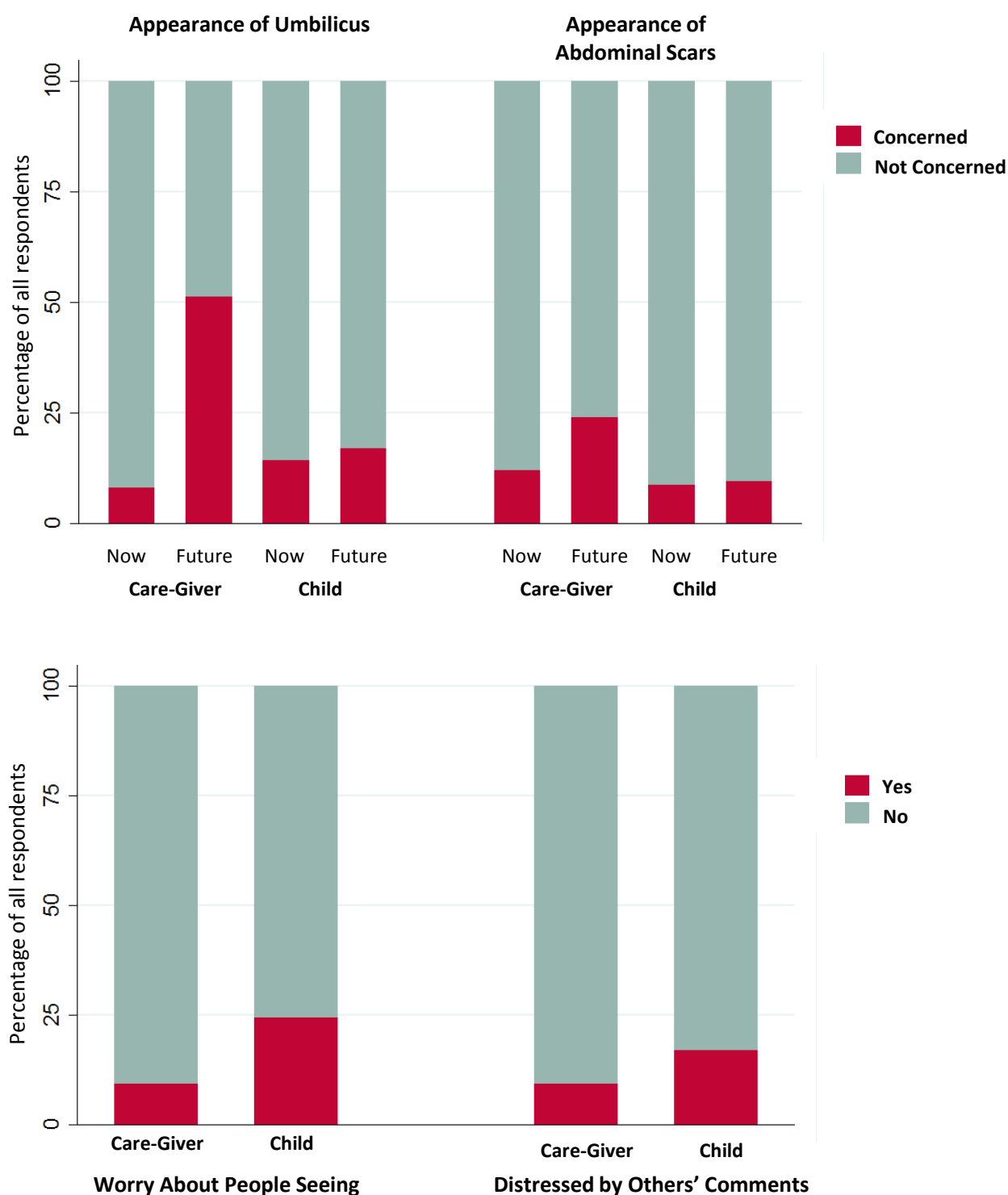
Table 5.10. Responses to questions concerning the child's umbilical area

	n (%)	OFC	PFS	p value
'Belly Button' Area:				
Looks normal	0	0	0	
Looks nearly normal	15 (36)	12 (48)	2 (17)	
Looks quite abnormal	21 (50)	10 (40)	7 (58)	
Looks very abnormal	6 (14)	3 (12)	2 (25)	
'Belly Button' Area:				
Looks normal/ nearly normal	15 (36)	12 (48)	2 (17)	0.08
Looks quite/ very abnormal	27 (64)	13 (52)	10 (83)	
Umbilical Hernia:				
Never Had	29 (70)	19 (76)	6 (55)	
Has, waiting for op	0	0	0	
Has, not waiting for op	5 (12)	1 (4)	3 (37)	
Had, been operated	3 (8)	3 (12)	0 (0)	
Had, got better	4 (10)	2 (8)	2 (18)	
Umbilical Hernia:				
Never had	29 (71)	19 (76)	6 (55)	0.25
Has/ had	12 (29)	6 (24)	5 (45)	

Care-givers were questioned about whether they were worried about the appearance of their child's umbilicus or other abdominal scars either currently or in the future. These were simple 'yes' or 'no' questions. In addition they were asked to assess whether their child was worried about these (Figure 5.3).

The majority of respondents were not concerned about the appearance of their child's umbilicus or scars and did not feel that their child was concerned. More parents were worried that the scars may cause them problems in the future. Twenty-two parents (51%) were worried about the future impact of the umbilical appearance and four of 17 with additional scars (24%) were worried about the abdominal scar appearance in the future. There was no difference noted in the frequency of future concern about umbilical appearance between parents of boys and parents of girls ($p=0.78$). Care-givers felt that children were less worried about future problems related to the umbilicus than they were (Figure 5.3).

Figure 5.3. Responses to questions on care-giver and children's feelings and experiences relating to the appearance of their abdomen



Parents were asked about the impact of the scars on themselves and their child using the following two questions.

- Do you ever worry about people seeing your child's tummy, for example when they are changing or at the beach?
- Have you ever been distressed by any comments made by other people (children or adults) about your child's belly button or scars?

Most care-givers and children were neither worried about others seeing their umbilicus or scars nor had experienced comments by others. Care givers were, however more likely to respond that their child was worried about others seeing their abdomen, (nine reporting this, 23%) or had been distressed by others' comments (seven, 18% reporting this) (Figure 5.3).

Two parents responded that their child had had an operation to improve the appearance of their umbilicus (5%).

There was a free-text box at the end of the section on cosmesis where respondents could provide more information about how they feel about how the child's abdomen looks or any experiences they had had related to this. A variety of responses were reported here with 25 (58%) care-givers filling this section. The common themes arising are summarised in Table 5.11.

5.3.3iii.c Health-Related Quality of Life – CHU-9D

The results of the parent-reported CHU-9D are shown in section 5.3.5a along with those from the children.

Table 5.11 Qualitative analysis of the free-text responses to questions on care-giver and children's feelings and experiences related to the appearance of their abdomen

Theme	Description	Example quotes from care-givers
Proud to be different	Some children liked to have a tummy that looked different from others as it made them special and different	<i>'Our daughter is proud she is special'</i> <i>'She loves her belly button because it makes her unique'</i> <i>'Lots of children have asked 'why does your belly button look like that, but my son confidently tells them it was because of an operation he had when he was a baby'</i>
The scar as a marker of a previous battle	For some care-givers the scar represented a reminder of the difficult times they had gone through when the child was a baby	<i>'Considering he was so poorly I think a slightly abnormal belly-button is a small price to pay'</i> <i>'We told our daughter that she has a specially made belly button that saved her life'</i> <i>'It makes me think back to what she went through'</i> <i>'I feel her scar is .. a reminder of how brave she was and still is'</i>
Not a big deal	Some children had experienced the curiosity of other children and taken it in their stride. Some care-givers clearly had no concerns about the appearance.	<i>'She gets asked why her belly button is different from her friends and she's been accepted the way she is by them.'</i> <i>'It did make him a little self-conscious about going swimming, but this has passed'</i> <i>'He sometimes says that classmates ask about his tummy but there has been no negativity so far'</i> <i>'His tummy is fine, not the usual look of a belly button but not far off.'</i> <i>'It is an extremely neat job!'</i>
Worries for the future	A number of care-givers expressed their concern that their child may experience problems in the future	<i>'She doesn't like it but we explain it's a special tummy button. I worry how she will feel as a teen/adult'</i> <i>'I don't think about it - it's not a problem. I worry she may become self-conscious when she's older'</i> <i>'I hope he won't get teased as he grows'</i> <i>'We worry how things are beneath the scars'</i>

5.3.3iv School

Seven children (17%) received special needs support at school. Two had a health-care plan in place (5%). Thirty-four of 43 respondents were happy for the child's teachers to be contacted. Teachers contact details were recorded by 32 respondents. Due to the small number of children for whom educational data could be obtained, a decision was made not to contact teachers with a questionnaire.

5.3.3v Parental concerns

Twenty-two responses were recorded in the free-text section where parents could report any concerns they had about their child. Several responded that they had no concerns.

'A very normal eight-year-old. Gastro has had no effect on him since he was two. He actually disbelieves us when we tell him what he went through.'

'I genuinely have no concerns. She is happy, well-adjusted, intelligent and popular among friends.'

Thirteen parents expressed concerns about their child's mental health, educational abilities or behaviour (30%). Five of these remarked on their child's poor concentration. These five were in addition to two parents who reported that their children were under assessment for ADHD.

Responses included the following:

'He doesn't seem to learn in the same way as his peers and struggles to retain information. He is a year or two behind in most areas.'

'My child finds staying still very hard. His school referred him to the educational psychologist to come and see him. The feedback I had was that he was a bright boy who needed to be more physically active during the school day. He does now fiddle with Blutac during group times on the carpet. He does move his body all of the time, even when he is absorbed in an activity.'

'She has very poor attention. This affects her school life. She has a tutor due to this. She has the same poor attention at home. She will "forget" to do as she is asked and be easily distracted. She is obsessed with cleaning her hands and will not kiss anyone - even me.'

'Struggling with school work. Lack of concentration.'

Some respondents mentioned concerns about their child's mood or anxiety levels. Examples are given below.

'She has also had a lot of anxiety and panic attacks growing up and had to be removed from nursery because of this.'

'He is a worrier and can get very frustrated.'

'He does have mood changes. Can become sad for no reason.'

A few parents mentioned concerns for their child in the future in this section.

'We worry that she may have issues with pregnancy when she is older. Also if her future children may have the same condition when they are born'

'I do worry what sort of effect it will have on her later in life: 1. will she develop any bowel problems, e.g. irritable bowel syndrome? 2. The appearance, how will it change as she gets older and grows?'

5.3.4 Child questionnaires

Forty questionnaires were received that had been completed by children. The median age at completion was eight years (IQR 8-9 years, range 7-9 years). Five of the children were less than eight years old (13%), this is the lower end of the recommended age for completion of the KIDSCREEN-52 tool. Twenty-three boys (58%) and 17 girls (42%) completed the questionnaire.

5.3.4i CHU-9D results

The scores calculated from both the parent and child responses are shown in Table 5.12. The means of these scores were directly compared between children and their parents. Although the children's scores were slightly lower, no statistically significant difference was found ($p=0.8$). The children's scores were compared to a sample of 148 school children from the UK between six and seven years-of-age (Canaway and Frew 2013). The mean of the children's utility values was slightly higher than that of the UK sample, suggesting a more favourable health status, although this was not statistically significant ($p=0.42$).

Table 5.12. Descriptive statistics of the CHU-9D results from care-givers and children

	Care Givers	Children*	p value Children vs care-givers [§]	UK Child Data ¹	p value Children vs UK child data ^{1§}
N	43	39	0.8	148	0.42
Mean	0.94	0.91		0.86	
Median	0.95	0.91		0.90	
SD	0.07	0.08		0.01	
IQR	0.89-1	0.87-0.97		0.81-0.96	
Range	-.71-1	0.69-1		0.33-1	

*One child had missing data for some of the responses and so could not be included in the analysis.

¹(Canaway and Frew 2013) [§]Two sample, two sided t-test assuming equal variance. At 95% level

5.3.4ii KIDSCREEN-52 results

All 40 children answered the KIDSCREEN-52 questionnaire. The children who answered the questionnaires scored their quality of life in every domain significantly higher, indicating a greater level of well-being, than the UK population with the exception of social acceptance and bullying where no difference was found ($p=0.08$). These results are shown in Table 5.13.

Table 5.13. Mean T-Scores for each KIDSCREEN-52 domain compared to UK normative data for children aged 8-11 years

KIDSCREEN Domain	Mean (SD) Respondents [¥]	Mean (SD) UK Population Norm [¥]	P value [§]
Physical well-being	61.1 (9.82)	50.85 (9.66)	<0.0001 [*]
Psychological well-being	56.35 (7.43)	49.67 (9.43)	<0.0001 [*]
Moods and Emotions	54.20 (9.85)	47.44 (9.05)	<0.0001 [*]
Self-perception	59.86 (9.59)	52.33 (9.73)	<0.0001 [*]
Autonomy	54.22 (10.75)	48.89 (10.49)	0.003 [*]
Parent relation and home life	56.71 (9.04)	51.39 (9.95)	0.001 [*]
Social support and peers	55.52 (10.22)	50.73 (10.18)	0.006 [*]
School environment	58.53 (10.13)	52.94 (10.28)	0.001 [*]
Financial resources	53.29 (9.53)	48.52 (9.79)	0.004 [*]
Social acceptance/bullying	48.49 (10.21)	45.09 (11.60)	0.08

[¥]T values based on the Rasch-Person-Parameter estimates

[§]Two sample, two sided t-test assuming equal variance. At 95% level

5.4 Discussion

This study represents the first childhood follow-up study in a UK national population cohort of children born with gastroschisis. A methodology for identifying participants and collecting responses from children and their parents using postal questionnaires was explored. Only 15% of parents who received a questionnaire responded, with 14% completing a questionnaire. Despite there being few differences between responders and non-responders in terms of their original birth characteristics, the low response means that affects the generalisability of the results to the population of children born with gastroschisis is questionable.

The poor response rate was not unique to this study and low follow-up rates are common to all of the gastroschisis studies shown in the tables in Appendix 10. Emma Harris who has published, with her co-authors, two regional population cohort follow-up studies of children born with gastroschisis in Western Australia, states in one publication: *‘despite intense efforts to locate and contact the families of surviving children, we were only able to recruit approximately half of the eligible children’* (Harris, Minutillo et al. 2014). This phenomenon is also not unique to neonatal surgical follow-up studies. A study published in October 2016 explored whether the use of a parent questionnaire was a cost-effective means of gathering later health-status data on ex-preterm babies (Field, Spata et al. 2016). Despite obtaining consent from over half of the potential participants before discharge from hospital and making two requests for data to parents, a disappointing response rate of 42-46%* was achieved. These authors concluded that this was not a methodology that should be pursued for the majority of families. Factors which may have affected the questionnaire response rate in the study described in this chapter are outlined in Table 5.14.

All results of this childhood outcome study must be interpreted in the context of the low response as a result are likely to be subject to reporting bias. It is clear that alternative methodologies for collecting parent and child reported outcome data from families of children born with gastroschisis need to be developed. These will be discussed further in Chapter Seven.

*These results were presented by year

Table 5.14. Potential factors contributing to low questionnaire response

Factor	Description and discussion
Impersonal nature of correspondence	Due to the fact that the materials sent to parents were created centrally, they were not able to be personally addressed to parents and could be seen by parents as originating from an unknown group of individuals rather than the hospitals that had treated them, with whom they had a relationship. Although parents were reassured that data would be anonymously reported, they may have been concerned about divulging personal information about themselves and their child to individuals that they had never met.
Sociodemographic factors	As has been described, gastroschisis is a condition associated with socio-demographic factors that do not favour response to a lengthy questionnaire, namely: young maternal age, low socio-economic status and in many cases a turbulent social set-up (see 1.1.2). Forty-two percent of respondents left school at 16 years or less, this is very similar to the number in the general population (approximately 40% in the 25-34 years age group according to the 2011 census (ONS 2011)). Although the questionnaire wording was pitched to be easily understandable, participants may have been intimidated by a long paper document (see below) when most communication will be undertaken by many of these individuals using digital media. There was variation between the response rate from different centres noted with better response rates in some potentially more affluent areas although the small number of children from each centre preclude comparison due to the small numbers involved.
Emotional response	Chapter Four has indicated the deep and lasting effect that having a baby that needed early surgery has on parents. Although this may reduce with time, as suggested by those who did respond, it is clear that memories of what may have been an extremely traumatic and difficult experience may still be fresh. This may have affected parents' willingness to participate. Three questionnaires were returned without being completed. The reasons for this are unknown but it may be due to the unwelcome emotional responses that describing their experiences and child's current condition could evoke.

Table 5.14 Continued. Potential factors contributing to low questionnaire response

Factor	Description and discussion
A lack of appreciation of the value of their contribution	A set of parents from the parent advisory group described how, as their child was well and had only had a short stay in hospital, they would not have seen the value of filling in a detailed questionnaire about them. This may have been a systematic factor affecting responses. Although a few parents responded that their children were well, many were having problems. This may affect the generalisability of the results as, for the majority of those who did not respond, their child's early diagnosis and treatment of gastroschisis may have had a minimal impact on their lives.
Questionnaire length and research fatigue	This long-term outcome study was seen as an opportunity to collect a broad range of data about the children and their parents. This meant the inclusion of many different questions and tools, some being rather lengthy. The final questionnaire was a booklet of 28 pages. This may have been too long for some of the parents with a young family to find time to complete. Questionnaire length is known to be inversely related to response rate (Edwards, Roberts et al 2007). In addition, in the current climate of quality improvement through consumer feedback, individuals are asked to complete questionnaires after the majority of transactions. This could mean that parents were not able to appreciate the value of filling in yet another questionnaire for this study. A parent of a child with gastroschisis who had a number of ongoing problems was telephoned to ask if they would be happy to review the questionnaires. They were unwilling to participate as they felt that during their child's interactions with hospital they had assisted in much teaching and research already. There was a feeling of 'research fatigue' that may have affected the response of other parents of children with complex needs.
Asking teachers	Parents were asked if researchers could contact their child's teacher for further information about them. In order to do this, they were required to ask for the teacher's consent to be contacted. Although they were not obliged to give these details, this may have been an unwelcome intrusion into their children's wider lives that may have affected their feelings about the study as a whole.

5.4.1 Summary of key results

The results of this study are summarised here with a view to describing the outcomes of those who responded in order to gain a sense of the impact that being born with gastroschisis has had on the few families that provided data. It should be noted that because of the low response, however, that the overall incidence of many of the outcomes in the population of children born with gastroschisis, remains unknown.

5.4.1i Neurodevelopment

Twenty-six percent of the children wore glasses. Estimates of the number of children in the population requiring spectacles vary between studies. A large cohort study from the UK noted that 5% of children wore spectacles at the age of seven years (Barnes M 2001). A regional cohort from Oxfordshire found that 3.9% of children between the ages of two and five years required glasses (Stayte, Johnson et al. 1990). These authors divided the children into 'high-risk' and 'low-risk', the former including all children that had stayed on a neonatal unit more than 24 hours after birth. Two percent of the high-risk children needed spectacles. The rate seen among respondents to the current study is comparable to that seen in the *EPiCure* study, a UK cohort of extremely preterm infants. At six years of age, 24% of these children wore glasses (Marlow, Wolke et al. 2005). Within the questionnaire study, the median gestation age of the children of respondents was 37 weeks (IQR 36-37 weeks) thus, they are markedly different from those in the *EPiCure* cohort with regard to risk of prematurity associated visual sequelae such as retinopathy of prematurity.

Despite 12% of children being reported to have problems hearing, the majority of these were related to 'glue ear', (the colloquial name for otitis media with effusion (OME)). The prevalence of OME has been estimated at 20% of two-year-old children in the UK although the majority of these will not be associated with hearing loss (Atkinson, Wallis et al. 2015). Many of the risk factors for OME, like the risk factors for gastroschisis, are associated with low socioeconomic status (Atkinson, Wallis et al. 2015).

The degree to which the neurosensory problems observed in the respondents' children are related to their original diagnosis or affect the entire population of children born with gastroschisis is unknown.

5.4.1ii Abdominal symptoms

Approximately half of the care-givers reported that their children had frequent abdominal pain. This appeared to be a long-standing issue in most, and in some, it had limited their participation in daily activities. Some children had on-going problems with constipation, leading to frequent soiling and the need for long-term medication. These findings are in keeping with the suggestions of other authors that some children with gastroschisis have gastrointestinal symptomatology that continues through childhood (South, Marshall et al. 2008, van Manen, Hendson et al. 2013, Harris, Minutillo et al. 2014) and may be life-long (Koivusalo, Lindahl et al. 2002).

5.4.1iii Growth

Children's weight, height and BMI were similar to that of the normal UK population of children; 23% of the children were overweight or obese. Recent UK data shows 34.1% of children in the UK were overweight or obese in the year 2015/16 (Public Health England 2017).

5.4.1iv Family impact

The most frequently reported adverse impact of having a child born with gastroschisis was on the parents' mood and energy levels in the past, with 33% responding that it had had a negative effect on these. Childcare and relationships with partners had been affected for some parents in the past. These effects, like all other negative consequences, seemed to reduce over time. It is notable that only 54% of parents were with the same partner as when their baby was born. This possibly reflects the young maternal age of the original cohort, the median being 21 years (IQR 19-25) (*unpublished data*).

These findings highlight a clear need for support for these families after discharge to ameliorate the sense of social isolation felt by some and to identify and assist mothers who have additional needs in terms of psychological or social support.

5.4.1v Cosmesis

None of the parents reported that their child's umbilicus looked normal. Sixty-four percent described it as quite, or very abnormal. More parents of children managed with a pre-formed silo responded that their child's umbilicus was abnormal than those managed with operative fascial closure although this difference was not statistically significant.

Very few parents responded that they or their children were worried about the appearance of their abdomen at present but just over half reported that they were worried about the impact this would have on their child in the future. A high degree of variation was noted in the parents and children's perceptions and experiences related to their umbilicus from children being proud to show it off to those who for whom it was a source of worry.

5.4.1vi Health-related quality of life

No difference was noted between the child and parent reported health-status. Mean scores obtained from both HrQOL tools were excellent and better than, or equal to, normative data from other children in the UK. In particular, children rated their physical well-being extremely highly despite health-related problems reported by a number of parents.

Assessing health-related quality of life and wellbeing in children and young people is a complex process that has generated much discussion and debate in the literature. Previous authors have noted age-related differences in the way children rate their social, physical and emotional well-being, meaning that this is an outcome that may vary with time (Jardine, Glinianaia et al. 2014).

Psychological well-being, additional comorbidity, culture and ethnicity may be among other factors that modulate children's responses (Jardine, Glinianaia et al. 2014, Lane, Nacion et al. 2016). Others have previously noted that disability, symptomatology or the need for frequent medical intervention do not necessarily negatively influence children's self-esteem, life enjoyment or social functioning (Dickinson, Parkinson et al. 2007, Bjornson, Belza et al. 2008).

This is due in part to the frame of reference of such individuals (not knowing any other life), a so-called "normalising self-concept" and the positive effect of having overcome adversity or previous struggle, a phenomenon seen in survivors of childhood cancer (Lavigne and Faier-Routman 1992, Stam, Grootenhuis et al. 2001, Faugli, Bjornland et al. 2009). The parental free-text responses provide additional context to this. Many of the respondents appeared to have instilled in their children a sense that they were a 'survivor of a battle' that had occurred early in their life and hence, perhaps, an appreciation of their health and abilities that other children may not necessarily have.

5.4.1vii Education and cognition

Formal assessment of educational outcomes of children born with gastroschisis was not possible in this study. Seventeen percent of the children received special needs support at school. This was not outside of the expected incidence, based on recent data from England, where approximately 14-21% of children are known to have special educational needs (Department for Education 2016).

Some parents mentioned their child's difficulties in concentration, attention and information retention. This echoes what other authors have found in children that have been managed in a neonatal intensive care environment, although previous work predominantly relates to the survivors of extreme prematurity (Samara, Marlow et al. 2008). In a recent paper from Argentina, researchers identified four children with ADHD in 38 born with gastroschisis assessed at three years of age (Giudici, Bokser et al. 2016).

Two of the respondents' children had been diagnosed or were being assessed for ADHD (5%). This proportion is not, however, outside of the normal expected incidence of 5-7% (Willcutt 2012).

5.4.2 Strengths of this study

This study represents an exploration into the use of a methodology for long-term outcome assessment of children born with congenital anomalies. As discussed in Chapter One, evaluating the long-term consequences of early surgical care is of vital importance in guiding management choices and informing parental counselling. The existence of a rigorously collected national population cohort of children born with gastroschisis who were now between seven and nine years of age provided an excellent opportunity for gathering childhood outcome data that could be mapped to information about clinical features and management practices collected around the time of the original repair.

This was the first time that childhood outcome data had been collected on a BAPS-CASS cohort and the first time national population-based longer-term outcome data had been collected on children with gastroschisis. Patient and parent reported outcomes are now an integral part of the assessment of healthcare interventions. This study attempted to collect these in a rigorous way, utilising, where possible, established and validated tools with strong psychometric data to support their use. It tested a methodology for doing so and through this process, lessons have been learned that can be taken forward in the planning of future studies.

5.4.3 Challenges encountered and limitations of this study

There were significant logistical challenges associated with collecting data on a population cohort of children that were managed in 28 different centres and where the researcher co-ordinating the study had no identifiable information about the children.

Achieving the local approvals for participating centres to act as Patient Identification Centres was a lengthy process taking approximately seven months from the time of central REC approval for all of the centres to be allowed to participate.

When local approval had been received, clinicians and research nurses were then required to identify the children from the original cohort. Where the identifiers had been kept from the time of the original BAPS-CASS study, this process was straightforward. Where this had not been done, or the folder had been lost (some hospitals had moved to new sites since the original study) this was more challenging. A number of children were not able to be identified despite extensive efforts by local teams. In some cases it took over a year to identify the children and one centre was never able to identify the previously reported children.

It might be anticipated that responses would be more likely from children experiencing on-going problems. When the birth characteristics were compared however, the only significant difference noted was the method of primary closure, suggesting that the responses were representative of the whole cohort. This difference was attributed to the fact that one of the UK centres that favoured PFS as an early management strategy sent out their forms much later than all of the others, allowing parents a shorter time-period in which to respond. Another similar centre did not send packs out at all.

5.5 Conclusion

It is clear that some children born with gastroschisis have on-going problems in the form of gastrointestinal symptomatology and a number of parents expressed concerns about their child's neurodevelopment. These findings are in accordance with those of other authors but have to be treated with extreme caution due to the low-response and high likelihood of reporting bias. What remains unknown is the frequency of these problems and what early factors may precipitate or ameliorate them.

Including the parent and child perspective in the assessment of childhood outcomes after early surgery clearly requires a different approach from the one employed in this study. Alternative methodological approaches to collecting these data will be discussed in Chapter Seven.

Chapter 6

A population-based prospective cohort study using the BAPS-CASS system to collect data about childhood clinical outcomes of children born with gastroschisis.

6.1 Introduction

In Chapter Five, a study is described that examined the outcomes of children born with gastroschisis, from a population cohort at seven to nine years of age from the perspective of the children and their parents. In this chapter the clinical outcomes of these same children as reported by clinicians at their original treating centre will be presented. This study was undertaken contemporaneously with the parent study, although the time taken for the clinical data to be collected was slightly longer, meaning that the oldest children were ten at the time that data were collected. This delay was due to the challenges faced by the clinicians who collected the data to retrieve the clinical notes and to find the time to complete the data collection forms. In this study, the children's clinical outcomes were mapped to their birth characteristics and early management in order to assess whether any risk-factors for adverse outcomes could be identified. The goal was to generate data of value in parental counselling, informing clinical management choices and will assist in the design of future surgical trials. This is the first time that childhood clinical outcomes of children born with gastroschisis have been assessed at a national population level.

6.1.1 Research questions

The main research questions that this study was designed to answer are:

- What are the clinical outcomes of children born with gastroschisis at seven to ten years of age?
- Can any factors that are associated with adverse outcomes be identified?

6.1.2 What is known about long-term clinical outcomes in gastroschisis?

As for the study described in Chapter Five, in order to inform the design of this study, a review of the literature was undertaken to identify the key clinical outcomes in gastroschisis that have previously been assessed in childhood. Concerns relating to growth, development of gastrointestinal symptoms including cow's milk protein intolerance (CMPI), and neurodevelopment are described in Chapter Five. These will not be discussed further here. The other key outcomes that were identified for these children were:

- i. Survival
- ii. The need for further medical or surgical intervention

6.1.2i. Survival

The systematic review and meta-analysis described in Chapter Two enabled the estimation of the proportion of children born with gastroschisis who do not survive to reach their first birthday as 7% (95% CI 5-10%). Few studies have assessed survival beyond this time period. Only two were identified in the literature that robustly estimated long-term survival. Both used Kaplan-Meier to predict survival in the first two decades of life. A UK regional population study using congenital anomaly register data from children born between 1985 and 2003 estimated survival in children born with gastroschisis to 20 years of age. These authors found that survival plateaued at 5 years of age, i.e. all deaths occurred before age 5 (Tennant, Pearce et al. 2010).

Another regional population-based study from New York state in the USA included children born between 1983-2006 and estimated survival to 21 years (Wang, Hu et al. 2011). The predicted survival rates from these two studies are shown in Table 6.1.

Table 6.1 Actual and predicted survival to 20/21 years in children born with gastroschisis

Author, Year, N	Cohort	5 year survival	10 year survival	15 year survival	20/21 year survival
Tennant 2010 <238*	North England	93.7 (89.2-96.4)	93.7 (89.2-96.4)	93.7 (89.2-96.4)	93.7 (89.2-96.4)
Wang 2011, 777	New York State	85.5 (82.8-87.8)	Not reported	84.8 (82.0-87.2)	81.7 (74.0-87.3)

Data are % (95% CI) *The number of infants with gastroschisis was not given in this publication, 238 represents all live born infants with an abdominal wall defect (including infants with exomphalos). Survival rates refer to children with gastroschisis alone.

Although their confidence intervals overlap, the figures generated from these two studies vary slightly and may reflect differing characteristics of the populations included, and for those in New York, their access to affordable healthcare.

6.1.2.ii The need for further medical or surgical intervention.

Studies reporting outcomes relating to readmission to hospital, Reoperation and adhesive bowel obstruction (ASBO) in children born with gastroschisis are shown in Table 6.2. Studies describing management of undescended testis (UDT) in boys with gastroschisis are shown in Table 6.3. The numbers included in all of these studies are small, none include more than one hundred children and only one is a prospective population cohort study. Harris et al (2014) prospectively followed-up a regional population from Western Australia, however, the number of children they followed up from five years of age was only 50.

Table 6.2. Long-term outcomes related to the need for further medical or surgical intervention in children born with gastroschisis in the published literature.

1st Author, Year, Institution, Location, Study type	Length of follow-up	Number of children included	Outcomes assessed	Key findings
Swartz , 1986, Portland, Oregon, USA MI AC	6m-16yrs	92/104 Children born with gastroschisis 36 were > 5yrs	• Additional surgery	• 12% required additional surgery
Davies 1997, Leeds, UK SI	12-23yrs,	23/33 survivors	• Additional surgery	• ASBO is an uncommon, late complication
South 2008, North Carolina, USA SI	16-24m Mean 20m	17/24 survivors	• Readmission	• 53% readmitted after initial discharge
van Eijck 2008, Nijmegen, Netherlands SI RC	5 days -32.5 years	55 infants and children	• ASBO	• 25% developed ASBO
van Manen 2013 Alberta, Canada SI PC	17-44m Median 20m	39/61 followed up	• Surgical intervention	• 26% had later surgery related to their original gastroschisis repair
Harris 2014, Perth Australia RPopn PC	Children >5yrs	50/99 survivors completed questionnaires	• Surgical intervention	• 54% had additional surgical intervention • 20% had ASBO
Giudici 2016, Buenos Aires, Argentina, PC	6 yrs	62 survivors 54 assessed at 1yr	• Readmission/ re-intervention	• 30% readmitted by first birthday • 9% had re-intervention by first birthday
Tullie 2016 London, UK SI RC	10m-8 yrs	50 survivors with complete data	• Umbilical hernia	• 22 (44%) developed umbilical hernia.
Risby 2016 Odense, Denmark SI RC	7-19 years	71 children 40 survivors consented for follow up (62.5%)	• Survival • ASBO • Hospital Admission	• 9.9% mortality • 30% developed ASBO, not related to number of initial operations • 40% readmitted with gastrointestinal symptoms

SI- Single institution. MI- Multiple Institution. PC: Prospective cohort AC: Ambispective cohort RC: Retrospective Cohort R Popn: Regional Population

ASBO: Adhesive small bowel obstruction

Table 6.3. Long-term outcomes related to undescended testes in boys born with gastroschisis in the published literature.

1st Author, Year Location, Study Type	Length of Follow-Up	Number of boys included	Outcomes assessed	Key findings[¥]
Hill 2011 Atlanta USA SI RC	1-21 years	62 boys, 23 (37%) had UDT 31 testes were undescended	• Operations for UDT and testicular atrophy	• 12/31 UDT managed with orchidopexy (39%). • 2/31 (9%) were removed (orchiectomy) • 8/12 operated testes were normal at follow up (67%)
Lawson 2001, Newcastle, UK SI RC	2-12 years	51 boys, 16 (31%) had UDT 20 testes were undescended	• Operations for UDT and testicular atrophy	• 6/20 UDT managed with orchidopexy (30%). • 3/20 were removed (orchiectomy) (15%) • 1/6 atrophied (17%)
Yardley 2012, Liverpool, UK SI RC	2 years	79 boys, 25 (32%) had UDT 35 testes were undescended	• Operations for UDT and testicular atrophy	• 15/35 had or were awaiting operative management (43%) • 4/9 having orchidopexy atrophied after surgery (44%)

SI: Single institution RC: Retrospective Cohort UDT: Undescended testis [¥]All authors discuss the number of operations per UDT at birth rather than per child

6.1.3 Childhood outcome assessment in this study

The outcomes assessed in this study were identified through the review of the literature described above and were defined *a priori* based on the clinical experience of the author, and consultation with the BAPS-CASS steering group, two paediatric gastroenterologists and parents of the children born with gastroschisis from the parent advisory group described in 3.2.5 (Table 6.4). The incidence of the given outcomes within the population as a whole were described and some were assessed in a comparative way between pre-defined sub-groups (Table 6.4). Three severe composite adverse outcomes were assessed (Table 6.5).

Table 6.4 Childhood clinical outcomes assessed in this study

Outcome	Type of analyses	Predictors explored
Death	Descriptive and comparative	• Gestational age • Birthweight • Ethnicity • SGA • Simple vs complex • Type of closure (simple only)
Regular use of parenteral nutrition more than one-year after initial surgery	Descriptive and comparative	• Simple vs complex • Type of closure (simple only)
Readmission	Descriptive and comparative	• Simple vs complex • Type of closure (simple only)
Reoperation (any)	Descriptive and comparative	• Simple vs complex • Type of closure (simple only)
Adhesive obstruction	Descriptive and comparative	• Simple vs complex • Type of closure (simple only) • Type of fascial closure (sutured vs sutureless)
Umbilical reoperation • Any • Umbilical hernia repair • Umbilicoplasty[†]	Descriptive and comparative	• Type of closure (simple only) • Type of fascial closure (sutured vs sutureless)
Severe sequelae of intestinal failure	Descriptive and comparative	• Simple vs complex • Type of closure (simple only) • Days of parenteral nutrition (ROC analysis)
Need for intestinal augmentation (Table 6.5)	Descriptive and comparative	• Simple vs complex • Type of closure (simple only) • Days of parenteral nutrition (ROC analysis)
Any severe outcome (Table 6.5)		• Simple vs complex • Type of closure (simple only)
Neurological impairment	Descriptive and comparative	• Simple vs complex
Gastrointestinal dysfunction • CMPI • GOR • Constipation • Abdominal pain • Sequelae of IF	Descriptive only	
Groin surgery • Operation for UDT • Inguinal herniotomy	Descriptive only	
Growth	Descriptive only	

SGA: Small for gestational age, <10th percentile for birth-weight at a given gestational age

[†] A cosmetic operation to the umbilicus ROC: Receiver operating characteristics

UDT: Undescended testis CMPI: Cows' milk protein intolerance GOR: Gastro-oesophageal reflux

IF: Intestinal failure

Table 6.5 Severe composite outcomes assessed in this study and their definitions

Composite Outcome	Definition
Need for intestinal augmentation	• Bowel transplant or bowel lengthening procedure.
Severe sequelae of intestinal failure	• Death due to a complication of intestinal failure • Liver or bowel transplant • Bowel lengthening procedure
Any severe outcome	• Severe sequelae of intestinal failure plus death from any cause

6.2 Methods

6.2.1 Study design

This was a national population cohort study using data from hospital records to assess the childhood clinical outcomes of children born with gastroschisis.

6.2.2 Research ethics approval

Conduct of this study was authorised as an amendment the previous ethical approval for the BAPS-CASS studies which was received from the London Research Ethics Committee ref: 12/SC/0416.

6.2.3 Case identification

All children from the cohort who were reported by centres in the British Isles were eligible for inclusion. As in the study described in Chapter Five, children from the Republic of Ireland were excluded. Centres were provided with data-sheets containing a list of the infants known to have been reported from the original cohort represented by their anonymous four-digit BAPS-CASS identifier as described in 5.2.3 and shown in (Appendix 11).

6.2.4 Data collection

Clinicians were provided with a data collection form (DCF) for all children from the cohort known to have survived beyond one year. This form is included as Appendix 19. On this form, they recorded information from the hospital records (Table 6.6). No data were requested from health-care professionals outside the specialist centre where the children were originally reported from.

Table 6.6 Domains covered on the data collection form

Domain	Areas covered
Hospital admissions	• Episodes of bowel obstruction • Surgical procedures • Other hospital admissions
Gastrointestinal function and nutrition	• Cow's milk protein intolerance (CMPI) • Parenteral nutrition (PN) use • Sequelae of intestinal failure ○ Liver disease associated with PN ○ Nutritional deficiency ○ Bacterial overgrowth ○ Kidney stones • Gastro-oesophageal reflux disease (GORD) • Constipation • Abdominal pain
Neurological impairment	• Hearing impairment • Visual impairment • Motor impairment • Developmental delay
Growth	• Height and weight measurements
Outpatient visits	• Length of paediatric surgery follow-up • Gastroenterology • Other specialities seen
Survival	• Timing and cause of death

Completed data collection forms were posted by clinicians to the central administrating office in the NPEU in Oxford. As in the other cohort studies described within this thesis, most questions were closed and required a tick-box answer. Where free-text answers were required, the author developed a coding manual.

Following coding, the data were double-entered into a customised database at the NPEU and any discrepancies between the first and second entries were addressed. Information about life status and date of death were obtained by clinicians from the *NHS Spine* or, for children not born in England, using the other sources described in Chapter Five.

6.2.4i. Additional data sources

Data on outcomes were collected from three sources for this study. These were:

- a. **The birth form.** This refers to the early data collection form that had been sent to clinicians after they had first reported a case to the cohort study of 2006-2008. This was completed by clinicians at varying lengths of time after first presentation, including in some cases, over a year after this date. All infants had a birth form completed.
- b. **The one-year form.** This was sent to clinicians one-year after the date of presentation. Not all of the original cohort had a one-year form completed (Figure 6.1).
- c. **The long-term outcome form** (Appendix 19). The new DCF that was sent to clinicians to collect data for this childhood study. Not all of the original cohort had a long-term outcome form completed (Figure 6.1).

Free-text searches of all three forms were performed in order to ensure complete ascertainment on all of the outcomes of interest. In addition, when the incidence of autistic spectrum disorder was assessed data from the parent questionnaire were used in addition to the clinician DCF.

6.2.5 Analysis

6.2.5i Software and statistical analysis

Statistical analyses were undertaken using *Stata 13 SE*.

6.2.5ii Descriptive analyses

A number of descriptive analyses were performed and continuous data were summarised using medians and IQR. When calculating the incidence of binary outcomes, the variable length of follow-up on infants from the birth cohort presented a challenge. All three data collection forms described above, contained information on some of the outcomes that were investigated in this study. In order to deal with the variable length of follow-up for different infants, two approaches were taken. These were:

- i. Calculation of the ‘maximum and minimum’ estimates of incidence of infants experiencing a given outcome
- ii. Calculation of the incidence rate of a given outcome using survival time analysis methodology

i. Calculation of the ‘maximum and minimum’ incidence estimates

If an outcome had been reported on any of the three forms it was counted in the numerator of the calculation of both the ‘minimum’ and ‘maximum’ estimated incidence of that outcome. What varied between these two estimates, was the denominator. For the ‘minimum’ incidence estimate, this was the total number of eligible infants in the whole cohort regardless of follow-up duration. The denominators for the calculation of minimum incidence varied slightly according to the outcome assessed, because of eligibility. For example; infants that died before first discharge from hospital were ineligible to be readmitted and were excluded from the denominator (Table 6.7). For the ‘maximum’ estimate, the denominator was the total number of infants that experienced the outcome at any time point combined with the number of other infants with a long-term outcome data collection form completed. The outcomes assessed and the denominators used to calculate the maximum and minimum estimates are shown in Table 6.7. Incidence estimates for these outcomes are reported in the text as a minimum-maximum range.

Table 6.7 Denominators for the maximum and minimum incidence estimates for outcomes assessed in this study

	‘Minimum’ estimation of incidence denominator	‘Maximum’ estimation of incidence denominator
Survival	Total number of infants in original cohort	Number of infants with long-term data on vital status
ASBO	Total number in cohort excluding those who died ≤ 28 days	Total number with the specified outcome recorded on any data collection form plus all other children with long-term outcome form completed
Bowel obstruction	Total number in cohort excluding those who died ≤ 28 days	
Readmission	Total number in cohort excluding those who died before first discharge	
Further operation	Total number of infants in original cohort	
Operation for UDT/ Any umbilical operation	Total number of infants in original cohort excluding those who died before one year after presentation	
PN at 1 year	Total number of infants in original cohort excluding those who died before one year after presentation	
Intestinal augmentation	Total number of infants in original cohort excluding those who died ≤ 28 days	
Severe IF sequelae	Total number of infants in original cohort	
Any severe outcome	Total number of infants in original cohort	

ASBO: Adhesive bowel obstruction Bowel obstruction: Acquired bowel obstruction from any cause

UDT: Undescended testis PN: Parenteral nutrition IF: Intestinal failure sequelae

For outcomes that were only able to be assessed using data from the long-term outcome form, the denominator was the number of infants with complete data for that outcome on the long-term form. These outcomes were as follows:

- Neurodevelopment,
- Gastrointestinal outcomes: cow's milk protein intolerance liver impairment, nutritional deficiency, bacterial overgrowth, GORD, abdominal pain and constipation.

ii. Incidence rate

The incidence rate of a given outcome was calculated using survival time analysis methods. Here the numerator was the occurrence of the outcome as recorded on any data collection form. The denominator in this instance, was time. For each infant in the cohort, the person time at risk was calculated. For all infants the 'entry' date was the date of gastroschisis reduction. The 'exit' date was the date on which the given adverse event occurred, (date of death in survival analyses), the date on which the last form was completed or the date of death if the infant had died before experiencing the adverse event. This gave a time denominator in days. This was divided by 1826.25, (365.25 x 5) to give the five-year specific incidence rate. This was multiplied by 1000 to give the five-year specific incidence rate per 1000 person years at risk (PYAR).

Five years was chosen as the time period for incidence rate calculation as this was the period for which most outcome data were available, it was more clinically meaningful than the one-year incidence rate and this is the time period used by the World Health Organisation (WHO) for assessing one of its key international development indicators, childhood mortality (WHO 2017).

6.2.5ii.a Other definitions used in this study

Height and weight centiles and SGA

Centiles for height and weight were derived using normative data from the LMS growth study (Cole 1990). Small for gestational age (SGA) was defined as a birth weight below the 10th centile.

Intestinal failure associated liver disease

Clinicians were asked to report whether the children had ever had liver disease associated with parenteral nutrition (PN) use. This was defined as '*raised serum alkaline phosphatase and gamma glutamyl transferase 1.5 times above the normal reference range for more than six weeks*'. This is the definition of 'Type 1, Early intestinal failure associated liver disease' used by The British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN 2009).

Simple and complex gastroschisis

The definition for simple and complex gastroschisis used in this study was that given in Chapter One, proposed by Molik et al in 2001. In order to ensure correct allocation to each outcome group, additional information on infants of 'unknown' status from participating centres was sought and free-text searches of key-words in the original birth-form provided additional information to aid classification.

6.2.5iii Comparative analyses

Differences between the children with follow-up data were compared using Chi-squared and Fisher's exact tests where appropriate, to assess differences in proportions, and the Mann Whitney test and Wilcoxon signed rank test were used to identify differences between continuous variables. The effect of infant characteristics on a number of outcomes was assessed using survival time analyses. Equality of 'survivor' function was tested using the log-rank test and hazard ratios between different groups were calculated using Cox proportional hazards regression analysis.

All comparisons that assessed the outcomes of children by type of surgical closure included children with simple gastroschisis only.

6.2.5iiv. Further analyses

Receiver operative characteristic curves (ROC) were generated to assess the relationship between duration of parenteral nutrition and severe composite outcomes relating to intestinal failure described in Table 6.5.

6.3 Results

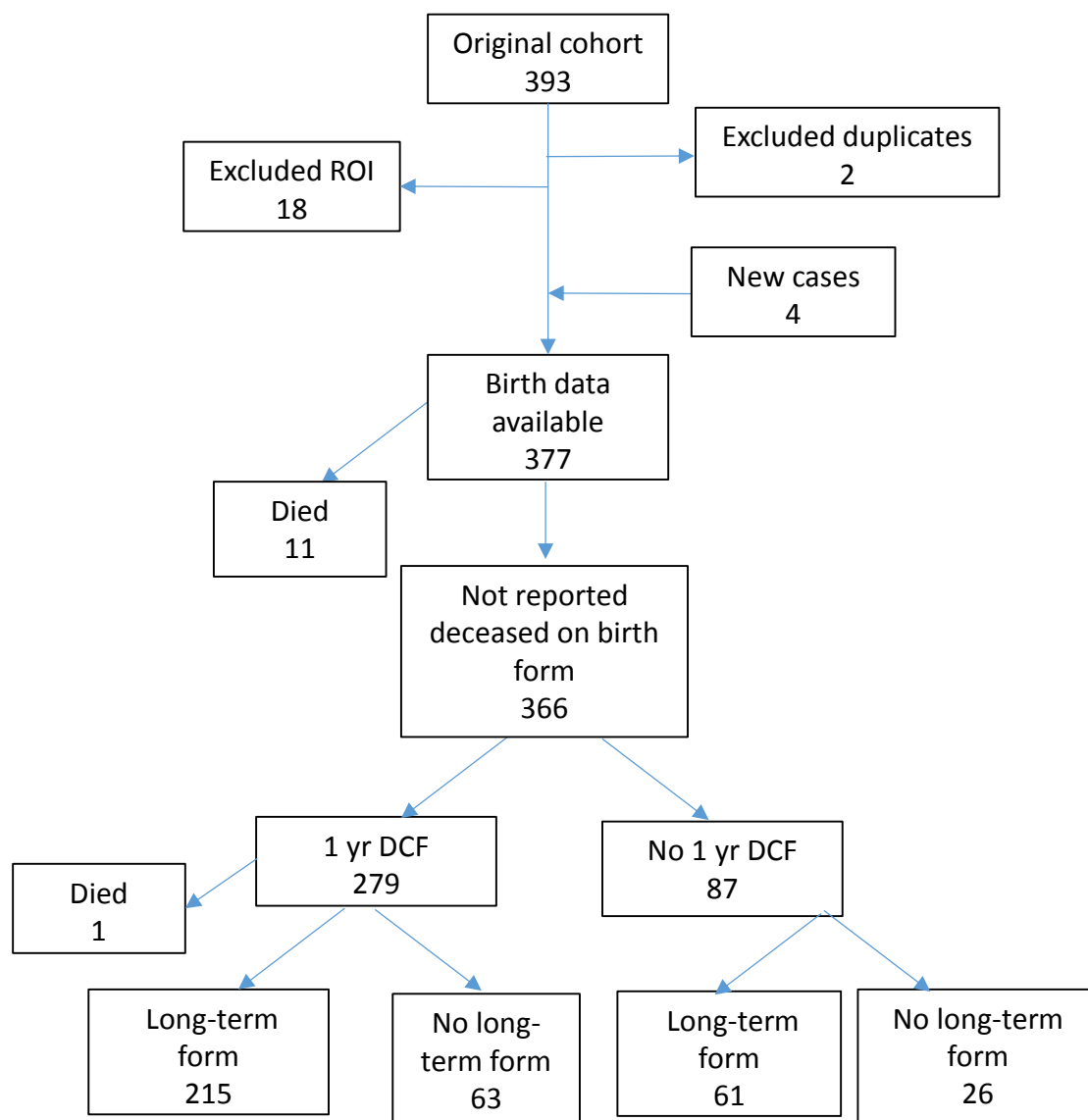
6.3.1 Case ascertainment and completeness of follow-up

Figure 6.1 shows the case ascertainment for this study and the completeness of follow-up. Two reports were found to be duplicates that had not been identified in the original cohort and were excluded. Four additional infants who fitted the original case definition were identified by reporting centres and included. Of 365 eligible infants who were not known to have died before their first birthday, 276 had data collection forms returned (76%). Data on survival status in sixteen other children were also included as these children had been traced and found to be alive using the *NHS Spine* for the study described in Chapter Five. No data collection forms were received for these children, however. Of the 89 infants without long-term outcome data, 63 (71%) had one-year outcome data available and 26 (29%) did not. Thus, of the total cohort of 377 infants:

- 12/377 (3%) were reported as deceased on birth or one-year forms
- 63/366 (17%) had follow-up to one year only
- 26/377 (7%) had birth data only.
- 292/377 (77%) had long-term follow-up data on survival
- 276/365 (76%) survivors had complete long-term outcome data collection forms

The characteristics of the infants from the original cohort with a completed data collection form returned were compared to those without (Table 6.8). No significant differences were noted between those that had a form completed and those that did not.

Figure 6.1 Completeness of follow-up of all infants in the cohort



ROI: Republic of Ireland
DCF: Data collection form

Table 6.8 Characteristics of those with a long-term data collection form compared with the rest of the eligible birth cohort.

Characteristic N=365	Data collection form returned n (%)	No data collection form returned [†] n (%)	p value
Number (%) with follow-up DCF	276 (76)	89 (24)	
Ethnicity of mother:			
White	239/265 (90)	79/85 (93)	0.52
Non-White	26/265 (10)	6/85 (7)	
Sex of child:			
Male	131/276 (47)	42/88 (43)	0.48
Female	144/276 (53)	58/88 (57)	
Maternal age (yrs)[‡]			
Median (IQR)	30 (28-34)	29 (28-34)	0.61
Children's age (yrs)^α			
Median (IQR)	9 (9-9)	9 (8-9)	0.84
Birthweight (g)			
≥ 2500	116/274 (42)	34/88 (39)	0.54
< 2500	158/274 (58)	54/88 (61)	
Gestational age (wks)			
< 37	124/275 (45)	41/88 (47)	0.81
≥ 37	151/275 (55)	47/88 (53)	
Type of gastroschisis			
Simple	241/275 (88)	75/84 (89)	0.97
Complex	34/275 (12)	9/84 (11)	
Initial management			
Operative fascial closure	117/273 (43)	39/89 (44)	0.19
Pre-formed Silo	103/273 (38)	26/89 (29)	
Custom silo	22/273 (8)	13/89 (15)	
Ward	13/273 (5)	2/89 (2)	
Primary patch	7/273 (3)	2/89 (2)	
Other primary	9/273 (3)	5/89 (6)	
Other staged	1/273 (<1)	0/89 (0)	
Unknown closure	1/273 (<1)	2/89 (2)	
Type of closure			
Operative fascial closure	117/220 (53)	38/65 (60)	0.40
Pre-formed silo	103/220 (47)	26/65 (40)	
Duration of PN			
≤ 28 days	145/236 (55)	52/82 (63)	0.20
> 28 days	118/263 (45)	30/82 (37)	
Intestinal Failure Associated Liver Disease (IFALD)[§]			
Yes	13/214 (6)	4/63 (6)	0.62
No	201/214 (94)	59/63 (94)	

[†]Excludes infants who were known to have died at study commencement (n=12)

[‡]Calculated by 2016 minus the mother's year of birth ^αChild age on 1.12.16

[§]As reported by clinicians on the birth form

6.3.2 Survival

Seventeen children are known to have died (min 5-max 6%), (Table 6.9). All deaths occurred within the first four years after birth. Nine deaths were within, or close to a month of birth (0-32 days), one more infant died before their first birthday and the remaining seven children died before their fourth birthday. Five of the ten deaths that occurred before one year were due either to sepsis, complications of prematurity or severe comorbidity. The other five were related to bowel ischaemia which was caused by either *in-utero* compromise, perinatal events or surgical management. Of the seven later deaths, four were related to complications of short-bowel and one was caused by an acute intra-abdominal catastrophe due to a problem associated with their original diagnosis of gastroschisis. The cause of the remaining two deaths is unknown.

Table 6.9 shows the univariable analysis examining the relationship between demographic factors and death. No significant associations were found.

Table 6.9 Univariable analysis of demographic factors associated with death of children born with gastroschisis

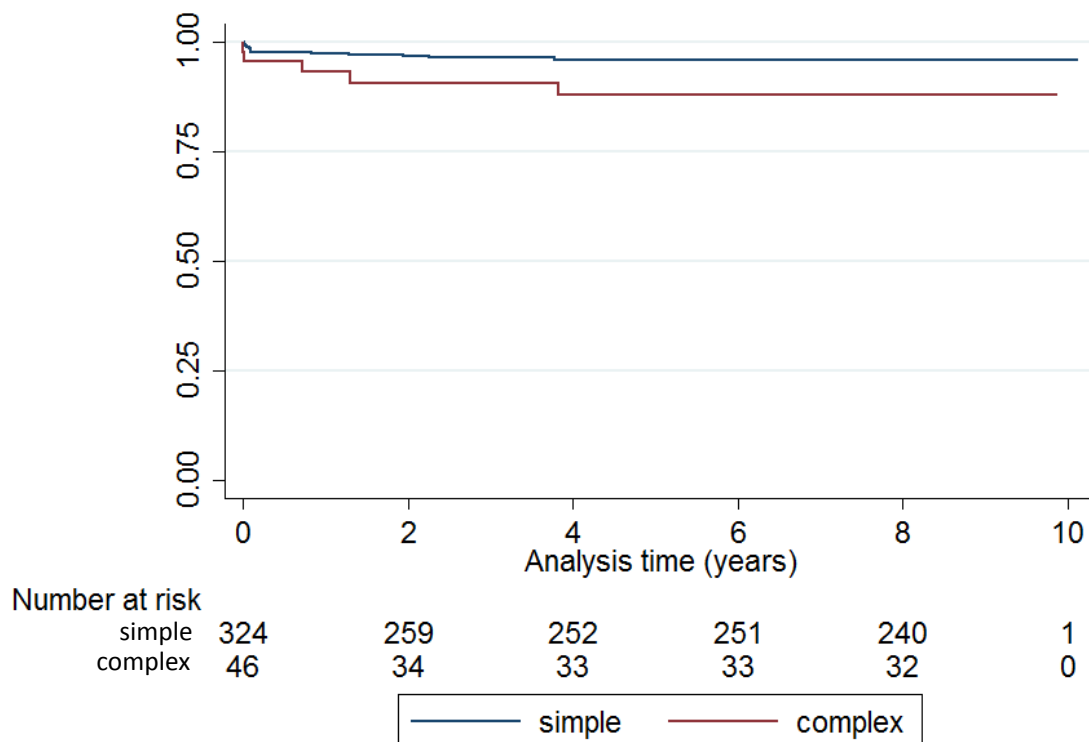
	n/N* (%)	Log rank p value	5 year specific IR/ 1000 PYAR (95% CI)	Hazard ratio (95% CI)
Gender				
Male	5/141 (4)	0.17	23 (9-54)	2.01 (0.71-5.72)
Female	12/151 (7)		45 (26-79)	
Ethnicity				
White	15/249 (6)	0.21	36 (21-59)	N/A
Non-white	0/27 (0)		N/A	
Term				
Pre-term	9/139 (6)	0.41	39 (20-76)	0.67 (0.24-1.79)
Term	7/163 (4)		27 (13-58)	
BW				
<2500	11/174 (6)	0.41	39 (21-70)	0.64 (0.22-1.86)
≥2500	5/122 (4)		25 (10-6)	
SGA				
Yes	6/80 (8)	0.28	43 (19-96)	0.56 (0.20-1.60)
No	9/210 (4)		24 (12-45)	

* Maximum estimate SGA: Small for gestational age (<10th percentile for birth-weight)

IR: Incidence rate PYAR: Person years at risk

Five of the children born with complex gastroschisis died (5/46, 11%). Twelve of the children who were born with simple gastroschisis died (12/325, 4%). Figure 6.2 shows Kaplan-Meier survival time curves comparing the infants with simple and complex gastroschisis. This difference was significant on log-rank testing $p=0.02$ (Table 6.10).

Fig 6.2 Kaplan-Meier graph showing survival of infants with simple vs complex gastroschisis



Four children with simple gastroschisis died after initial management with OFC and four after PFS. Three of the four in the PFS group died because of bowel ischaemia or inadequate bowel length after early gastrointestinal complications. None of the four deaths in the OFC group were related to either of these complications

Table 6.10 shows the relationship between death and other key outcomes in children born with simple and complex gastroschisis as well as children with simple gastroschisis managed initially with either a PFS or OFC.

Table 6.10 Assessment of the influence of simple vs complex and type of closure on outcome

	All infants n (%; 95% CI)	5 yr specific IR/ 1000 PYAR (95% CI)	Simple* n (%)	Complex* n (%)	Log rank p value	Hazard ratio (Complex) (95% CI)	OFC* n (%)	PFS* n (%)	Log rank p value	Hazard ratio (PFS) (95% CI)
	Minimum estimate Maximum estimate									
Death	17/377 (5, 3-7) 17/304 (6, 3-9)	30 (20-50)	12/265 (5)	5/38 (13)	0.02	3.11 (1.09-8.82)	4/116 (3)	4/98 (4)	0.81	1.18 (0.30-4.74)
ASBO	28/370 ^β (8, 5-11) 28/283 (10, 7-14)	48 (32-72)	19/246 (8)	7/35 (20)	0.02	2.78 (1.10-7.00)	10/105 (10)	5/96 (5)	0.44	0.65 (0.22-1.95)
Bowel obstruct^{n‡}	41/370 ^β (11, 8-15) 41/283 (15, 11-19)	82 (60-112)	30/246 (12)	10/35 (29)	0.002	2.90 (1.41-5.95)	12/105 (11)	10/96 (10)	0.99	0.99 (0.43-2.30)
Readmisⁿ	122/367 ^δ (33, 28-38) 122/278 (44, 40-52)	340 (284-406)	101/243 (42)	21/34 (62)	0.003	2.01 (1.25-3.23)	38/104 (37)	44/95 (46)	0.12	1.37 (0.92-2.06)
Further operation	169/377 (45, 40-50) 169/307 (55, 49-61)	529 (455-616)	123/261 (47)	44/44 (100)	<0.0001	6.46 (4.44-9.40)	41/108 (38)	52/103 (50)	0.01	1.69 (0.01-1.12)

* Estimations based on the 'maximum' incidence estimate IR: Incidence rate PYAR: Person years at risk [†]From univariable Cox regression [‡]Acquired bowel obstruction
from any cause Readmisⁿ: Readmission to hospital ^βChildren who died <28 days excluded from the denominator
^δ Infants who died before discharge excluded from the denominator

6.3.3 Inpatient episodes

The following outcomes relating to inpatient episodes are described in this section:

- i. Hospital readmission for any cause
- ii. Any surgical intervention after initial closure with a specific focus on;
 - a. Surgery for bowel obstruction
 - b. Surgery for inguinal hernia, undescended testes, umbilical hernia or scar cosmesis

Operative interventions for intestinal failure or its sequelae are discussed in 6.3.4.

6.3.3i Hospital re-admission

One-hundred and twenty-two infants were re-admitted after their initial discharge (min 33- max 44%) (Table 6.10). Readmissions were either due to medical or surgical causes, the latter being elective, such as inguinal or umbilical hernia repair, stoma closure or operation of undescended testis or emergency, such as bowel obstruction or removal of infected central venous line. Sixty-four of 276 infants with long-term data were admitted for a medical indication (23%). The most common cause for this was gastrointestinal upset which included: vomiting, diarrhoea, constipation, rectal bleeding, abdominal pain and constipation. This affected 34 children (34/276, 12%). Significantly more infants with complex gastroschisis were readmitted (21/34 vs 101/243 $p=0.003$).

6.3.3ii Further operative intervention

One-hundred and eighty-one children had another operation following their fascial closure procedure, (min 48%-max 59%). Only two of the children born with complex gastroschisis did not have a second operation; one had died shortly after birth. Nearly twice as many who were born with complex than simple gastroschisis had another operation ($p=0.0004$) (Table 6.10). Those who were treated initially with PFS were more likely to require a further operation ($p=0.01$).

6.3.3ii.a Adhesive bowel obstruction (ASBO)

Twenty-eight infants had an episode of bowel obstruction related to adhesions (8-10%). Two had more than one episode of adhesive obstruction. ASBO was more common among children born with complex gastroschisis ($p=0.04$) and no difference was noted in children born with simple gastroschisis managed with a pre-formed silo compared with those managed with OFC ($p=0.23$) (Table 6.10).

A sensitivity analysis to assess the incidence in ASBO in those managed with a sutureless procedure, compared with sutured fascial closure revealed no difference, although the numbers were smaller, limiting statistical power (3/47 (6%) sutureless, 16/187 sutured (9%), ($p=0.71$)). The hazard ratio for sutured closure, compared to sutureless was 1.25 (95% CI 0.37-4.32).

6.3.3ii.b Acquired bowel obstruction from any cause

The incidence of acquired bowel obstruction from any cause was min 11%- max 15% and the incidence was significantly higher in children born with complex gastroschisis ($p=0.048$), (Table 6.10). Causes, other than adhesions, included strictures (both anastomotic and following necrotising enterocolitis), volvulus[†], milk-curd obstruction[‡] and intussusception[‡].

6.3.3ii.c Other operative intervention

Inguinal surgery

Fifteen children had an operation for inguinal hernia (min 4-max 5%); 9% of boys and 2% of girls (12/133 and 3/146 respectively).

Fifteen boys were known to have had an operation for undescended testis (9-11%). The median age at operation for undescended testis was 23 months (IQR 18 months-34 months).

[†] **Volvulus:** twisting of the bowel [‡] **Milk-curd obstruction:** blockage of the bowel by solidified milk

[‡] **Intussusception:** pathological telescoping of a segment of bowel inside an adjacent segment

Umbilical surgery

Thirteen children had undergone surgery for an umbilical hernia (min 3-max 5%) at a median age of 40 months (IQR 20 months-54 months). Table 6.11 shows the ‘umbilical outcomes’ by method of closure. Twelve children were known to have had an operation to improve the appearance of their umbilicus (4%) at a median age of 43 months (IQR 16 months-55 months).

There was some limited evidence that the use of PFS was associated with later cosmetic operation on the umbilicus. A sensitivity analysis looking at the mode of fascial closure additionally showed that the incidence of umbilical hernia was significantly more common in those closed without sutures (including those who had a primary or a secondary patch) ($p=0.03$)(Table 6.11).

Table 6.11 Umbilical outcomes by method of closure

	All infants* n (%)	5 year specific IR/ 1000 PYAR (95% CI)	OFC* n (%)	PFS* n (%)	Log rank p value	Hazard ratio (PFS) (95% CI)
Umbilical Hernia	13/276 (5)	25 (15-44)	3/103 (3)	7/94 (7)	0.13	2.84 (0.73-10.99)
Cosmetic operation	12/276 (4)	23 (13-10)	2/103 (2)	7/94 (7)	0.05‡	4.29 (0.89-20.65)
Any umbilical surgery	19/276 (7)	37 (23-58)	4/103 (4)	10/94 (11)	0.08	2.77 (0.86-8.95)
			Sutured n (%)	Sutureless n (%)	Log rank p value	Hazard ratio (Sutureless) 95% CI
Umbilical Hernia			6/182 (3)	5/50 (10)	0.03	3.49 (1.07-11.08)
Cosmetic operation			7/175 (4)	4/50 (8)	0.16	2.35 (0.69-8.04)
Any umbilical surgery			11/182 (6)	6/50 (12)	0.09	2.29 (0.85-6.20)

*Maximum estimate IR: Incidence rate PYAR: Person years at risk ‡Simple only †p=0.047

6.3.4 Gastrointestinal function and nutrition

6.3.4i. Intestinal failure and its sequelae

6.3.4 i.a Parenteral nutrition (PN) and intestinal augmentation

Ten infants were reported to be receiving PN at one-year (min 3-max 4%). Six of these ten children had later organ transplantation. Eight of the ten underwent either a surgical procedure to lengthen the bowel or a bowel transplantation (intestinal augmentation); the other two reached enteral independence without either of these interventions. Two of the ten children died. Eight were classified as complex gastroschisis after birth and 24% of children born with complex gastroschisis were receiving PN at one year (8/34). Two children with simple gastroschisis were receiving PN at one year (1%), ($p < 0.0001$).

6.3.4i.b Liver impairment

Clinicians were asked whether the child had ever had evidence of liver disease associated with PN use, according to the definition given in 6.2.5ii. Thirty-six of 253 were reported to have had this (14%). This occurred in 13/34 children with complex gastroschisis (38%) and 23/218 children with simple gastroschisis (11%), ($p < 0.001$). Thirteen children were reviewed as an outpatient by gastroenterology because of ongoing problems with liver dysfunction (5%). Five children underwent a liver transplant either as an isolated graft or in combination with a small-bowel transplant (2%).

6.3.4i.c Nutritional deficiency and bacterial overgrowth

Nine percent of children had a nutritional deficiency managed by supplementation (23/250). The proportions were significantly different in children with simple gastroschisis (15/218, 7%) and complex gastroschisis (8/24, 25%) ($p = 0.004$).

Six percent of children had had an episode of bacterial overgrowth which was treated (14/253). This again affected statistically significantly more children with complex (7/33, 21%) than simple gastroschisis (7/219, 3%), $p=0.001$.

6.3.4ii Other gastrointestinal symptomatology

Information about ongoing gastrointestinal symptomatology was less well reported than other long-term outcomes, possibly because children with these symptoms were treated outside the tertiary centre. Seventeen children were known to have been diagnosed with cow's milk protein intolerance (17/211, 8%). Eleven percent received medical treatment for gastro-oesophageal reflux after one-year of age (21/189). Twenty-one percent were known to have been treated for constipation after one-year of age (41/191). Ten children were known to be receiving medication for constipation at the time the form was completed.

Nine percent of children were known to have complained of abdominal pain while in follow-up (23/251). This was more common in children born with complex (8/34, 24%) than simple gastroschisis (15/216, 7%), $p=0.006$. Management of the pain was variable, from laxative administration or bowel decontamination with antibiotics to adhesiolysis, suggesting a variety of possible causes.

6.3.5 Neurodevelopment

Neurodevelopmental outcomes were also less well reported. Five (3%) of 197 children were reported to have hearing impairment, 8 (4%) had visual impairment and 9 (5%) had motor impairment. The causes of all of these motor and sensory impairments were varied, with both congenital and acquired aetiologies and in many, the cause was unknown.

Twenty-one children (10%) were reported to have developmental delay. In some, this was due to prolonged hospitalisation, prematurity or cerebrovascular accident, in others it was linked to a co-existing problem, such as autistic spectrum disorder. The incidence of developmental delay from any cause was statistically significantly higher in children born with complex (6/24, 25%) compared with simple gastroschisis (15/177, 8%), $p=0.02$.

Seven children with long-term follow-up data had been diagnosed with, or were under investigation for an autistic spectrum disorder (3%). An additional child whose parent filled in a questionnaire for the study described in Chapter Five was also under investigation for a possible diagnosis of autism.

6.3.6 Growth

6.3.6i Weight

On the basis of birth data, 29% of children (106/371) in the entire cohort were small-for gestational age with a birth-weight below the 10th centile. The median birthweight centile for all children in the cohort was 23 (IQR 8-41). Table 6.12 shows the distribution of centiles for weight and length/ height as measured at given time points in the early life of the children with long-term follow-up data; available data were sparse. The higher proportion of children with complex gastroschisis that were weighed at each time-point suggests that it is these children that were considered to be having growth and weight problems.

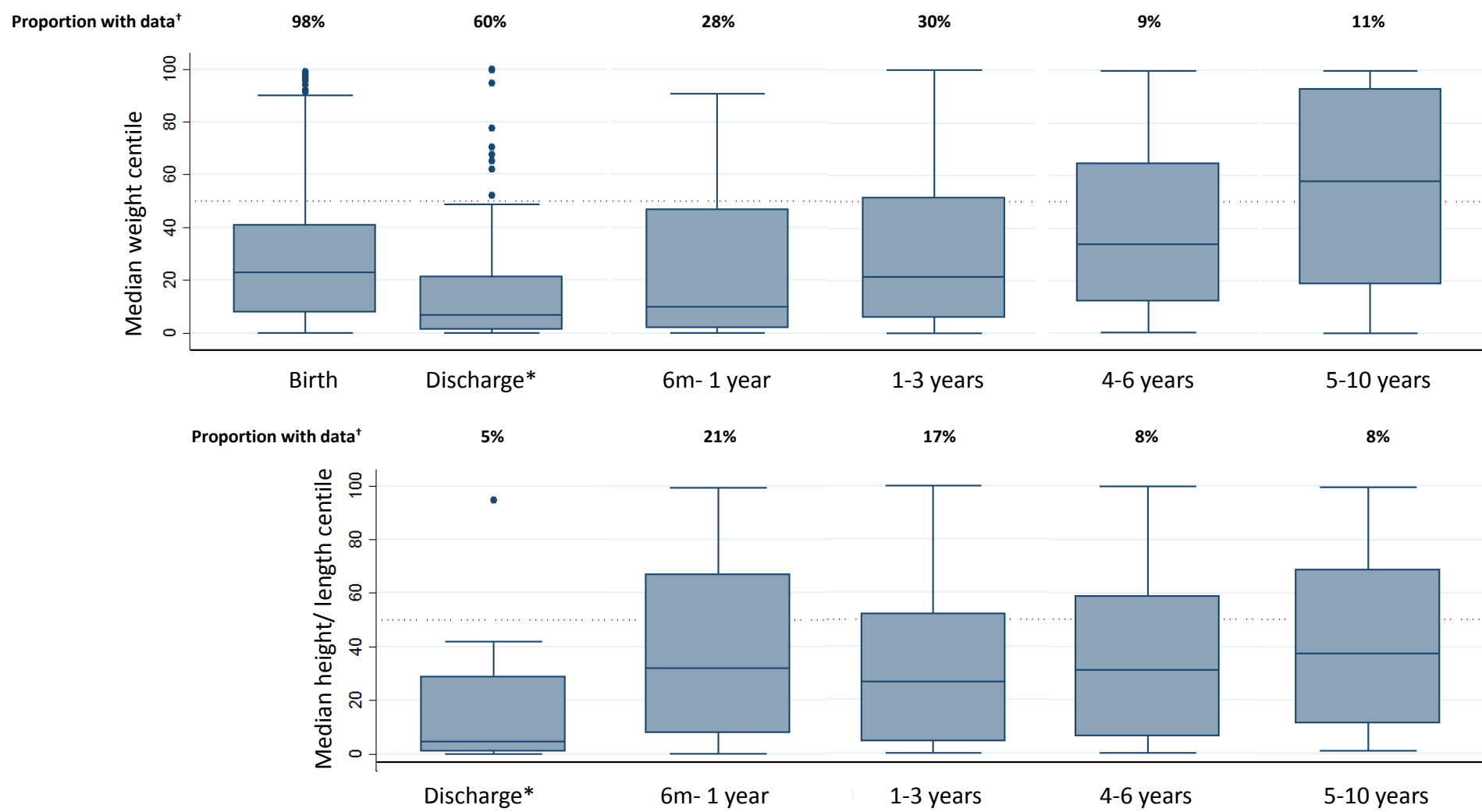
These data show that the majority of children who had weight measurements at discharge experienced a drop in their weight centile from birth. Eighty-eight percent of 172 children had a drop in their centile by discharge ($n=152$), 3% remained the same ($n=6$) and 8% had an increase in their weight centile ($n=14$). Forty-nine percent of children experienced a drop of more than 25% of their original centile value between birth and discharge (77/157).

Those who were weighed later appeared to experience a slow recovery in their weight gain after this. Their median centile did not approach the birth centile for one to three years. The relatively few children who had later weight measurements continued to gain weight and the median weight centile of those who were measured age of four to six years was greater than the median birthweight centile. The few who were measured after five years achieved a median centile of 58 between five and ten years of age (Figure 6.3).

Table 6.12 Weight and length/height measurements of children at different ages with proportion of all children measured

Time of measurement	n (%) with weight centile measurement	n complex/ N with measurement (%)	Median (IQR) centile for weight		n (%) with height centile measurement	n complex/ N with measurement (%)	Median (IQR) centile for height
Birth	371/377 (98)	45/371(12)	23 (8-41)				
First discharge	166/276 (60)	17/ 166 (10)	7 (1-21)		14/276 (5)	2/14 (14)	5 (1-29)
6 months	77/276 (28)	11/77 (14)	10 (2-47)		58/276 (21)	9/58 (16)	32 (8-67)
1-3 years	84/276 (30)	15/ 84 (18)	22 (6-52)		47/276 (17)	9/47 (19)	30 (4-52)
4-6 years	26/276 (9)	6/ 26 (23)	34 (12-65)		23/276 (8)	10/23 (57)	31 (6-59)
Over 5 years	30/276 (11)	10/30 (33)	58 (19-93)		21/276 (8)	8/21 (62)	37 (11-69)

Figure 6.3 Box and whisker plot of weight and length/height measurements by age of children born with gastroschisis



[†]Proportion of infants with data for this measurement (Table 6.12)

6.3.6ii Height/ length

Height or length data were even sparser with less than 21% of children having a measurement at any point. For this reason, no conclusions can be drawn about the longitudinal growth of children in the cohort.

6.3.7 Severe adverse composite long-term outcomes

Table 6.13 illustrates the incidence rates and influence of simple or complex gastroschisis and type of closure on the severe adverse composite outcomes, requirement for intestinal augmentation, severe sequelae or intestinal failure or 'any severe outcome'.

Table 6.13 Univariable analysis of severe composite outcomes by simple vs complex gastroschisis and type of closure

			Simple vs complex gastroschisis				Type of closure in children with simple gastroschisis			
	All infants n (% , 95% CI) Min estimate Max estimate	5 year specific IR/ 1000 PYAR (95% CI)	Simple* n (%)	Complex* n (%)	Log rank p value	Hazard ratio (Complex) (95% CI)	OFC* n (%)	PFS* n (%)	Log rank p value	Hazard ratio (PFS) (95% CI)
Intestinal augmentatⁿ	9/370 (2, 1-5) 9/277 (3, 1-6)	20 (10-30)	2/242 (1)	7/34 (21)	<0.0001	66.67 (8.33-533.08)	1/104 (1)	0/94 (0)	0.37	NE
Severe IF sequelae	12/370 (3, 2-6) 12/279 (4, 2-7)	20 (10-40)	4/244 (2)	8/34 (24)	<0.0001	16.62 (5.00-55.20)	1/104 (1)	1/95 (1)	0.89	1.22 (0.08-19.55)
Any severe outcome	25/377 (7, 4-10) 25/305 (8, 5-12)	50 (30-70)	14/266 (5)	11/38 (29)	<0.0001	6.23 (2.83-13.74)	5/117 (4)	4/98 (4)	0.94	0.95 (0.26-3.54)

Intestinal augmentatⁿ: Intestinal augmentation IR: Incidence rate PYAR: Person years at risk IF: Intestinal failure NE: Not estimable

OFC: Operative fascial closure PFS: Pre-formed silo *Maximum rates shown

6.3.7i Intestinal augmentation

Nine children are known to have undergone intestinal augmentation in the form of a bowel transplant (with or without prior lengthening procedure) (n=5) or a bowel lengthening procedure only (n=4). This was undertaken in 21% of children with complex gastroschisis (7/34) and 1% of those with simple gastroschisis (2/242), ($p<0.0001$).

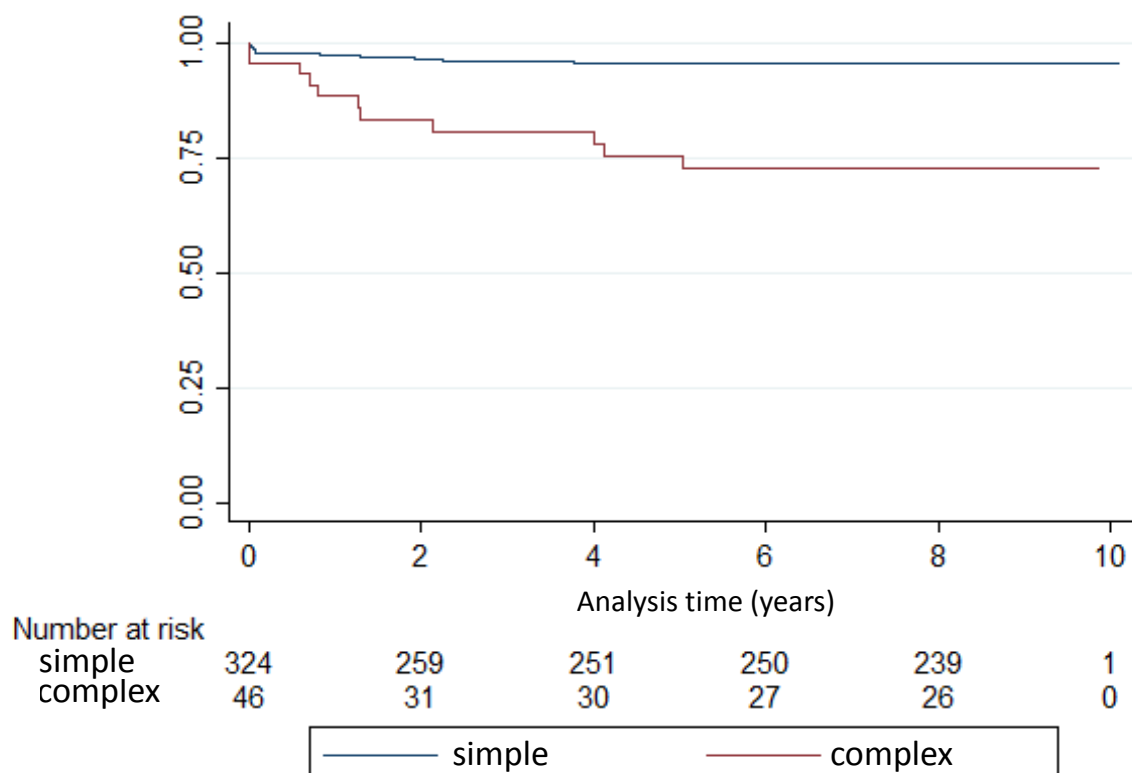
6.3.7ii Severe sequelae of intestinal failure

More children with complex gastroschisis experienced severe sequelae of intestinal failure compared with those born with simple gastroschisis (24% 8/34 vs 2% 2/244, $p<0.0001$).

6.3.7iii Any severe adverse outcome

Twenty-nine percent of the children with complex gastroschisis experienced 'any severe outcome', (11/38). This was statistically significantly more than children born with simple gastroschisis (14/266, 5%, $p<0.0001$). The event free survival curve for this outcome is shown in Figure 6.4.

Figure 6.4 Kaplan-Meier curve showing the event-free survival for the outcome 'any severe adverse outcome' in children with simple and complex gastroschisis



Based on relatively few adverse outcomes, the incidence of the severe composite outcome was not statistically significantly different by method of closure among children born with simple gastroschisis (Table 6.13)

6.3.7iv The impact of parenteral nutrition (PN) duration on outcomes related to intestinal failure

The relationship between the duration of PN following gastroschisis reduction and severe outcomes relating to intestinal failure was assessed (Tables 6.14 and 6.15). ROC analysis showed PN duration to be a strong predictor of both the need for intestinal augmentation (area under the curve /AUC 0.99, 95% CI 0.99-1.0) and severe sequelae of intestinal failure (AUC 0.99, 95% CI 0.99-1.0) (Figures 6.5 and 6.6). The cut off of PN duration that was highly discriminatory, correctly identifying the greatest number of children who underwent intestinal augmentation was ≥ 365 days, with 99% correctly classified. The duration that correctly classified the greatest number of children who experienced a severe sequela of intestinal failure was ≥ 294 days, with 99% correctly classified.

Table 6.14 The relationship between PN duration and the need for intestinal augmentation

	Minimum estimate	Maximum estimate	% correctly classified (ROC)	Sensitivity %	Specificity %
All	8/354 (2)	8/264 (3)			
>30 days	8/138 (6)	8/108 (7)	61	100	60
>60 days	8/50 (16)	8/42 (19)	100	100	87
>90 days	8/22 (27)	8/25 (32)	93	100	93
>180 days	8/16 (50)	8/14 (57)	97 [‡]	100	97
≥ 365 days	8/10 * (80)	8/10* (80)	99	100	99

‡ ≥ 178 days from ROC calculation * These show the same data, derived from the long-term outcome DCF

Table 6.15 The relationship between PN duration and severe sequelae of intestinal failure

	Minimum estimate		Maximum estimate		% correctly classified (ROC)	Sensitivity %	Specificity %
	n/N	(%)	n/N	(%)			
0-30 days	10/354	(3)	10/265	(4)			
>30 days	10/138	(7)	10/109	(9)	62	100	61
>60 days	10/50	(20)	10/43	(23)	88	100	88
>90 days	10/30	(33)	10/26	(38)	94	100	94
>180 days	10/16	(63)	10/50	(67)	98 [‡]	100	98
>=365 days	9/10*	(90)	9/10*	(90)	99	90	99

[‡]>178 days from ROC calculation * These show the same data, derived from the long-term outcome DCF

Fig 6.5 ROC graph indicating the AUC for prediction of the need for intestinal augmentation by PN duration

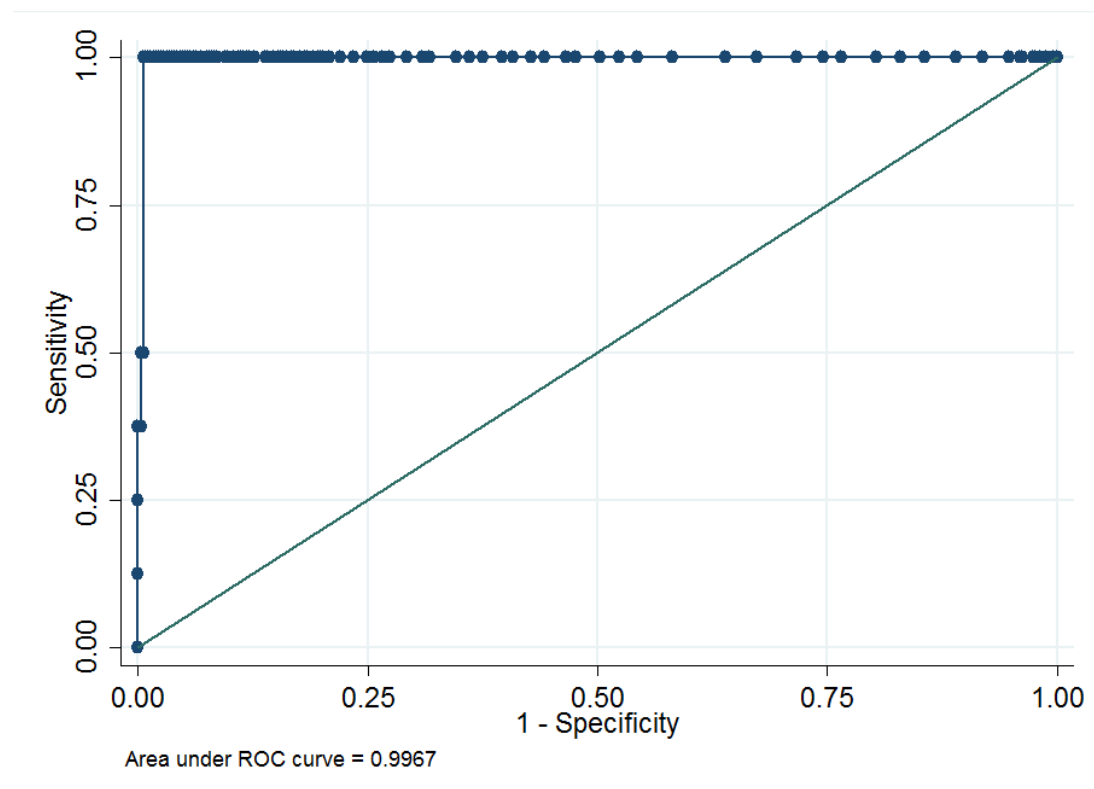
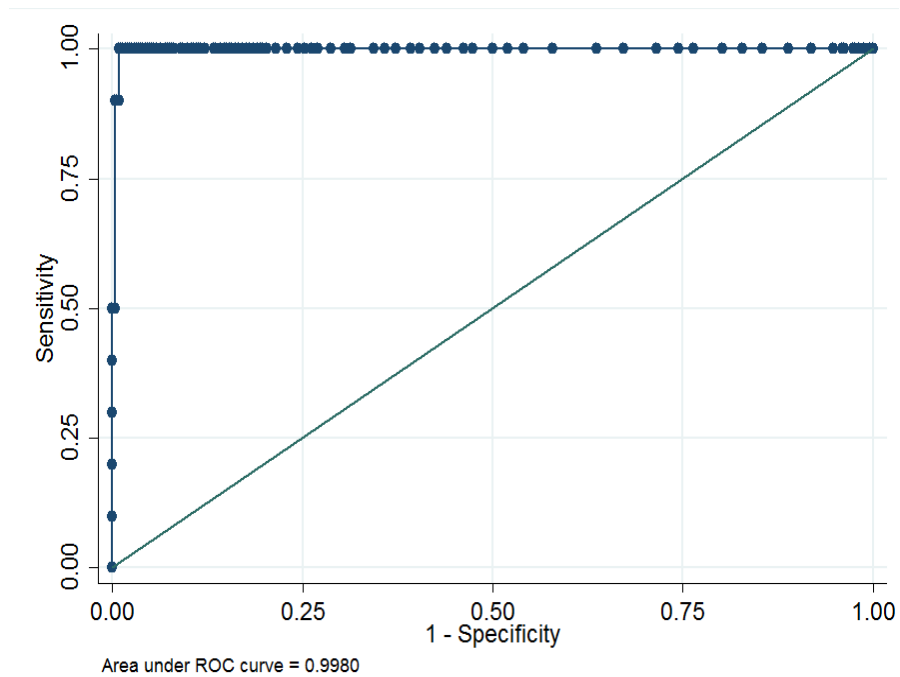


Fig 6.6 ROC graph indicating the AUC for prediction of severe sequelae of intestinal failure by PN duration



6.3.8 Summary of the key childhood outcome of children born with simple and complex gastroschisis (Table 6.16)

Table 6.16 Summary of key childhood outcomes of children born with simple and complex gastroschisis

Outcome	Maximum estimated incidence		p value*
	Simple gastroschisis	Complex gastroschisis	
Death	5%	13%	0.03
Adhesive bowel obstruction (ASBO)	7%	20%	0.04
Bowel obstruction [†]	12%	29%	0.048
Readmission	42%	62%	0.65
Reoperation	51%	100%	0.0004
Developmental delay	8%	25%	0.02
Intestinal augmentation	1%	21%	<0.001
Severe sequelae of intestinal failure	2%	24%	<0.001
Any severe adverse outcome	5%	29%	<0.001

[†] Acquired bowel obstruction from any cause

6.4 Discussion

6.4.1 Main results

6.4.1i Death

The case fatality by age nine years was estimated at between 5-6% for all children born with gastroschisis. This is lower than the pooled estimate for case fatality by age one-year estimated from the literature and reported in Chapter Two (7%, 95% CI 5-10%). This may reflect the more contemporary nature of this cohort than the older and more heterogeneous retrospective studies that formed the majority of those contributing to the pooled estimate. It is, however, noteworthy that the case fatality rate by age five for children born with gastroschisis in this cohort is 12-14 times higher than the childhood mortality rate before the age of five for all children born in the UK in 2015 (4.2 per 1000 live births) (CMEInfo 2015).

Most of the children born with gastroschisis who did not survive, died early in life, with almost two-thirds dying before reaching their first birthday and all deaths had occurred before age four. This echoes the findings of Tennant et al (2010) who found that mortality plateaued at five years (Tennant, Pearce et al. 2010). With the exception of complex gastroschisis none of the birth characteristics assessed in this study were associated with an increased risk of death.

6.1.4ii Other severe adverse outcomes

The proportion of children undergoing intestinal augmentation was estimated to be between 2-3% and 3-4% of children experienced severe sequelae of intestinal failure. These represent the most severe end-points for children who have had long-term enteral dysfunction. The overall occurrence of death from any cause or severe sequelae of intestinal failure was 7-8%, meaning that approximately one in 13 children born with gastroschisis may experience one of these outcomes before the age of nine.

Not surprisingly, the length of time that a child received parenteral nutrition (PN) was a very strong predictor of both of these very serious outcomes. The data generated from the assessment of the relationship between PN duration and these outcomes will be of value for clinicians managing children on long-term PN, particularly in the provision of prognostic estimates for their parents.

6.4.1iii Outcomes of infants born with simple and complex gastroschisis

The significant impact that being born with complex gastroschisis has on many of the childhood outcomes assessed in this study is clear, with an adverse outcome including death affecting nearly a third of all children with complex gastroschisis compared with one in 20 children with simple gastroschisis. These data will be of use in parental counselling based on post-natal appearances of the bowel and also highlight the importance of publishing risk-stratified outcomes as first suggested by Molik et al in 2008 and discussed in depth in Chapter Two (Molik, Gingalewski et al. 2001).

It is striking that approximately one in eight children born with complex gastroschisis died, one in four survivors experienced developmental delay, one in five underwent intestinal augmentation and almost one in three either died or suffered a severe sequela of intestinal failure. For children born with simple gastroschisis, one in twenty died, one in two had another operation after closure and almost the same number were readmitted to hospital after discharge.

With the limitations described in Chapter Two, the outcome data generated by this population cohort study provide a contemporary estimate of key outcomes in gastroschisis for the purposes of audit and performance assessment as well as informing the design of future clinical trials.

6.4.1iv The impact of method of early management

The previous publication of outcome data to one-year in this cohort highlighted differences in the length of hospital stay and duration of PN treatment in favour of OFC (Bradnock, Marven et al. 2011). There was at least one neonatal death in the series directly attributable to the use of a preformed silo and instances of acquired bowel ischaemia, volvulus and intestinal perforation associated with PFS were experienced by members of the cohort.

Although these events may have impacted before one year of age, a long-term effect on children with simple gastroschisis on the overall outcomes remains questionable. Although a significant association was found between method of closure (OFC vs PFS) and the likelihood of further surgical intervention in children born with simple gastroschisis, the clinical significance of this finding is unknown. This is because the outcome measure 'reoperation' included *any* further surgery after initial closure. The operations included in this definition were diverse and in some cases may be unrelated to the original pathology. In order to assess this further, this outcome could be refined to either include unplanned abdominal operations, all additional general anaesthetics or use the Clavien-Dindo system as described in Chapter Two (Dindo, Demartines et al. 2004). The lack of any significant difference in any of the other outcomes is likely to be because, with the exception of readmission and reoperation, the incidence of these outcomes in the simple group was very low. The further division of this group into smaller groups by closure method was likely to have limited statistical power and thus, if any real effect was present, the sample sizes may not have been large enough to detect it.

The different causes of death in the two management groups are noteworthy, with early bowel complications predominating as a factor in the early deaths of children with simple gastroschisis who were treated with PFS. This again highlights the need for large sample sizes in order to detect differences in adverse events when they are relatively rare.

6.4.1v Other outcomes

6.4.1v.a Other surgical procedures

Umbilical surgery

Some evidence was found of an association between the use of PFS and later cosmetic umbilical operation in the cohort. In addition a planned sensitivity analysis showed a higher rate of umbilical hernia development in children managed with sutureless umbilical closure. No large studies have previously assessed this. A recent systematic review assessing outcomes for children treated with sutured vs sutureless closure of gastroschisis found a higher incidence of post-operative umbilical hernia in the sutureless group. The rates of umbilical hernia *repair*, were not, however synthesised and were very low in most of the included studies (Youssef, Gorgy et al. 2016).

Two single centre studies, one from the USA (Orion, Krein et al. 2011) and one from the UK (Tullie, Bough et al. 2016) have reported considerably higher rates of umbilical hernia repair than those noted in the present study, 20% and 22% respectively. Both reports included a much smaller total number of children than the present study, and whether the rate of 5% observed in this study represents under-ascertainment is unclear.

Inguinal surgery

Four percent of children born with gastroschisis underwent inguinal herniotomy and nine percent of boys had an operation for undescended testis. It is not possible to compare this rate to that of the three recent studies shown in Table 6.3 as these only report the rate per testis rather than per boy (Yardley, Bostock et al. 2012) (Lawson and De 2001, Hill and Durham 2011). The denominator was chosen as boys, rather than testes for the study described in this chapter as this was felt to be of greater value for parental counselling.

6.4.1iv.b Gastrointestinal sequelae

Ten children were known to still be receiving PN by their first birthday (4% of those with long-term outcome data). Thirty-six were reported to have met the criteria for Type 1 intestinal failure associated liver disease (IFALD), (14% of those with long-term outcome data). Beyond the requirement for liver transplantation, the ongoing sequelae of IFALD were not able to be assessed. Data on long-term gastrointestinal sequelae among the cohort were poorly reported, however, these data suggest that a substantial proportion of children do have on-going problems with gastrointestinal dysfunction. This was a cause of readmission to the tertiary centre for 12% of children. The rate of readmission for such symptoms to *any* centre, may in-fact, be higher. Eleven percent were known to have been given medication for GORD after one year and 21% were on laxatives at that time point. Ten children were known to be receiving long-term medication for constipation.

Estimates of the prevalence of cow's milk protein intolerance (CMPI) in children as a whole vary from 2-7.5% (du Toit, Meyer et al. 2010). CMPI was found in eight percent in the present study which is considerably lower than that observed in a recent UK series of children born with gastroschisis in a single UK centre, (45%) (Burge, Drewett et al. 2015). Whether the collection of data from tertiary centres involved in this study was inadequate to assess a condition that may be more likely to be managed locally or whether it was under-recognised or misdiagnosed by centres prior to the publication of the work of Burge et al (2015) is not known.

6.4.1v.c Neurodevelopment

Ten percent of those children with long-term follow-up were reported as having had developmental delay. The causes of this were varied, and not known in many cases. It was not possible to determine whether developmental delay or neurosensory impairment was directly associated with gastroschisis for all of the children.

For some, however, this was clearly the case, where congenital causes included septo-optic dysplasia or amyoplasia which are causes of visual impairment and musculoskeletal problems known to be associated with gastroschisis, (Hunter and Stevenson 2008, Kamien, Zankl et al. 2010). Other acquired causes included developmental delay associated with prolonged hospitalisation or motor impairment due to cerebrovascular insults.

Three percent of children with follow-up data were diagnosed with or were under investigation for autistic spectrum disorders (ASD). This is considerably higher than the population incidence of ASD which is estimated at 9 per 1000 (Johnson, Hollis et al. 2010). How many of the eight children in this study would end up with a final diagnosis of ASD is unknown. Other authors have identified an association between extreme prematurity and increased incidence of autism (Johnson and Marlow 2014). The biological or environmental explanation for this is not yet known (Johnson, Hollis et al. 2010). Not all of the children that were under assessment for ASD in this cohort were born prematurely. Although no definite association between gastroschisis and later developed of ASD can be inferred from the findings of the present study, further investigation is warranted in future prospective studies.

6.4.1.v.d Growth

This study represents the first time that birth-weight for gestational age, or weight for age has been assessed in a population-based cohort of children with gastroschisis. The high proportion of SGA infants and the low median birthweight centile are notable and in line with the findings of other authors (Payne, Simonton et al. 2011, Girsén, Do et al. 2015, Miquel-Verges, Mosley et al. 2015).

What does not appear to be evident in the published literature are other examples of the profound drop in weight centile that children experienced between birth and discharge. This parallels recent findings in preterm newborns who will, like those born with gastroschisis, have been managed with a prolonged course of parenteral nutrition (Cole, Statnikov et al. 2014, Rochow, Raja et al. 2016). In this study, the impact of gestational age or complexity of gastroschisis on early weight gain has not been analysed, but future work should assess postnatal growth and nutrition in more detail and evaluate whether the findings of this study remain true with contemporary nutritional management. Growth data beyond discharge were sparse and became more so with advancing age. Only 8% and 11% of the cohort had height and weight data beyond five years of age. It was not therefore possible to reach robust conclusions about the children's later growth trajectories.

6.4.2 Strengths of this study

This study achieved 77% follow-up regarding survival data and complete childhood outcome data were collected for 76% of the cohort. This is therefore the largest and most complete follow-up study that has ever been undertaken on children born with gastroschisis and the only one that includes a prospectively collected national population cohort. No significant differences in any of the demographic or management parameters between the original cohort and those with complete follow-up data were observed, lending weight to the conclusion that the long-term follow-up data are representative of the whole population of gastroschisis survivors.

Data collection was detailed, exploring a variety of outcomes and mapping these to existing information about birth characteristics and early management. The use of free-text searches within the original, early and one-year data collection forms meant that all of those with given outcomes were able to be included. The use of survival time techniques assured appropriate comparisons of event rates between groups.

The use of the *NHS Spine* and other robust search methods for children living outside of England meant that survival data were complete and clinicians did not have to rely on hospital records to assess this outcome, which may have not been updated if children died out-of-area.

6.4.3 Challenges encountered and limitations of this study

6.4.3i. Challenges encountered

Several challenges were encountered during the completion of this multicentre study. Those associated with the re-identification of children from the original cohort in centres where BAPS-CASS cards had been lost have been described in Chapter Five. In addition, after re-identification, reporting clinicians faced several difficulties in obtaining case records as many centres had electronically archived them and they were difficult or impossible to access. The follow-up rate for this study was affected by these difficulties and inaccessible case records meant a number of identified children were not able to be included. Beyond this, clinicians reported that in some cases, records were incomplete. This may have led to under ascertainment of some outcomes .

Finally, data collection was carried out by collaborating clinicians around their normal workload. Some found it difficult to find the time to complete the data collection. This meant that data had to be repeatedly requested by the author and, for three centres, data were never received.

6.4.3ii Use of tertiary centre data

Beyond the use of databases such as the *NHS Spine* to assess survival, data for this study were collected by clinicians using the clinical records at the specialist paediatric surgical centres only. For many of the cohort, this would not have been their local hospital, meaning that they may have had interactions with health-care services that were not captured in the children's case-notes in the tertiary centre.

Although many of the more acute outcomes such as bowel obstruction, sequelae of intestinal failure and readmissions with severe illness would have been managed at the tertiary centre, admissions for less severe problems, minor operations and longer-term surgical or paediatric follow-up would have been more likely to occur at their local centre. This may have affected the ascertainment of some of the 'softer' outcomes such as minor procedures and neurodevelopmental impairment. It is likely that in many cases, when clinicians in the tertiary centre were not aware of any problems, such as developmental delay this was marked as a 'no' rather than a 'don't know' answer leading to apparently lower rates than in reality. Such estimates should therefore always be treated as minimum incidence estimates.

Where children had moved out of the area completely (as some clinicians had recorded in the free-text section of the clinical data), this would have resulted in a 'hidden loss to follow-up'. Surgeons treating a child in another surgical centre may not have been aware that that child was part of a cohort study and data on further interactions in another surgical centre would have been missing.

6.4.3iii Low long-term adverse event rates in children born with simple gastroschisis.

This study did not find a statistically significant difference in the rate of any of the severe composite adverse childhood outcomes according to method of closure among children born with simple gastroschisis. Being born with complex gastroschisis has such a major impact on both management choice and outcome, that any comparison between different modes of closure should either look at outcomes in the simple group only (as was done in the previously published analysis of early data from this cohort (Bradnock, Marven et al. 2011)) or present stratified outcomes.

The low rate of all outcomes and limited statistical power precluded multivariable analysis. It is clear that much larger numbers of infants would be needed in order to detect any differences as statistically significant if in reality, such differences exist.

6.4.3iv Changes in contemporary management since cohort inception

There have been some significant changes in clinical practice affecting the management of infants born with gastroschisis in the last ten years which mean that contemporary outcomes could be different to those of this cohort. The most significant change has been in the composition and use of PN. Following concerns about the relationship between plant-derived sterols contained in soybean derived lipids, used as a constituent of PN for many years, and the development of cholestatic liver disease; newer lipid formulations have been introduced (Vanek, Seidner et al. 2012). *SMOF-LE*, composed of soybean oil, medium-chain triglycerides, fish and olive oil is a popular commercially available alternative to the previous formulations with a lower concentration of plant-derived sterols, that has recently been widely adopted throughout the UK. Although no Type 1 evidence exists to support its use in surgical neonates, many believe it causes less cholestatic liver disease in infants requiring prolonged PN (Finn, Chung et al. 2015) (Al-Shahwani and Sigalet 2016, Dai, Sun et al. 2016).

Another important change is a general reduction in the use of preformed silos as a primary management technique. Following the publication of the early data from this cohort, which suggested episodes of bowel ischaemia and intestinal loss in preformed silos (Bradnock, Marven et al. 2011), in the author's clinical experience, surgeons in many centres have stopped using PFS. A recent debate at the British Association of Paediatric Surgeons Annual Congress, on the safety and efficacy of the use of silos in the early management of gastroschisis suggested strong opinions on both sides.

More recently, in May 2016, the main manufacturer of preformed silos recalled all bags due to concerns about non-organic contamination of these devices and they were not available for some time (Medicina 2016). It is likely that contemporary abdominal closure of children with gastroschisis, whose bowels are able to be reduced primarily is more often achieved with OFC than it was in 2006-2008.

6.5 Conclusion

This study has clearly demonstrated the significant effect that being born with complex gastroschisis has on childhood outcomes in children born with this condition. The most severe of these outcomes relate to an inability to gain enteral autonomy, the sequelae of intestinal failure and early mortality. Chapter Seven will discuss how further study is necessary to identify ways of preventing complex gastroschisis, to better treat children with it, and reduce the incidence of further adverse consequences, should it develop prenatally.

The optimal method of managing children born with simple gastroschisis suitable for primary closure remains unclear. The data generated from this study provide no additional evidence in favour of OFC or PFS to guide management choice. Regarding the mode of fascial closure, a higher rate of umbilical hernia repair was observed in children treated with sutureless closure. This later procedure was, however, only performed in one in ten children managed in this way, and the potential avoidance of general anaesthesia by undertaking sutureless closure in the other nine, is offset against this. A detailed cost-benefit analysis of the interventions required in childhood in children treated with OFC compared with PFS would provide further information to answer the question about the optimum management choice for infants who are suitable for primary closure.

The data presented in this chapter, like those in Chapter Three, were collected by surgical personnel throughout the British Isles working tenaciously to collect them despite an already heavy clinical workload and the challenges of record retrieval. It is through this collaborative effort that such an extensive and thorough follow-up study has been possible. This methodology for long-term follow-up clearly has limitations however, and ways in which more robust long-term follow-up data could be collected are discussed in Chapter Seven.

Chapter 7

Discussion

7.1 Introduction

The work presented in this thesis has focussed on assessing the short and longer-term outcomes of children born with abdominal wall defects (AWD) and the experiences of their parents in order to improve future care. This has been achieved through the generation of new population-based data that can be used to inform parental counselling, to identify standards for clinicians and surgical centres to aim for and exceed, and to understand how these outcomes should be reported. The findings of the studies described provide a stimulus for further research into the early management of these conditions through future observational and interventional studies. The assessment of the experiences of parents of children born with AWD has identified key messages to facilitate the delivery of high-quality care.

Some of the conclusions of this work are specific only to the care of children with AWD, but many of the key findings have more universal messages to drive improvements in wider areas of healthcare. The challenges encountered during these studies and the methodological learning points that have arisen from them will be discussed in the following section. Suggestions for how these challenges can be overcome in future research are also outlined.

7.2 Challenges in outcome assessment and methodological leaning points

7.2i The importance of infant characteristics in the interpretation and analysis of outcomes

The studies described here have highlighted the importance of interpreting the outcomes of surgical management of AWD in the context of key characteristics of the infant at birth. These are the chief components of what the Royal College of Surgeons describes as ‘case-mix’ (RCS 2013). Within the studies described in this thesis, the following characteristics significantly affected outcomes either directly, or through the differing management choices that they necessitated:

- Simple vs complex gastroschisis
- Method of closure in exomphalos (primary vs staged)
- Defect size/ weight ratio in exomphalos (DWR)

Another important infant characteristic suggested by the study findings, that may have an important effect on outcome, is the presence of comorbidity. The impact of comorbidity was described in the cohort study of children born with exomphalos, but was not able to be explored any further due to the limitations of a small sample size even in this national study.

It is essential that the influence of the above characteristics is recognised during the assessment of outcomes of children born with abdominal wall defects. Outcomes must either be interpreted in distinct groups, the process of ‘risk-stratification’, or adjusted for these factors. Case-mix adjustment presents its own challenges due to the relatively small sample sizes that are involved in any study assessing the outcomes of newborn surgical management. However, a recent example of outcomes not being interpreted with appropriate adjustment was partly responsible for major service-disruption, public outrage and a degree of embarrassment for NHS England after the temporary suspension of paediatric cardiac surgical services in Leeds in 2013 (NHS 2014); an episode which further emphasises the importance of these considerations.

7.2i.a Simple vs complex gastroschisis

The definition of complex gastroschisis proposed by Molik et al in 2001 (Molik, Gingalewski et al. 2001) has been shown to impact on both short and longer-term outcomes in gastroschisis. This is not, however, the only method of characterising bowel compromise at birth discussed in the literature. The most commonly used alternative is a score developed in Canada for the CAPSNET gastroschisis cohort studies (Emami, Youssef et al. 2015, Youssef, Laberge et al. 2015). The CAPSNET group developed and validated the 'gastroschisis prognostic score' (GPS) and have positively assessed the ability of a GPS of ≥ 4 to predict in-hospital mortality, length of hospital stay and days on PN (Cowan, Puligandla et al. 2012). The GPS differs in its defining characteristics from the simple vs complex classification, in that it includes bowel 'matting' or the degree in which intestinal loops are stuck together, as a marker of severity. This Canadian system has not been widely adopted outside of the CAPSNET studies.

The definition of complex gastroschisis proposed by Molik and co-workers (2001) does however have important limitations, which must be acknowledged if researchers are to use it in the process of outcome assessment. These limitations relate to the fact that there are infants with significantly compromised bowel who do not fit criteria for classification as 'complex' defined by Molik et al. Such children include those with severe bowel matting which may preclude primary closure (a component of the GPS), mesenteric injury during delivery, (a cause of significant blood loss and bowel compromise that may evolve with time) and bowel ischaemia. The term 'bowel ischaemia', describes a spectrum of varying severity and, importantly, reversibility.

Acknowledging that significant bowel compromise may be present in some infants with 'simple' gastroschisis is a noteworthy caveat to risk-stratifying outcomes using the simple vs complex dichotomy and a key limitation in the interpretation of unadjusted outcomes of infants by type of closure even when only those with simple gastroschisis are included.

This is important because a child with a compromised bowel may be more likely to be treated with a silo to keep the bowel in a lower-pressure environment and to monitor it for colour change. As such, when interpreting observational data to assess the superiority of one technique over another, or as a trial entry criterion, it is important to note that the surgeon is unlikely to be in equipoise over management choice for all infants with 'simple' gastroschisis.

7.2.i.b Method of closure and DWR for children born with exomphalos

The study described in Chapter Three demonstrated that children born with exomphalos do not exist as two separate, identifiable groups whose defect could be described as 'major' or 'minor' with a distinct prognostic outlook. An approach was therefore tested that used surgical decision-making as a surrogate gold-standard for defining groups who may have a similar outcome. Among this cohort, a defect diameter: weight ratio (DWR) of ≥ 1.64 predicted the need for staged closure and as a consequence it was not surprising that both the need for staged closure and DWR of ≥ 1.64 were associated with poorer outcomes.

This finding requires further prospective validation in a future study in order to assess whether DWR ≥ 1.64 is a useful prognosticator in other populations. It is, however, clear that infants who had a primary closure and had no associated comorbidity, had an excellent prognostic outlook. It is therefore inappropriate to assess outcomes of children born with exomphalos without separating those that had primary or staged management into distinct groups.

7.2.i.c Comorbidity

Comorbidities, for the purposes of this discussion, are defined as structural or genetic abnormalities that occur alongside an AWD. Some of these comorbidities unquestionably impact on outcome and examples include those that are known to affect survival, such as lethal aneuploidy, severe pulmonary hypoplasia or complex congenital cardiac anomalies. For the majority of other comorbidities, their impact is likely to be more variable and may have a particular effect on a specific outcome, for example the presence of intestinal atresia may influence time to full enteral feed tolerance.

Comorbidities in children born with abdominal defects are diverse and individual anomalies are rare. As has been observed in the infants with exomphalos, some may affect only one individual in a cohort. The challenges relating to adjusting outcomes or 'risk-stratifying' for comorbidity relate to the lack of a universally accepted definition or system of classification. UK paediatric cardiac surgeons, because of the drive to produce robust, risk-adjusted outcome data, have a universal classification of, 'low-' 'medium-' and 'high-risk' cardiac anomalies, based on their 30 day post-operative mortality (Pagel, Brown et al. 2013). For most other types of structural or genetic anomaly, there is no clear way to define which will have a prognostic impact or affect a given outcome. Coupled with this is the fact that the sequelae of some abnormalities may only become clear as children grow and age, for example, the effect of a genetic defect on neurodevelopment or whether an atrial septal defect in the heart will lead to haemodynamic changes or will close spontaneously.

A further problem of case-mix adjustment for comorbidity relates again to the challenges of sample size. This was evident in the exomphalos cohort study, where, despite this being the largest population-based study of the condition conducted to date, small numbers in each category of comorbidity precluded statistical assessment of outcomes according to these groupings.

7.2.ii The challenges of data collection for outcome assessment using central anonymised data

The cohort studies described in this thesis used anonymised data collected by clinicians in surgical centres which were submitted centrally and analysed by the author. This approach has the advantage of allowing the assimilation of national population data with high levels of case-ascertainment as no consent from individual parents was required. It undoubtedly facilitated the successful completion of the only national population cohort study to have been undertaken in exomphalos and the most comprehensive assessment of long-term childhood outcomes in gastroschisis completed to-date. These have generated relatively large contemporary samples unseen for these conditions before, with the notable exception of the CAPSNET studies in gastroschisis (Skarsgard 2006).

This methodology did, however, present a number of challenges throughout the conduct of these studies. Firstly, the author had no control over the quality and timing of the data collection which was undertaken by health-care professionals in addition to their clinical workload. In some cases, data collection was known to have been carried out by the most junior members of the team, whose lack of clinical experience could have affected the content and quality of data collected. Furthermore, it took over twelve months from the point of dispatch of the data collection forms, to receipt of a sufficient proportion for robust and reliable analysis, and, despite repeated requests, some centres never returned any data.

As described in the parent-reported outcome study, not all children from the original cohort were able to be identified. This related in part to the physical recording of subject details next to the anonymous identifiers during the original case reporting instead of entering these in a computerised database. The BAPS-CASS cards or other records where centres had matched these details to the anonymous identifiers had been lost as previous reporters had moved-on or hospitals had changed sites.

Some hospitals had to re-identify the children using demographic data provided by the author. This process relied on departmental databases, theatre records or a search for all infants admitted to a centre in a given time-period using the International Classification of Diseases version 10 (ICD10) code for gastroschisis and was lengthy and challenging.

7.2.iii. The challenges of data collection and interpretation of short-term outcomes

The major challenge encountered in the interpretation of short-term outcome data relates to the rarity of abdominal wall defects and the low incidence of key adverse outcomes. These issues will also affect the design of any clinical trials and were strikingly in evidence in the exomphalos cohort study. Taking the estimated number of paediatric surgeons in the UK and Ireland as 200, it is notable that during the study period, on average, one practicing paediatric surgeon managed one infant with exomphalos every two years. Of the challenging group that did not undergo primary closure, there were 58 live born infants, approximately one per centre per year. These data once again highlight the serious difficulties that paediatric surgery faces as a speciality in assessing the outcomes of treatment by individual centre, practitioner or treatment strategy and in the generation of robust evidence to guide management. In this cohort, the infants whose defect was not closed primarily and where the surgeon might have been in equipoise about the choice of management numbered 37 in two years. This therefore represents the sum total of infants that could potentially be recruited to a trial comparing methods of staged closure within a two-year period in the British Isles. Thus any differences in outcomes would have to be large to be detectable in any such trial even if all eligible babies were recruited.

Another important consideration relating to the interpretation of the findings of the short-term outcomes of the exomphalos cohort study, relates to their generalisability. A significant proportion of pregnancies with fetuses diagnosed with exomphalos antenatally are terminated (Lakasing, Cicero et al. 2006, Springett, Budd et al. 2014) (Appendix 3). The tone of prenatal counselling and the cultural or religious beliefs of the affected parents will strongly influence the characteristics of the live-born population by affecting the rate of termination. This may be different both regionally in the UK and internationally. This highlights the need for an accurate description of the distribution of the infant characteristics within a cohort, which may, in turn affect their outcomes (7.2.i).

7.2.iv The challenges of data collection and interpretation of longer-term outcomes

The use of anonymised identifiers and the problems of infant identification outlined above particularly affected the long-term gastroschisis cohort studies. Clinicians collecting data from hospital records for the long term study faced the additional challenge of case-note retrieval. When this was up to nine years since the child's last interaction with the hospital, this proved difficult and affected the proportion of children with complete long-term follow-up data. Even when tertiary centre case-notes were available, in many cases they provided an incomplete picture of the child's on-going need for medical intervention, because the child may have had follow-up at their local centre or have moved to another region. The true extent of missing data is unknown. Survival data were felt to be as accurate as possible, at least for children in England, who comprised over 90% of the cohort, where the *NHS Spine* provided a way of tracing children and reliably identifying their vital status. Outside of England and Scotland, no robust system exists for doing this.

An inevitable and unavoidable aspect of long-term outcome assessment is the fact that it will always provide a description of the outcomes of practices that will have changed and evolved in the time that has elapsed between early and later data collection. Thus, the findings of a future gastroschisis cohort study, may be different if the children were born in 2017, for example due to a lower utilisation of PFS or the use of new lipid formulations as part of PN.

7.2.v The challenges of data collection and interpretation patient and parent-reported outcomes

The study described in Chapter Five tested a methodology for collecting parent and patient-reported data for the assessment of childhood outcomes in gastroschisis. This methodology, namely a postal questionnaire, clearly had limitations that affected the generation of useable information due to a low-response rate. Authors have begun to question the utility of postal questionnaires as a research tool and have suggested that public willingness to participate in studies conducted in this way may now have declined to the extent that it is not possible to generalise from the findings (Marlow 2013, Field, Spata et al. 2016, Henderson and Redshaw 2017). Particularly low response rates have been noted amongst respondents of lower socioeconomic status. This may have been a particular factor in the gastroschisis parent study due to the epidemiology of this condition which is associated with young maternal age and markers of lower socio-economic status (Morris 2009, Johnson, Evans et al. 2015, Henderson and Redshaw 2017) (Paranjothy, Broughton et al. 2011).

Beyond this, the long-term parent and child reported outcome study faced a number of challenges as a result of existing UK research governance regulations which presented a series of complex and time-consuming logistical challenges. Another group of researchers, who aimed to study long-term outcomes after cardiac surgery in response to an expert recommendation from the Bristol enquiry, (Kennedy 2001) describe similar frustrations and a complex process of recruitment that they suggested, critically influenced their results. These researchers concluded:

“Decision making concerning childhood interventions should be influenced by evidence on long-term outcomes. However, current UK research regulations hinder follow-up in multicentre studies. Stipulations preventing researchers contacting families directly with research invitations appear disproportionate to the risks, impede equitable access to research opportunities and introduce bias.”
(Knowles, Bull et al. 2011)

Many identical challenges were faced in the gastroschisis parent study.

Another significant question raised by the parent and child study was: do appropriate tools exist to measure the outcomes of interest in children born with gastroschisis? For two of the key domains, abdominal symptomatology and abdominal wall cosmesis, the answer was clearly 'no'. Despite efforts to identify appropriate tools, none could be found.

A challenge of child-reported outcome assessment relates to changes with advancing age or the problem of trying to measure a constantly '*moving target*' (Wong, Forrest et al. 2013). Child perception of many outcomes may alter with advancing maturity, differing life-priorities and preoccupations, interpersonal relationships, responsibilities and self-awareness (Matza, Swensen et al. 2004). James Clarke, an adult male writer, who described his life after being born with gastroschisis in *The Guardian* newspaper evocatively portrayed his change in sensitivities with age concerning his abdominal appearance:

"At university, my scar became a secret. Being scarred meant being scared, afraid of how a misunderstanding heart and mind might respond when confronted by my twisted skin. I felt self-conscious and embarrassed. As a child, I enjoyed walking along the edge of the pool with face after face drifting their gaze towards me for a moment. Now, as much as I wanted to, I never went swimming."

(Clarke 2006)

Other researchers have described altered feelings about scarring and appearance with advancing age and the potential negative long-term impacts of these (Rumsey and Harcourt 2004, Wong, Forrest et al. 2013). The limited studies that have collected data from adults with gastroschisis suggest that abdominal wall cosmesis is a life-long concern (Davies and Stringer 1997, Koivusalo, Lindahl et al. 2002). It will clearly be important in future studies to explore cosmesis and other patient-reported outcomes (PROMs), for example those related to well-being, at different stages of life in order to fully appreciate the impact of early AWD management.

7.3 Incorporating parent and child experiences into evaluation of management in AWD

Providing the best possible care to children born with abdominal wall defects and their families necessarily requires an understanding of their experiences as well as their outcomes. There is now widespread appreciation of the need to understand these experiences in order to improve the quality of care (Darzi 2008). Listening to parent and patient experiences is clearly only the first stage of the process, however. The next will be to act on these and disseminate the messages to other health-care professionals. The conduct of a wider version of the exomphalos parent interview study would be of value in robustly assessing the depth and breadth of these experiences. Such a study could, for example, start to identify whether experiences are more or less positive with different staged management strategies or what the wider ranges of experience of vaginal and operative delivery are for mothers of babies with exomphalos. The challenges of conducting interventional studies into management in exomphalos have been described and as yet there are no observational data to support management decisions. Patient choice is an essential element of modern healthcare (Department of Health 2015) and where no current evidence of a difference in efficacy exists, it is reasonable to offer parents a choice of management strategy. Such a choice would be better informed by a richer understanding of the holistic lived experience of parents following each management strategy.

7.4 Messages for clinical practice

7.4i Communication and professional attitude

The findings of the parent interview study highlight the importance of the style, frequency and consistency of communication from health-care professionals which can seemingly ‘make or break’ the parents’ experience. In particular, the joy of pregnancy and childbirth should not be lost for these families.

Related to this should be the adoption of an approach that cares for the whole child as a person who will be a future contributor to society rather than as 'an anomaly' in isolation which can lead to a mechanistic action-reaction attitude to their clinical problems that lacks empathy.

An extension of this is the need to consider the wider family context of the child and their requirements for support which may be emotional, financial or logistical, and relate to parental employment or care of other siblings. Parents, and the decisions they make, should be respected by health professionals and as a result of the work presented here, these decisions will now be able to be informed by the best quality data currently available on the short and long term outcomes of children born with abdominal wall defects.

7.4.ii Prenatal counselling

Exomphalos

The exomphalos cohort study reports early outcomes and a longer-term view of these outcomes will clearly be essential. The data from this study and that of a planned one-year follow-up study could be used in the future to update the parent and clinician leaflets on exomphalos produced by the Fetal Anomaly Screening Programme (FASP) which currently contain inaccurate and outdated information (FASP-I 2013, FASP-II 2013).

In the current absence of robustly verified prognostic antenatal markers (beyond the results of invasive prenatal tests showing major chromosomal abnormality), fetal medicine consultants must strike a cautious balance in the tone of their counselling. The uncomplicated course of most infants born with exomphalos, particularly those without severe associated anomalies, is emphasised although the clear message from the parent interview study was that a frank discussion about possible long-term sequelae could help to ameliorate distress when later problems did occur. The inclusion of paediatric surgeons in discussions with parents both before and after the decision to continue the pregnancy would allow a key perspective to be included.

When planning delivery, the lack of current evidence to suggest that one mode is favourable over another should be made clear and, as described earlier, women should be counselled concerning all of the potential consequences of their choice. This is particularly important with regard to the physical limitations for mothers following caesarean section and, sometimes, the geographical separation from their newborn that may accompany this choice.

Gastroschisis

To date, no robust means of identifying infants with intestinal complications occurring antenatally has been reported (D'Antonio, Virgone et al. 2015). For this reason, prenatal counselling should address all of the possible sequelae of gastroschisis described in this thesis, with a strong emphasis on the fact that the vast majority of infants do not appear to have long-term sequelae.

All infants with AWD

Delivery in a facility that is closely linked to a paediatric surgical centre is recommended for all infants with AWD. In exomphalos, this is to develop and draw-on existing expertise in preservation of the sac both during and after delivery and so that any immediate neonatal concerns can be anticipated and managed appropriately. For infants with gastroschisis, the exteriorised bowel can be appropriately protected and should ischaemia or volvulus be apparent at birth or develop postnatally, this can be managed by an experienced team in a timely manner.

7.4iii Clinical management

Exomphalos

Medical sequelae of exomphalos and its related conditions should be anticipated before birth and managed appropriately. These include: pulmonary hypoplasia and the need for ventilatory support, careful attention to blood glucose levels due to the significant proportion of these infants with Beckwith Wiedemann syndrome, and careful screening for associated anomalies. As a result of the findings reported in this thesis, it is suggested that all infants undergo: echocardiogram, renal, spinal and cranial ultrasound scans as well as a thorough clinical examination for associated structural anomalies that could be missed, for example anorectal malformations, cleft-palate and subtle urogenital abnormalities.

No evidence of superior safety and efficacy of one method of staged closure over another has yet been demonstrated and a more robust evaluation will need to involve the collection of longer-term safety data. The early data from the cohort study can, however, inform discussion with parents about the different modalities and their potential risks and benefits.

Gastroschisis

Childhood outcome data from the clinical outcome study can be used for parental counselling. The long-term outlook for children who survive the neonatal period and are not at risk of the sequelae of intestinal failure was extremely good. The chances of readmission after initial discharge as well as the long-term risk of adhesive bowel obstruction should be discussed with parents before they leave hospital.

For those who do have significantly compromised bowel, strategies to minimise the sequelae of intestinal failure such as nutritional management to avoid cholestatic liver disease, prevention of sepsis and careful preservation of vascular access are essential to prolong life and prevent the need for organ transplantation (Coletta, Khalil et al. 2014). Early discussion with a centre that has experience of multidisciplinary intestinal failure management and autologous reconstruction is also crucial for such children (Hess, Welch et al. 2011) (Wood, Khalil et al. 2013).

The parent reported outcome study highlighted the psychological distress and social isolation that many parents feel when they take their babies born with gastroschisis, home. This suggests a need for health-care providers to anticipate these responses and facilitate the provision of support from health-visitors, neonatal specialist nurses and social workers where appropriate.

All infants

With relatively few infants in the gastroschisis cohort study experiencing severe adverse long-term sequelae, attention must now be drawn to subtler early management factors that may influence long-term neurodevelopmental outcomes of children born with abdominal wall defects.

Some parents in the gastroschisis follow-up study raised concerns about their child's ability to concentrate and retain information; the extent to which these concerns are more widespread within the cohort or differ from the normal population is unknown. Similar findings have been noted in the survivors of prematurity who will have spent prolonged periods on a neonatal unit, although it should be noted that many of these babies may have suffered a direct cerebral insult, for example, as a result of an intra-cranial haemorrhage (Johnson and Marlow 2014). In this respect, neonatal surgical research is some way behind that of long-term follow-up of preterm infants, where the influence of being born early on long-term neurodevelopment and behaviour has been extensively assessed (Johnson and Marlow 2017).

The multidisciplinary team caring for infants that spend time on neonatal intensive care as a result of early surgery must shift the focus to also consider the implications of all aspects of care on long-term neurodevelopmental outcome. This should include factors that are well established, such as close attention to tight glycaemic control and antisepsis, and also more subtle factors that may have long-term effects such as certain modalities of general anaesthesia, environmental stressors and enteral feeding with breast-milk (Johnson and Marlow 2014) (Johnson, Kochhar et al. 2016) (Marlow 2014).

7.5 Recommendations for future research

Future research will be key to building on the work described in this thesis and understanding many of the research questions it triggers. Examples of research questions and the findings of these studies that have stimulated them are shown in Tables 7.1 and 7.2.

Table 7.1 Examples of research questions generated by this work, to be answered in future studies into children born with gastroschisis

Domain	Research Questions	Research findings that stimulated this question
Parent experiences	Are parents of children born with gastroschisis sufficiently well supported by health-care and allied professionals?	33% of parents in the questionnaire study reported past negative effects of the experience on their mood/ energy levels. (5)
	Are parents given enough information about what the future holds for their children?	Parents in the questionnaire study described concerns about their children's future fertility and symptomatology. (5)
Antenatal/perinatal	What causes antenatal vascular compromise to the bowel in some fetuses with gastroschisis and can prenatal sonographic changes or biomarkers be identified to detect when this begins to occur?	Children with complex gastrochisis have a significantly worse prognostic outcome in the longer-term. (2) & (6)
	Should the definition of complex gastroschisis be further refined?	Not all children with 'simple' gastroschisis had a straightforward course. (2) & (6)
Early management and outcomes	What is the appropriate operative choice in children that require bowel resection in gastroschisis?	A high incidence of reoperation and acquired bowel obstruction was noted in children born with complex gastroschisis. (6)
	Which method of umbilical closure gives the best cosmetic result?	None of the parents in the questionnaire study thought that their child's umbilicus looked normal. (5)
	Which surgical, nutritional and central venous access management measures ameliorate the long-term adverse effects of intestinal failure?	Most of the severe adverse outcomes in these children related to those associated with intestinal failure. (6)
Childhood	How common and life-disrupting is abdominal pain, what are its causes and which managements are effective in treating it?	44% of children in the questionnaire study reported recent abdominal pain (5); 9% were known to have complained of this in tertiary centre follow-up. (6)
	What is the impact of being born with gastroschisis and its early management on neurodevelopmental and behavioural outcomes in children?	Significantly more children with complex gastroschisis had developmental delay. (6) Some parents commented on their child's inability to concentrate and retain information (5).
Adulthood	Do adults with gastroschisis continue to experience abdominal symptomatology?	See childhood abdominal pain question above (5) & (6)
	What are the long term educational outcomes and do children born with gastroschisis achieve employment equal to their matched peers?	See childhood neurodevelopment question above. (6)

(2-6) Chapter numbers the findings relate to

Table 7.2 Examples of research questions generated by this work to be answered in future studies into children born with exomphalos

Domain	Research Questions	Research findings that stimulated this question
Parent experiences	What is the breadth of experiences of parents of children diagnosed with exomphalos?	Rich and varied data on parents experiences were collected from small subset of parents (4)
	Do parents of children managed with a silo have less positive experiences than those managed conservatively?	The few parents interviewed seemed to describe experiences of conservative management more positively (4)
Antenatal/perinatal	Can antenatal sonographic or other imaging [¥] prognostic markers be identified [‡]	Many infants required ventilation after birth, some died as a result of pulmonary hypoplasia (3)
	What is the optimum mode of delivery for infants diagnosed with exomphalos?	Infants with defects of varying sizes experienced sac rupture from all modes of delivery (3)
Early management and outcomes	What is the optimum mode of surgical management of children that cannot be closed primarily?	The small sample sizes in each management group in the cohort study precluded comparative assessment (3)
	Is DWR ≥ 1.64 a reliable predictor for the use of staged closure?	DWR ≥ 1.64 was associated with the use of staged closure (3)
Childhood	Which comorbidities have prognostic significance?	Diverse comorbidities captured as a 'snapshot' from image findings only. The consequences of these are unknown. (3)
	How many infants require long-term ventilatory support? Can these infants be identified early?	7% remained ventilated at 28 days and details of those requiring modes of non-invasive ventilation and oxygen therapy is so far unknown. (3)
	What are the outcomes of ventral hernia repair after conservative management?	Favourable early outcomes of conservative management were noted but 'high-risk' procedure yet to come in these infants (later fascial closure). (3)
Adulthood	What is the burden of ongoing morbidity with regards to ventilatory insufficiency, neurodisability, cosmetic, gastrointestinal symptomatology in children born with exomphalos?	A large burden of comorbidity was observed in the cohort and the early data suggest that some are likely to require prolonged future hospitalisation. (3)

(3-4) Chapter numbers the findings relate to ¥ eg fetal Magnetic Resonance Imaging ‡ Or further evaluated in the case of Omphalocele Ratio (Fawley, Peterson et al. 2016)

7.5i The ideal study

The multicentre studies described in this thesis were designed and conducted within the limitations of time, constrained by the duration of the funding that supported them and cost, constrained by the funding itself. The methodologies were therefore chosen for pragmatic and financial reasons as well as their ability to fit into the regulatory requirements governing the conduct of this research involving children and their families. The limitations of these methodologies have been discussed in the context of the individual studies. It therefore remains to ask: what would be the best way to answer the research questions outlined in Tables 7.1 and 7.2? It would not be possible, within the limits of this chapter, to describe how all of these questions could be answered. Instead, a methodological approach to answering many of the questions shown in Table 7.1 regarding the short and long-term outcomes of children born with gastroschisis and the impact of early management on these is discussed.

7.5i.a Refining the research questions: which outcomes to assess?

Heterogeneity in outcome reporting in the published literature was evident from the systematic review and meta-analysis of short-term outcomes in gastroschisis and the relatively small number of studies that were able to be combined in the quantitative synthesis. A recent systematic review explored this further and identified a total of 50 outcomes of gastroschisis explored in published randomised controlled trials and systematic reviews (Ross and Hall 2016). The development of core outcome sets (COS) provides a methodology for homogenising outcome reporting. This approach which is increasing in popularity and scope, ensures that the key outcomes that are reported in future research into a particular condition, are those that are of prime importance to all stakeholders (Gargon 2016).

This process is already underway in paediatric surgery with the successful development of a core outcome set for Hirschsprung's disease (Allin, Bradnock et al. 2016), and these researchers are now working on the development of a core-outcome set for use in gastroschisis studies.

The results of this process are eagerly awaited, however, what is evident from the parent questionnaire study, is that the tools for assessing parent and child reported outcomes in childhood are clearly lacking. If this problem is to be tackled, for example through the development of a tool for cosmetic abdominal wall outcome, a rigorous approach would be required. This would have to follow the well-described methodology used for patient reported outcome measure (PROM) development involving the initial collection of qualitative data from a sample of children, adolescents and adults who were born with gastroschisis as well as parents of such individuals in order to ensure content validity (Fitzpatrick, Davey et al. 1998). Careful design and evaluation would ensure any potential tool met the other essential criteria of a PROM, namely: reliability, construct validity, responsiveness, precision, interpretability, acceptability and feasibility (Fitzpatrick, Davey et al. 1998).

The design of a PROM to assess the cosmetic and functional outcomes of cleft palate repair: the CLEFT-Q is currently in progress (Wong, Forrest et al. 2013). This has similarities to umbilical appearance in gastrochisis in that 'normal' may be achievable and lessons can be learnt from the way these researchers have tackled the methodological challenges of the influence of growing up on responses, and the need to look beyond appearance 'satisfaction' to the life-impacts of physical difference (Wong, Forrest et al. 2013).

7.5i.b Study design

Four potential study designs could be used to answer the research questions about the short and long-term outcomes of children born with gastroschisis:

1. A 'one-off' prospective cohort study using anonymised data
2. Secondary use of prospective audit with compulsory data submission for the purposes of research
3. An ongoing prospective consented cohort study with voluntary data submission (a registry study)
4. A consented cohort study

The first of these is exemplified in the BAPS-CASS studies described in this thesis and the limitations of this methodology have been discussed. An example of the second type is seen in use of the data from the national clinical audit into congenital heart disease surgery for the purposes of research (NICOR 2017). Centres performing this surgery have a mandatory obligation to submit data, including patient identifiers to a secure central database. Regular data quality audits are produced and there is a high level of technical and analytical support both centrally and within contributing centres, where data entry and analysis are undertaken by personnel employed within a trust specifically for that purpose (NICOR 2017). This is a robust resource which may be used for the purposes of research and has been made possible due to research investment within the wider field of cardiac care, as well as, close scrutiny of paediatric cardiac surgical outcomes as a result of the Kennedy report into paediatric cardiac surgery in Bristol (Kennedy 2001). This approach is, however, very limited in the data collected, as it was not designed for the purpose of gathering research data but for the collection and publication of short-term outcome data on mortality for ongoing clinical audit. The challenges faced by researchers using this resource as a starting point to collect more holistic long-term outcome data have previously been discussed (Knowles, Bull et al. 2011).

A UK national registry collecting outcome data for children born with gastroschisis was set up in 2016 for the purposes of future research and audit (BAPS 2016). The Gastroschisis Outcomes Registry UK (GORUK), invites voluntary submission of data from clinicians caring for infants with gastroschisis following written consent from their parents. Although no obligation to submit data exists, there is an emphasis from BAPS on the necessity for clinicians to participate in national audit in order to fulfil the criteria for revalidation (RCS 2013a). How data quality, case-ascertainment and reporting bias within GORUK will be checked is unclear, although the use of HES data to cross-check inpatient episodes may assist. The limitations of voluntarily submitted data have been discussed in Chapter Two and relate to the fact that such data are likely to be subject to reporting bias.

Although a consented cohort study is likely to be the most costly and logistically challenging of the four suggested designs, it would be the author's first choice for assessing short and long-term outcomes of children born with gastroschisis. Such a study would ideally enrol parents at antenatal diagnosis and involve fetal medicine consultants so that antenatal findings could be mapped to outcomes.

Samantha Johnson, a developmental psychologist at the University of Leicester, and Neil Marlow, professor of neonatology at University College London, who have designed and conducted a large number of neonatal follow-up studies in the UK, offer much useful advice throughout a number of publications, on the design and conduct of this type of study (Johnson and Marlow 2014, Johnson and Marlow 2017). In a similar manner to when planning a clinical trial, they suggest a clear hypothesis should be established at the outset and that, *"pre-study power calculations using realistic estimates of group differences are computed"* (Johnson and Marlow 2014). The primary research question, and the resulting calculation would therefore guide the necessary sample size of such a study.

Due to the relatively small number of infants born yearly in the UK with gastroschisis it is likely that there would be a necessity to prospectively collect population-based data over a considerable period of time, i.e. years (Owen, Marven et al. 2010). If logistics and finances were no object, an international study would help to produce an even larger sample size and increase the statistical power to detect smaller differences in less-common outcomes as well as allowing for adjustment for potential confounders. This approach would, however, pose challenges related to differing management practices and different background population characteristics. An example of this potential population difference is seen in the very different background rates of NEC in infants with the same median gestational age, defined using the same criteria, observed in the placebo arms of two recent large neonatal trials of probiotic therapy published from two different countries. NEC rates were 4.4% in an Australasian trial (Jacobs, Tobin et al. 2013) and 9.4% in the UK trial (Costeloe, Bowler et al. 2016). The cause of this difference is unknown but suggests that unmeasured confounding may be a significant problem in the design of international studies.

In order to robustly assess long-term neurodevelopmental and cognitive outcomes, the enrolment of controls from the same hospital as the case is recruited from would allow the opportunity for long-term comparison. These could, for example, be the next infant to be born in the same unit as the 'case'. Parental consent would be necessary and this could potentially introduce recruitment bias. Gestational age matching of controls would generate a cohort of controls with a similar distribution of prematurity to the cases, although if this were undertaken, the impact of gestational age would not be able to be assessed in the analysis, which would clearly be a disadvantage of this approach. Gestational age matching would present logistical challenges due to the variability in gestational age within the population of children born with gastroschisis as their gestational age matched counterparts may either be managed on the postnatal ward or the neonatal unit. Having a dedicated research nurse identifying and recruiting controls would be essential to the success of this methodology.

Collection of information at recruitment from cases and controls about potential confounders such as socio-demographic data and information about parental mental health would be essential (Johnson and Marlow 2014). Loss to follow-up is an important source of bias in these studies and long-term engagement from 'controls' would be as important as that of the 'cases' (Marlow 2013). Approaches from neonatal follow-up studies that have been proven to improve follow-up rates should be adopted. Examples of these include study-logo 'branded' gifts such as small toys; having a dedicated follow-up coordinator; regular contact via social media, post and email; thanking participants; and regular feedback of study results (Marlow 2013).

Data should be collected about the first admission episode of cases and controls and, with appropriate initial consent, information about events after transfer from the tertiary centre or information about subsequent admissions, or these could be tracked using electronic health records. Whilst the child is in neonatal care, data submitted to the National Neonatal Database could be used (Spencer and Modi 2013). This widely adopted neonatal data-sharing system has the potential to be a useful repository of information regarding this early period. Subsequent episodes of admission could be tracked using Hospital Episode Statistics (HES) as the central research team would possess key identifiers such as the NHS number. The limitations of HES data have been discussed in Chapter Two but briefly, its reliance on the accurate clinical coding of episodes of inpatient admission as well as effective linking of independent episodes using the NHS number mean that it may not always provide a complete picture. Furthermore, episodes of ill-health that did not result in a hospital admission will also be missed.

Childhood assessment should commence at two years, a standard time-point for developmental assessment after neonatal care (Marlow 2015). Neurodevelopmental and cognitive data would be best collected through formal assessments using validated tools with assessors blinded to the child's early history (Marlow 2013). Other outcome data on parameters of interest such as growth and symptomatology could be collected at the same time.

Later follow-up assessments would be necessary at pre-selected time-points as children mature, but it is noteworthy that the impact of early factors on neurological and cognitive outcomes are likely to become diluted by other social and environmental influences as age progresses (Marlow 2013). In addition to face-to-face assessment, educational data from early assessments could be compared both to that of controls as well as population norms, adjusted for key confounders such as socioeconomic status (Quigley, Poulsen et al. 2012).

A similar long-term consented cohort study has been set-up to undertake long-term follow-up of children in England born with cleft-lip and/or palate (CLP) under the auspices of a UK-wide programme of research known as 'The Cleft Collective' (Stock, Humphries et al. 2016). In a recent publication, the research team outline what they regard to be the key components of success and of their study that differ from previous studies as well as describing the challenges that they have faced in study set-up (Stock, Humphries et al. 2016). The components of success are summarised in Table 7.3 along with comments on the relevance of these points to a gastroschisis consented cohort study.

It is noteworthy that the Cleft Collective estimate the set-up costs of their two cohort studies, which have recruited 1232 individuals from 430 families to date, at £10 million (Stock, Humphries et al. 2016). However, the benefits of this type of approach and level of resource investment over a registry study in order to obtain detailed, unbiased short and long-term outcome data cannot be over-emphasised.

Table 7.3 Components of success in the UK CLP cohort studies (Stock, Humphries et al. 2016)

Key components of success in CLP cohort studies	Application within a gastroschisis consented cohort study
1. Multi-disciplinary collaboration - Holistic approach to follow-up, e.g. psychological assessment, neurodevelopment and involvement of allied health-professionals. 2. Universal recruitment 3. Parent and patient involvement in study development 4. Collection of baseline information 5. NIHR portfolio adoption – Financial support vital to successful recruitment 6. Site visits and staff training 7. Recruitment ‘targets’ based on known incidence 8. Antenatal recruitment	Involvement of fetal medicine, neonatology and paediatrics (general and specialities, such as developmental, gastroenterology, respiratory, nursing, psychology and allied health professionals) Aim to include all families, with particular efforts to recruit and retain those with socioeconomic disadvantage Learn from parents about best methods of recruiting and retaining individuals, what concerns they may have and how to reach the ‘hard-to-reach’ Detailed early and perinatal data collection along with perinatal and sociodemographic information and data on parental mental health This reduces the burden of work from clinical teams and could, for example, provide funding for a neonatal research nurse with established family rapport who could assist recruitment Face-to face interaction from the research team to motivate, engage centres, ensure methodological rigour and comprehensive data collection A more rigorous approach to case-ascertainment This would facilitate the collection of robust antenatal data

7.6 Summary

The studies described in this thesis have contributed significantly to contemporary understanding of the population characteristics, management and short-term outcomes of children born with exomphalos and the outcomes in childhood of children born with gastroschisis. The data generated can be used to inform parental counselling and clinical practice and have stimulated questions to be answered in future research studies.

The necessity for an understanding of the impacts of early surgical care on the later lives of the children we treat is undeniable and was a recommendation of the inquiry into children's cardiac surgery in Bristol (Kennedy 2001). To quote Dr Jay Wilson, Associate Professor of Paediatric Surgery at Harvard Medical School on the subject of long-term follow-up of neonatal surgery: *"If you don't know how they are doing, how can you know how you are doing?"* (Wilson 2013). The difficulties encountered in the long-term follow-up studies described here and their methodological limitations highlight the fact that this is a challenging and complex process, particularly within the current constraints of research funding and governance (Marlow 2013) (Knowles, Bull et al. 2011). It is clear that robust long-term follow-up assessment will require significant resource investment, multidisciplinary collaboration, and focused and dedicated research leadership.

Evolving methodologies such as the development of core outcome sets and increasing emphasis in governmental policy on the collection of patient-reported outcome data offer hope for a more considered and holistic approach to the collection of outcome data in the future. However rationalisation of research regulation and governance is needed in order facilitate this vital endeavour.

Improving parent and child experiences must also be at the heart of future work and it is clear from the small but data-rich parent interview study that there is much that is yet to be achieved in this field. As the author of this thesis I am motivated to take this work forward, build on its findings and work towards answering some of the many research questions that it has inspired.

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Appendix 1

The normal embryological development of the abdominal wall

After implantation in the uterine wall, the collection of cells that have proliferated from the original zygote, (first cell), form into a three-dimensional structure composed of two fluid filled cavities on either side of a flat disc. After the end of the third week post-conception, the flat disc bends and folds in on itself in a purse-string like manner. This folding occurs towards the surface of the embryo that will form the future abdominal wall, (known anatomically as the ventral surface) due to differential rates of growth of structures at the poles and edges of the disc. The folding 'pinches off' a length of the sac of fluid adjacent to the ventral surface to form a tube that runs along the length of the embryo. This tube will eventually form the gastrointestinal tract and for a while this 'gut tube' remains in contact with the sac outside of the embryo via a small connection at the point where the body folds converge, the site of the umbilical cord insertion, which is known as the umbilical ring (Human Embryology, 2008).

Following this, between approximately six to eight weeks post-conception, the gut tube then elongates out of proportion to the growth of the rest of the embryo. In order to achieve this sudden increase in length, the developing gut protrudes outside of the embryo, into the surrounding fluid. Thus, in all normal developing fetuses, herniation of the bowel outside of the body, through the umbilical ring occurs early in gestation. After ten to twelve weeks the bowel returns to the now expanding abdominal cavity to lie in its final position. The umbilical ring reduces in size relative to the fetus and the connection between the bowel and the surrounding fluid degenerates so that the cord will eventually only contain the blood vessels between the fetus and the placenta (ibid).

The muscle layers of the left and right halves of the abdominal wall then fuse together above and below the umbilical cord insertion either through migration of progenitor cells from the area at the back of the embryo, either side of the developing spine, to the ventral surface or through the differential growth of areas of the muscular body wall throughout gestation (Brewer and Williams 2004, Mekonen, Hikspoors et al. 2015).

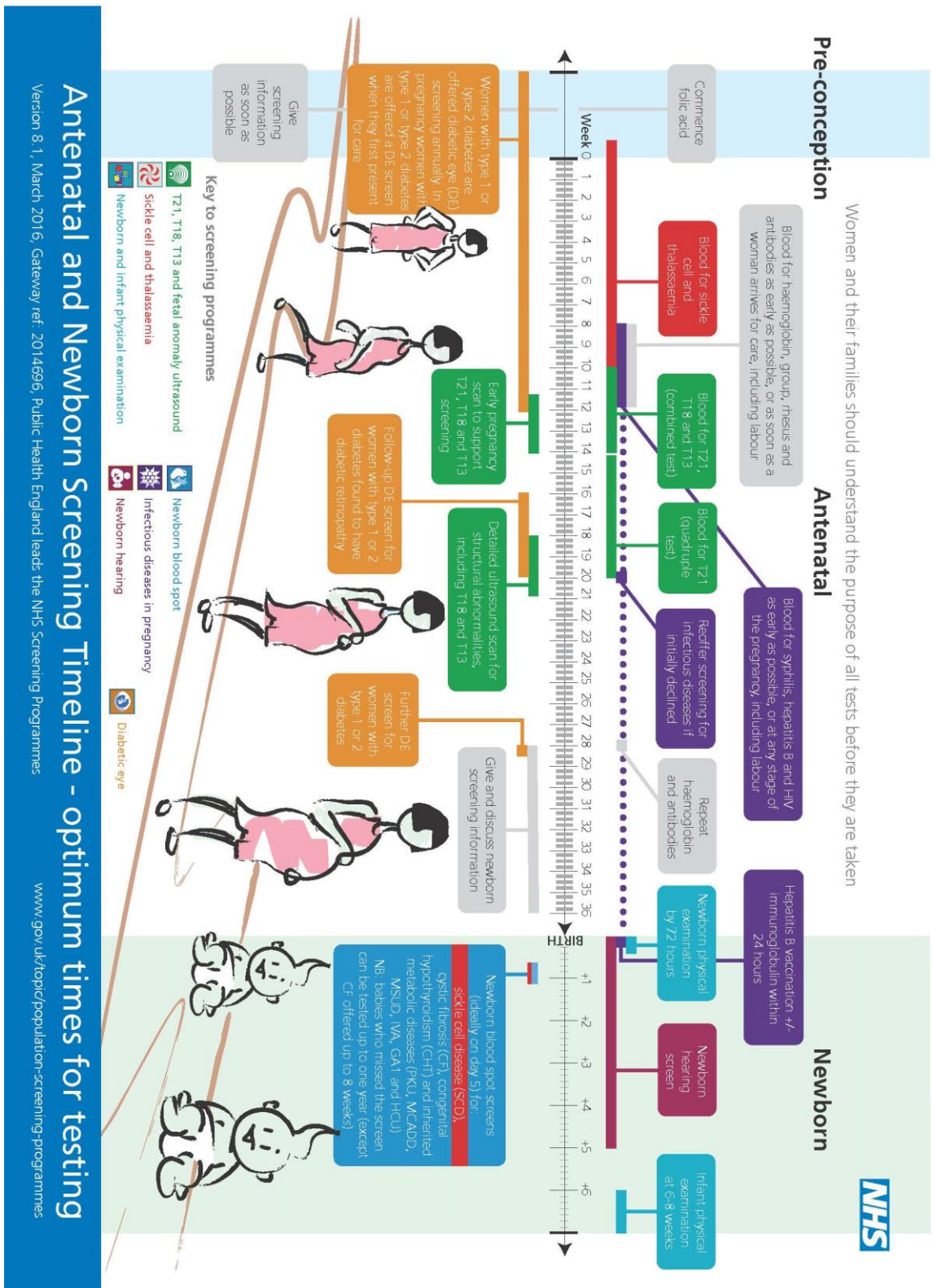
The exact developmental origin of gastroschisis and exomphalos remain somewhat elusive and numerous theories abound, a description of which are outside of the scope of this thesis (Hoyme, HE. Higginbottom, MC. et al. 1981, Feldkamp, Carey et al. 2007, Rittler 2013 Lubinsky 2014, Brewer & Williams 2004, Dauvé & McLin 2013). Both conditions are however thought to be aberrations in the normal processes of abdominal wall and gastrointestinal development that have been described above.

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Appendix 2

The UK antenatal screening timeline

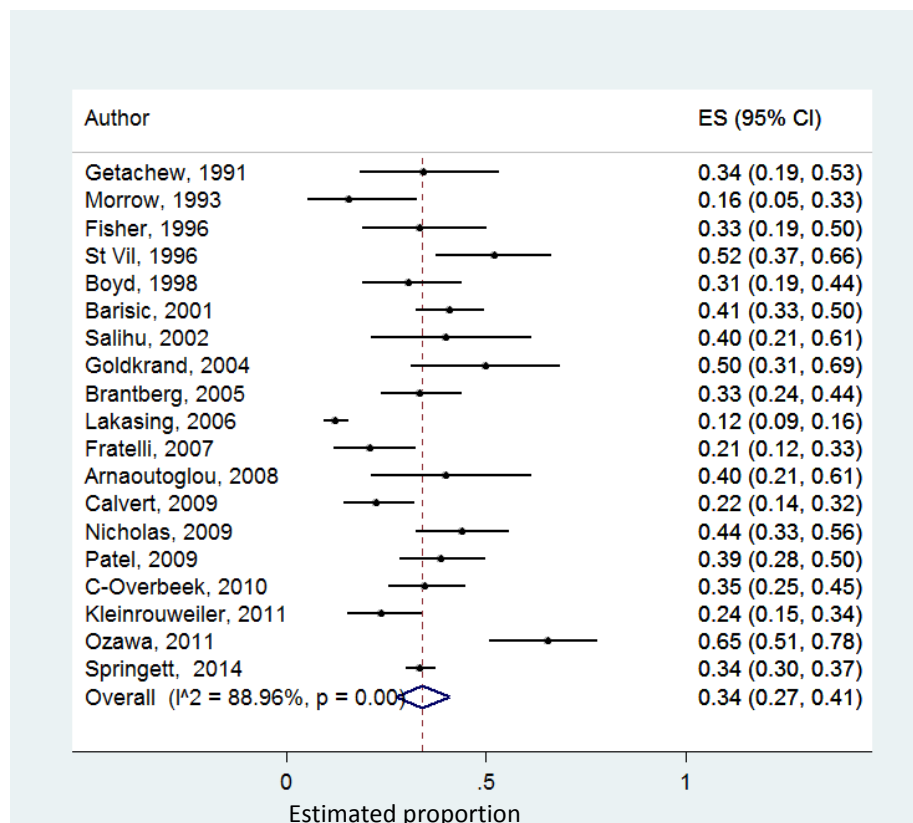


Appendix 3

Proportion of antenatally diagnosed fetuses with exomphalos that are born alive

The author undertook a literature review using *Medline* to identify published data regarding the proportion of infants with antenatally diagnosed exomphalos that are live-born as documented within recent published studies. Studies reporting the outcomes of exomphalos pregnancies in more than ten women, regardless of location were included. The results were synthesised using the *metaprop* function in *Stata 13 SE* and are illustrated below.

The proportion of all infants with exomphalos diagnosed antenatally that are born alive

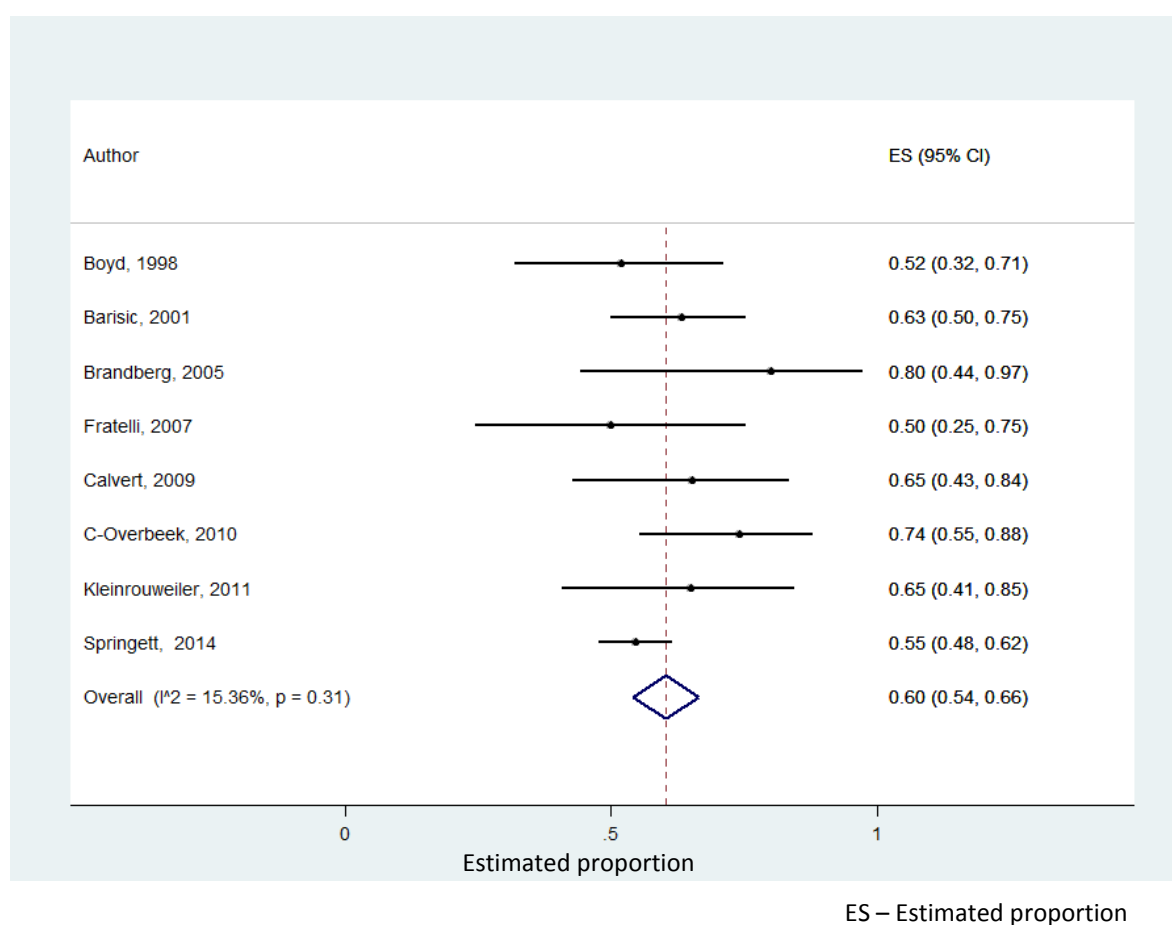


ES – Estimated proportion

The proportion is highly variable but was estimated at 34% (95%CI 27-41%).

A further comparison from the same literature review that is more illustrative of practice variation are the differing rates of both live-birth and termination of fetuses with of apparently isolated exomphalos[†], reported between studies where this information was provided. This figure below shows the synthesised data from recent studies where rates have been able to be calculated.

The proportion of infants with isolated exomphalos diagnosed antenatally that are born alive



Wide variation is again seen with one of the lowest proportions observed in a recent UK cohort study (Springett 2014). The pooled proportion was 60% (95%CI 54-66%).

[†]Exomphalos with no other associated structural or genetic abnormalities

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Appendix 4

Modified Newcastle Ottawa Quality Assessment Scale for cohort studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

- 1) Representativeness of the exposed cohort
 - a) truly representative of the average _____ (describe) in the community *
 - b) somewhat representative of the average _____ in the community *
 - c) selected group of users eg nurses, volunteers
 - d) no description of the derivation of the cohort
- 2) Sample size[€]
 - a) Justified and satisfactory. *
 - b) Not justified.
- 3) Ascertainment of exposure
 - a) secure record (eg surgical records) *
 - b) structured interview *
 - c) written self report
 - d) no description
- 4) Demonstration that outcome of interest was not present at start of study
 - a) yes *
 - b) no

Comparability[€]

- 1) The subjects in different outcome groups are comparable, based on the study design or analysis.
Confounding factors are controlled.
 - a) The study controls for the most important factor (select one). *
 - b) The study controls for any additional factor. *

Outcome

- 1) Assessment of outcome
 - a) independent blind assessment *
 - b) record linkage *
 - c) self report
 - d) no description
- 2) Was follow-up long enough for outcomes to occur
 - a) yes (select an adequate follow up period for outcome of interest) *
 - b) no
- 3) Adequacy of follow up of cohorts
 - a) complete follow up - all subjects accounted for *
 - b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
 - c) follow up rate < ____% (select an adequate %) and no description of those lost
 - d) no statement

Appendix 5

Table of excluded studies (n=149)

Reason for Exclusion	Study ID
Not consecutive cohort n= 34	Abdel-Latif, 2008, Aina-Mumuney, 2004, Ajayi, 2011, Algert, 2008, Banyard, 2010, Baud, 2013, Bulhak Guz 2007, Cherian, 2006, Chilarski 2005, Clark, 2009, Clark, 2011, Curry, 2004, Hassan, 2011, Houben, 2009, How, 2000, Jensen, 2009, Kidd, 2003, Krause, 2009, Logghe, 2005, Long, 2011, Mahieu-Caputo, 2002, Moir, 2004, Ogasawara, 2009, Olesevich, 2005, Pastor, 2008, Salihu, 2004, Sandler, 2004, Segal, 2014, South, 2011, Strauss, 2003, Werbeck, 2011, Wilson, 2012, Wu, 2003,
Ineligible* n= 82	Abdelhafeez, 2011, Akhtar, 2012, Alali, 2011, Aljahdali, 2013, Alvarez, 2007, Arnaoutoglou, 2008, Baerg, 2003, Baird, 2011, Baird 2012, Bianchi, 2002, Brindle, 2012, Bulhak Guz 2006, Calisti, 2012, Carnaghan, 2014, Cauchi, 2006, Centers, 2007, Chesley, 2015, Chivukula, 2012, Dastgiri 2003, Davies, 2005, Davis, 2009, Ergun, 2005, Gorra, 2012, Gover, 2014, Hadidi, 2008, Hidaka, 2009, Hill, 2013, Hook-Dufresne, 2015, Hougland, 2005, Huang, 2002, Juhasz-Boss, 2012, Kandasamy, 2010, Kimble, 2001, Kitchanan, 2000, Kohler, 2013, Lansdale, 2009, Leadbeater, 2010, Lund, 2007, Luis 2003, Lusk, 2014, Maramreddy, 2009, Martinez, 2012, McClellan, 2011, McGuigan 2004, Mears, 2010, Midrio, 2007, Mills, 2010, Minkes, 2000, Nasr, 2012, Nasr, 2013, Nazer, 2013, Nicholas 2009, Owen, 2006, Payne, 2010, Polnik, 2004, Puligandla, 2004, Puligandla, 2004, Rahn, 2008, Ramadan, 2010, Riboh, 2009, Rygl, 2004, Safavi, 2012, Saxena, 2002, Serra, 2008, Skarsgard, 2008, Snyder, 2001, Snyder, 2005, Stanger, 2014, Soares, 2010, Szczepinska-Sobutka, 2007, Tennant 2010, Van, 2006, Van Eijck, 2008, Vandewalle, 2015, Van, 2012, Van, 2013, Weil, 2012, Whitehall, 2010, Yagi, 2015
Overlapping cohort n = 33	Abdullah, 2007, Alfaraj, 2011, Arnold 2007, Arnold, 2007, Berger 2002, Boutros, 2009, Chang, 2010, Contro, 2010, Cowan, 2012, Driver, 2000, Durfee, 2013, Fillingham, 2008, Fratelli, 2007, Ghionzoli, 2012, Huh, 2010, Jansen, 2012, Japaraj, 2003, Kaiser, 2000, Lao, 2010, Lobo, 2010, Manson, 2012, Nembhard, 2001, Owen, 2010, Piper, 2006, Raghavan, 2008, Rao, 2009, Reid, 2003, Ruano, 2011, Salihu, 2004, Salihu, 2003, Snyder, 2011, Walter-Nicolet, 2009, Weinsheimer, 2008

***These studies did not report any of the selected outcomes or reported them in a way that could not be meta-analysed**

Appendix 6

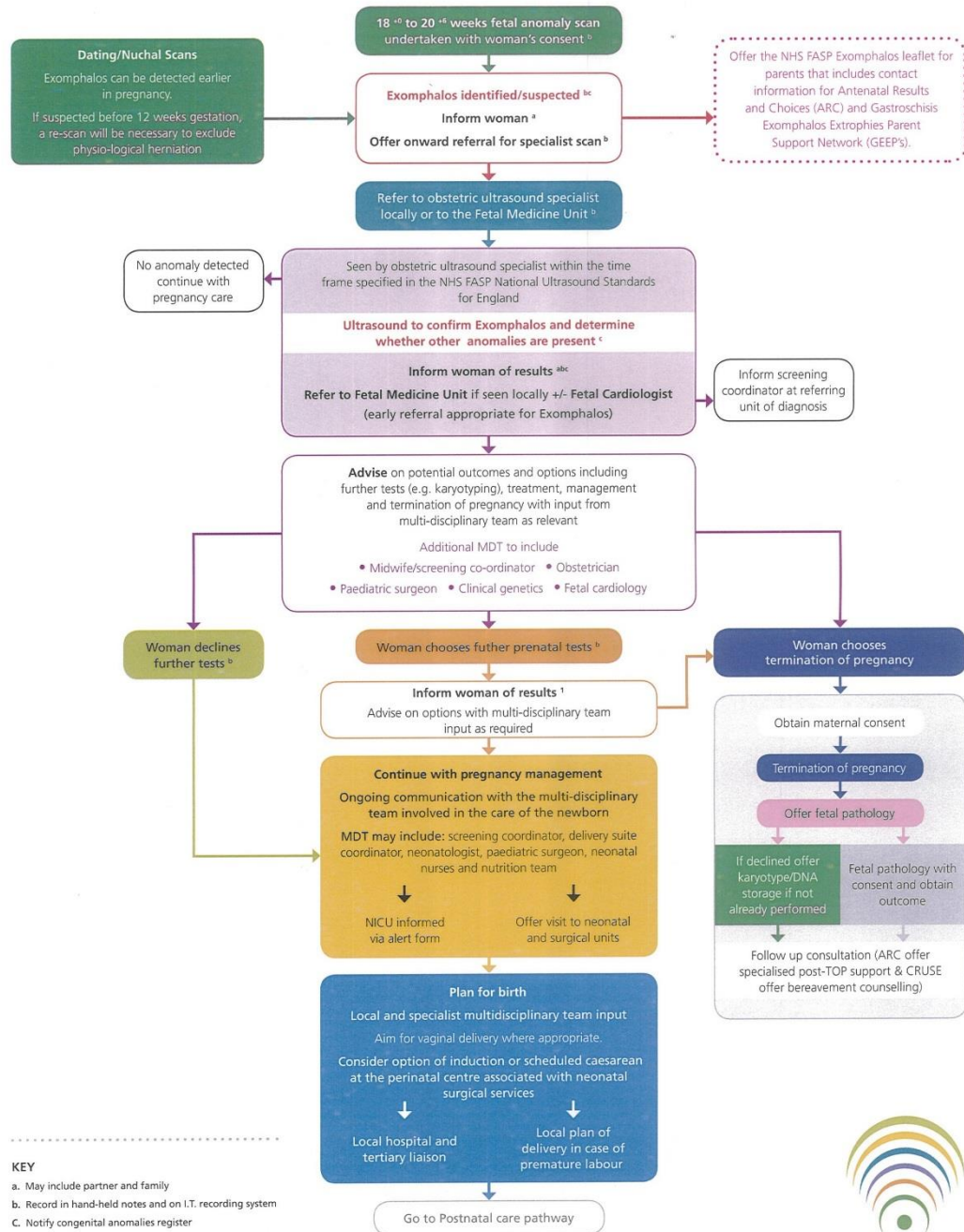
Inclusion criteria for categories of comorbidity in exomphalos

	Definition	Included
Isolated	Exomphalos with no identified structural or genetic defects other than those listed	5. Infants with respiratory distress/ pulmonary hypoplasia 6. Infants with gastrointestinal malrotation 7. Normal variants including positional talipes, Liver haemangioma 8. PDA only 9. Undescended testes/ inguinal hernia 10. Calcification of the spleen 11. Acquired pathology e.g. intra-ventricular haemorrhage 12. Non dilating vesico-ureteric reflux
Syndromic/ Chromosomal/ Genetic	All named structural malformation syndromes, single gene disorders and chromosomal anomalies	• All trisomies • Translocations and microdeletions • CHARGE • Pierre Robin sequence • Apert's syndrome • Axial mesodermal dysplasia • Pentalogy of Cantrell
Structural	Single or multiple structural anomalies in the absence of a named syndrome, malformation sequence or genetic abnormality	• Any structural cardiac defect including ASD/ PFO • Major vessel anomalies • Any USS detected renal tract anomaly including: - Single/ duplex/ pelvic kidneys - Hydronephrosis (any) - Echogenic kidneys • Structural cranial ultrasound scan anomalies with prognostic significance • Vitello-intestinal duct remnants • Any intestinal atresia including anorectal malformation • Macrocephaly/ dysmorphic features • Limb abnormalities including polydactyly and overlapping digits • Ambiguous genitalia • Abnormal gall bladder • Pineal gland cyst
Beckwith Wiedemann Syndrome (BWS)	Beckwith Wiedemann syndrome	• Confirmed BWS • Clinical features of BWS and family history where not confirmed before death and no post-mortem examination

Appendix 7

Antenatal care pathway for health-professionals for children born with exomphalos

Antenatal care pathway for abdominal wall defects: exomphalos (omphalocele)
for health professionals



Postnatal care pathway for health-professionals for children born with exomphalos

Postnatal care pathway for abdominal wall defects: exomphalos (omphalocele) for health professionals



Screening programmes

Fetal Anomaly

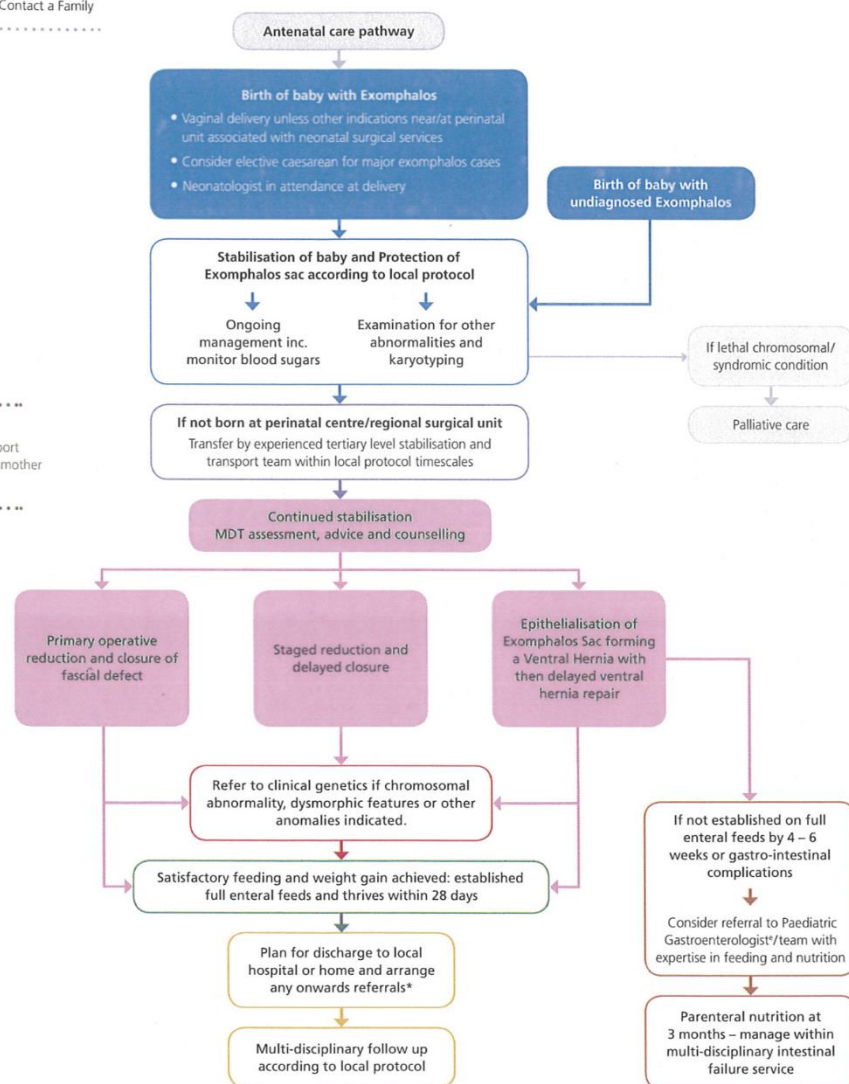
Offer parents information on support services: counselling, BLISS, GEEP's and Contact a Family

NUTRITION
MDT and expert nutrition support team discuss feeding with the mother as soon as possible.

* Referrals may include:
Local paediatrician
Community nursing
Dietician
GP
Health visitor

KEY

- * notify congenital anomalies register
- * Inform screening coordinator/midwife at referring unit and GP.
- * Refer to BSPGHAN pathway for surgical neonates with intestinal failure



An example of a BAPS-CASS reporting card

353

Appendix 9

Exomphalos cohort study data collection form

ID Number:

British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS)

Exomphalos

Data Collection Form

Details of treatment up to 28 days following surgery/decision for non-operative treatment

Infants presenting on or after 1st March 2014 and before the 1st March 2015

Exclude:

All infants with gastroschisis

Case Definition:

Any live-born infant with herniation of abdominal content through the umbilical ring, the contents being covered by a membrane. This membrane may have been ruptured at the time of delivery.

Instructions

1. Please do not enter any personally identifiable information (e.g. name, address or hospital number) on this form.
2. Please record the ID number from the front of this form against the infant's name on the Clinician's Section of the blue card retained in the BAPS-CASS folder.
3. Fill in the form using the information available in the infant's case notes.
4. If codes or examples are required, some lists (not exhaustive) are included on the back page of the form.
5. Tick the boxes as appropriate. If you require any additional space to answer a question please use the space provided in section 8.
6. Please complete all dates in the format DD/MM/YY, and all times using the 24hr clock e.g. 18:37
7. **If you do not know the answers to some questions, please indicate this in section 8.**
8. If you encounter any problems with completing the form please contact the Study Administrator or use the space in section 8 to describe the problem.

Please return the completed form to:

BAPS-CASS
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Oxford
OX3 7LF
Fax: 01865 617775
Phone: 01865 289714



Case reported in: _____

Section 1: Antenatal / Birth Data

- 1.1 What was the mother's year of birth?
- 1.2 Please give the first alphabetical part of mother's postcode
(e.g. OX for Oxfordshire, EH for Edinburgh, L for Liverpool)
- 1.3 Ethnic group^{1*}
- 1.4 Has the mother ever had a pregnancy where the fetus has been diagnosed with either exomphalos, a structural anomaly, a chromosomal anomaly or malformation syndrome? (excluding this pregnancy) Yes ☐ No ☐
If Yes, please specify _____
- 1.5 Is there any family history of exomphalos or related conditions including syndromes? Yes ☐ No ☐
If Yes, please specify _____
- 1.6 Gestational age at birth (completed weeks)
- 1.7 Gender male ☐ female ☐ indeterminate ☐
- 1.8 Birthweight g
- 1.9 What was the planned mode of delivery prior to the onset of labour? Vaginal ☐ Caesarean ☐
If Caesarean was planned, what was the indication _____
- 1.10 What was the mode of delivery? Spontaneous vaginal ☐ Ventouse ☐ Forceps ☐
Breech ☐ Pre-labour caesarean section ☐ Caesarean section after onset of labour ☐
- 1.11 Was exomphalos suspected antenatally? Yes ☐ No ☐
If Yes, at what gestational age was it first suspected weeks
- 1.12 Was the mother offered amniocentesis and/or CVS? Yes ☐ No ☐
If Yes, did the mother refuse these tests? Yes ☐ No ☐
If No, please tick all that were performed and give details of results Amniocentesis ☐ CVS ☐
Results: _____
- 1.13 Were any other anomalies detected antenatally? Yes ☐ No ☐
If Yes, please specify _____
- 1.14 Was a syndrome suspected? Yes ☐ No ☐
If Yes, please specify _____
- 1.15 Did the mother receive prenatal surgical counselling? Yes ☐ No ☐

Section 2: Initial Presentation and Management

- 2.1 Age in days at first presentation to your hospital days
- 2.2 What was the date of presentation? / /
- 2.3 Was the infant transferred from another hospital? Yes ☐ No ☐
If Yes, please specify where the infant was born? _____
- 2.4 Was the defect size at the level of the abdominal wall measured/estimated? Yes ☐ No ☐
If Yes, what was the diameter? cm
If No, Was the infant considered to have an exomphalos major? Yes ☐ No ☐

2.5 Was the maximum width of the sac measured/estimated? Yes ☐ No ☐
 If Yes, what was the diameter? cm

2.6 Was the liver in the sac? Yes ☐ No ☐

2.7 Was the sac ruptured? Yes ☐ No ☐
 If Yes, when was the sac known to have ruptured?
 Before delivery ☐ During delivery ☐ After delivery ☐ Time not known ☐

2.8 Apart from exomphalos, were there any other anomalies detected on clinical examination? Yes ☐ No ☐
 If Yes, please specify all _____

2.9 Was the infant commenced on antibiotics in the first 48 hours of life? Yes ☐ No ☐
 If Yes, please complete the table below:

Agent	Route of administration	Indication	Duration (days)

2.10 Were any imaging investigations undertaken on the infant? Yes ☐ No ☐
 If Yes, please complete the table below:

Investigation	Date	Describe any abnormalities detected (please state if none)
Ultrasound KUB Yes ☐ No ☐	DD MM YY	
Ultrasound Head Yes ☐ No ☐	DD MM YY	
Ultrasound Spine Yes ☐ No ☐	DD / MM YY	
Echo Yes ☐ No ☐	DD MM YY	
MRI Head Yes ☐ No ☐	DD MM YY	
UGI Contrast Yes ☐ No ☐	DD MM YY	
Other Yes ☐ No ☐	DD / MM / YY	

If Other, please specify: _____

Section 3: Management of the Sac

3.1 Did the infant have bowel reduction and cord ligation whilst on the unit without attending theatre? Yes ☐ No ☐
 If Yes, please go to section 5
 If No, please continue

Non-Operative Therapy

3.2 Did the infant have non-operative therapy? Yes ☐ No ☐
 If No, please go to section 4

3.3 What was the indication? (tick one only)

Consultant's routine practice in viscerio-abdominal disproportion ☐

Infant unfit for surgery ☐

Concern about comorbidities ☐

Other ☐

If Other, please specify: _____

3.4 Were any dressings applied to the sac? Yes ☐ No ☐
 If Yes, please give details of any dressing applied: _____
 What date were dressings stopped altogether? / /

3.5 Were any topical therapies applied to the sac/ skin? Yes ☐ No ☐
 If Yes, please give details of any topical therapies: _____
 What date were topical therapies stopped altogether? / /

3.6 Were silver levels measured in the infant? Yes ☐ No ☐
 If Yes, what was the highest recorded level mg/L OR nmol/L

3.7 Was there any evidence of sac damage or leak during non-operative therapy? Yes ☐ No ☐
 If Yes, did the infant require surgery because of this? Yes ☐ No ☐

3.8 Was the infant discharged home or transferred before full epithelialisation? Yes ☐ No ☐

3.9 How long did the defect take to completely epithelialise? weeks
 Not epithelialised yet ☐

3.10 Were elastic compression devices used on the abdomen? Yes ☐ No ☐

Section 4: Surgical Management

4.1 Did the infant have surgery? Yes ☐ No ☐
 If Yes, please specify date: / /
 If No, please go to Section 5

4.2 Please specify the sequence of operative procedures, including all those attempted at first closure (tick all that apply)

Procedure	Attempted	Successful	Unsuccessful	Please indicate the order in which procedures were attempted (1,2,3 etc)	Please indicate the date when procedures were attempted
Closure of fascia	☐	☐	☐ Reason: _____		
Silo Formation	☐	☐	☐ Reason: _____		
Bridging of fascia with a patch	☐	☐	☐ Reason: _____		
Skin closure without fascial closure	☐	☐	☐ Reason: _____		

4.3 Was a silo used? Yes ☐ No ☐

If Yes, was the sac removed? Yes ☐ No ☐

What materials were used to construct the silo? _____

Was controlled reduction, (silo tucking) undertaken? Yes ☐ No ☐

If Yes, were there any adverse sequelae? Yes ☐ No ☐

If Yes, please give details: _____

Was this silo operatively revised at any point? Yes ☐ No ☐

If Yes, what was the date of the revision? DD / MM / YY

What was the indication? _____

What materials were used to construct the revised silo? _____

Was the silo removed? Yes ☐ No ☐

If Yes, what date was the silo removed? DD / MM / YY

4.4 Was a patch used? Yes ☐ No ☐

If Yes, what material was used for the patch? _____

Was there a plan to remove this at a later date? Yes ☐ No ☐

Was skin apposed over the patch? Yes ☐ No ☐

4.5 Were any additional procedures performed at the time of the initial operation? (tick all that apply) Yes ☐ No ☐

Placement of a tunnelled central venous line ☐ Correction of malrotation ☐

Appendicectomy ☐ Other ☐

If Other, please specify: _____

4.6 Did any intra-operative surgical complications occur? Yes ☐ No ☐

If Yes, please specify: _____

4.7 Did the infant receive monitoring for abdominal compartment syndrome? Yes ☐ No ☐

If Yes, please specify what monitoring method was used _____

4.8 Was vacuum assisted therapy used at any point? Yes ☐ No ☐

If Yes, what was the duration? days

Section 5: Ongoing Management

5.1 Did the infant develop infection or receive intravenous, oral or topical antimicrobials during their stay for prophylaxis or treatment of proven or suspected infection (including antifungals)? Yes ☐ No ☐

If Yes, please give details below: (If agent used more than once, please add as separate episode)

Treatment (T) / Prophylaxis (P)	Agent(s) used	Indication	Duration (days)

Continue in section 8 if necessary

5.2 Was the infant ever colonised or infected by a multi-resistant organism? Yes ☐ No ☐

If Yes, please give details below:

Organism	Site of infection/colonisation	Infected	Colonised
		☐	☐
		☐	☐

5.3 Was invasive ventilatory support used (excluding CPAP)? Yes ☐ No ☐

If managed non-operatively – total number of days of ventilation days

If managed operatively – number of days of ventilation before surgery days

– number of days ventilation after surgery days

5.4 How many Peripherally Inserted Central Catheters (PICC lines) did the infant have inserted?

5.5 How many Central Venous Lines did the infant have inserted?

Section 6: Nutrition at 28 days after surgery or 28 days after decision for non-operative management

6.1 Has the infant ever received parenteral nutrition? Yes ☐ No ☐

If Yes, was the infant still receiving parenteral nutrition at 28 days? Yes ☐ No ☐

If No, give total number of days on parenteral nutrition days

6.2 What date was the infant first enterally fed (including tube feeding)? / /

6.3 Is the infant now fully enterally fed (including tube feeding)? Yes ☐ No ☐

If Yes, what date were full enteral feeds started? / /

6.4 Did the infant ever receive breast milk (including expressed or donor milk)? Yes ☐ No ☐

If Yes, was this exclusive? Yes ☐ No ☐

6.5 Did the infant receive any probiotic therapy? Yes ☐ No ☐

If Yes, please give details below:

Agent	Route of administration	Duration (hours/days)

6.6 What was the mode of feeding at 28 days or point of discharge (whichever was sooner)?

Exclusively oral ☐ Nasogastric plus oral ☐ Exclusively Nasogastric ☐

Nasojejunal plus oral ☐ Exclusively Nasojejunal ☐ Other ☐

If Other, please specify: _____

Section 7: Early Morbidity up to 28 days after surgery or up to 28 days after decision for non-operative management

7.1 Were any further surgical procedures required (If not included in table 4.2)? Yes ☐ No ☐

If Yes, please give details below:

Date of surgery	Details of further surgical procedure
/ /	
/ /	
/ /	

7.2 Did any complications relating to surgical or non-operative therapy occur? Yes ☐ No ☐

If Yes, please tick all that apply:

Abdominal wall hernia (if not intended) ☐

Wound Dehiscence ☐ Abdominal Compartment syndrome ☐

How was Abdominal Compartment syndrome diagnosed?

Other ☐

If Other, please specify:

7.3 Did the infant have any other morbidity? Yes ☐ No ☐

If Yes, please give details:

Section 8: Outcomes/Other information

8.1 Has the infant been discharged home? Yes ☐ No ☐

If Yes, specify date of discharge

/ /

8.2 What was the weight and head circumference of the infant at 28 days or point of discharge (whichever was sooner)?

Weight g

Head Circumference cm

Date / /

8.3 Has the infant been discharged to another hospital? Yes ☐ No ☐

If Yes, please give name of hospital

Name of responsible consultant at transfer hospital

Date of transfer / /

8.4 Was the infant ever diagnosed with a syndrome or a chromosomal anomaly? Yes ☐ No ☐

If Yes, please give details

8.5 Did the infant have a malrotation? Yes ☐ No ☐ Not identified through imaging or surgery ☐

If Yes, was this communicated to parents? Yes ☐ No ☐ Unclear ☐

8.6 Did the infant die?

Yes ☐ No ☐

If Yes, please give date of death

/ /

Cause of death as stated on the death certificate (*please state if not known*)

Was a post-mortem performed?

Yes ☐ No ☐

Were any additional abnormalities detected?

Yes ☐ No ☐

If Yes, please give details

8.7 Please add other relevant information below

Section 9:

Name of person completing the form

Designation

Today's date

/ /

You may find it useful in the case of queries to keep a copy of this form.

Definitions

1. UK Census Coding for ethnic group

WHITE

- 01. British
- 02. Irish
- 03. Any other white background

MIXED

- 04. White and black Caribbean
- 05. White and black African
- 06. White and Asian
- 07. Any other mixed background

ASIAN OR ASIAN BRITISH

- 08. Indian
- 09. Pakistani
- 10. Bangladeshi
- 11. Any other Asian background

BLACK OR BLACK BRITISH

- 12. Caribbean
- 13. African
- 14. Any other black background

CHINESE OR OTHER ETHNIC GROUP

- 15. Chinese
- 16. Any other ethnic group

Appendix 10

Long-term outcomes studies in children born with gastroschisis.

Table 9.1 Studies reporting outcomes of infants with gastroschisis only

Table 9.2 Studies reporting outcomes of infants with gastroschisis and those with exomphalos

Table 9.1. Long-term outcomes studies in children born with gastroschisis.

Studies reporting outcomes of infants with gastroschisis only

1 st Author, Year Institution, Location, Study Type	Length of Follow-Up	Cases Included	Outcomes Assessed	Tools Used	Key Findings
Swartz , 1986, Portland, Oregon, USA MI RC & Interview	6m-16yrs	92/104 Children born with gastroschisis 36 were > 5yrs	• Growth • Neurodevelopment • GI function • Repeat surgery	• Centile • Subjective parental assessment	• Bowel/ peritoneal inflammation is a reversible injury without long-term effect • Those who had bowel resection had more 'long-term bowel problems' and poor growth • Slow growth during infancy, with normal percentile attainment after 5yrs
Davies 1997, Leeds, UK SI Interview	12-23yrs, Median 16 yrs	23/33 survivors	• Growth • General health • Repeat surgery • Cosmesis • Abdominal symptoms • School/ employment • Social • Reproductive health	• Structured, bespoke telephone questionnaire	• Normal growth and good health in most • Cosmesis of the umbilicus is important
South 2008, North Carolina, USA SI, Evaluation at a special infant care clinic	16-24m Mean 20m	17/ 24 survivors	• Growth • Neurodevelopment • Morbidity	• z-scores • Bayley II • Bespoke questionnaire • Rome criteria • Functional status II questionnaire	• 1/3 have growth delay - SGA infants are at higher risk • Neurodevelopment is not delayed - SGA/ preterm scored lower • Continued bowel dysfunction is common

Key: SGA- Small for gestational age
SI- Single institution. MI- Multiple Institution
RC Retrospective cohort

Table 9.1. Continued. Long-term outcomes studies in children born with gastroschisis.

Studies reporting outcomes of infants with gastroschisis only

1 st Author, Year, Location, Study Type	Length of Follow-Up	Cases Included	Outcomes Assessed	Tools Used	Key Findings
Gorra 2012, Nebraska USA MI Case Control Multi-disciplinary follow-up clinic	2 yrs	46/105 followed up. All simple gastroschisis	• Neurodevelopment	• Bayley II • Mental & Psychomotor Development indices • BINS • Infant Toddler Checklist of the Communication and Symbolic Behaviour Scales • Developmental Profile • ASQ III	Infants born with gastroschisis had similar neurodevelopmental outcomes at 2 years as nonsurgical, non-syndromic NICU children of similar GA and BW (controls)
Van Manen 2013 Alberta, Canada SI PC Multi-disciplinary follow-up clinic	17-44m Median 20m	39/61 followed up	• Growth • Neurodevelopment • Feeding • GI Medication • Surgical intervention	• z-scores • Bayley III • WPSSI –III • Ophthalmology/ Audiology /Physiotherapy/ OT/ Cerebral Palsy specialist assessment • Clinical assessment	• Neurosensory deficits were common - 5% had visual impairment - 10% had hearing loss • No child tested had mental delay or cerebral palsy. • Early gestational age predicted disability • 90% were on medication for GORD (Gastro-Oesophageal Reflux Disease)

Key: SI- Single institution PC- Prospective cohort GA- Gestational age
BW- Birthweight OT – Occupational Therapist
BINS – Bayley Infant Neurodevelopment Screener
WPSSI –III, Wechsler Preschool and Primary Scale of Intelligence

Table 9.1. Continued. Long-term outcomes studies in children born with gastroschisis.

Studies reporting outcomes of infants with gastroschisis only

1 st Author, Year Location, Study Type	Length of Follow- Up	Cases Included	Outcomes Assessed	Tools Used	Key Findings
Harris 2014, Perth Australia RPopn PC	Children >5yrs	46/ 99 survivors completed questionnaires	• Growth • Stool consistency • Abdominal pain • Cosmesis	• z-scores • Bristol Stool Chart • Bespoke questionnaire	• Abdominal pain frequent • Concerns about cosmesis common • 24% had bowel habits at the extremes of Bristol scale • 24% were overweight, population norm is 20% - possible risk of obesity
Gupta 2015, NSW Australia SI Case Control	1 yr	20 infants	• Neurodevelopment	• Bayley III	• No difference in development between infants born with gastroschisis and controls at one year of age (controls were infants of the same GA and BW). • SGA neonates had statistically significant delay in receptive and expressive language compared to those without SGA
Harris 2016, Perth Australia RPopn PC	5-17yrs Median 10yrs	42/ 99 survivors	• Neurodevelopment • Behaviour • Parenting style	• WPSSI –III or WISC-IV • Strengths and Difficulties Questionnaire (SDQ) • Parenting Relationship Questionnaire (PRQ)	• No child had cerebral palsy, two had delayed motor milestones • Intellectual ability of those tested in normal range • 24% scored in abnormal range for SDQ • Significantly lower than average scores in some domains of the PRQ

Key: SI- Single institution PC- Prospective cohort RPopn- Regional population GA, gestational age SGA- Small for Gestational Age
BW, birthweight WPSSI –III, Wechsler Preschool and Primary Scale of Intelligence WISC-IV, Wechsler Intelligence Scale for Children-IV

Table 9.1. Continued. Long-term outcomes studies in children born with gastroschisis.

Studies reporting outcomes of infants with gastroschisis only

1 st Author, Year Location, Study Type	Length of Follow-Up	Cases Included	Outcomes Assessed	Tools Used	Key Findings
Giudici 2016, Buenos Aires, Argentina PC Multi-disciplinary follow-up clinic	6 yrs	62 survivors 54 assessed at 1yr 38 at 3 yrs 17 at 6 yrs	• Growth • Neurodevelopment • Mental health • Respiratory Function • Rehospitalisation/ re-intervention	• WHO centiles • Protocolised hearing and vision testing • Speech and language • Neurology Psychomotor Developmental Index (NPDl) - CAT/CLAMS - PRUNAPE • Language development	• Normal growth in those assessed at age 6 • Late-onset hearing loss a concern • Developmental delay in half at age 3yrs • Defects in expressive language common • ADHD in 4/38 at age 3 yrs • 6 attended special school at age 6 • Family dysfunction and attachment problems in 16/36 assessed (44%) -4 children referred for psychiatric evaluation -3 developed behavioral problems • Some expressed concerns about cosmesis • Surgical re-intervention common
Rankin 2016, Newcastle, UK Cross-Sectional. Postal Questionnaire	8-11 yrs	10/40 children 10/40 parents	• Quality of Life (QOL)	• KIDSCREEN	• Children reported similar QOL scores to UK reference population except psychological well- being which was significantly better • Parent reported - no significant difference from UK norms

Key: PC- prospective cohort WHO- World Health Organisation ADHD – Attention Deficit Hyperactivity Disorder
CAT/CLAMS Capute Scale Clinical Adaptive Test/Clinical Auditory Milestone Scale
PRUNAPE - Psychomotor development in primary care

Table 9.2. Long-term outcomes studies in children born with gastroschisis.

Studies reporting outcomes of infants with gastroschisis and exomphalos together

1 st Author, Year Institution,	Length of Follow-Up	Cases Included	Outcomes Assessed	Tools Used	Key Findings -Infants with Gastroschisis Only (unless stated otherwise)
Lindham 1984, Stockholm Sweden SI RC Postal Questionnaire	1-23 yrs Mean 8.8yrs	20 infants born with gastroschisis	• Growth • ‘State of health’ • GI symptoms • Cosmesis	• Ht and wt‡ • Bespoke Questionnaire	• Height and weight within normal limits • Good health in all • Some had abnormal GI symptomatology • Some had cosmetic concerns
Lunzer 2001, Innsbruck Austria SI PC Interview	3.5yrs-13 yrs Mean 7yrs	10 infants born with gastroschisis	• Growth • Neurodevelopment • Medical problems • Impact on Mothers	• Interview	• 2/10 had learning difficulties. • Having a child born with gastroschisis had affected decisions and feelings about future pregnancies in most
Koivusalo, Helsinki, Finland 2002 SI RC Postal Questionnaire	17-48yrs Median 26.5yrs	11/23 adults born with gastroschisis 57/68 adults born with exomphalos	• Body habitus • GI symptoms • Scar concerns • Psychosocial functioning • QOL	• BMI • Bespoke questionnaire • BDI • RSE • CTM • SF-36	• Similar long-term patterns of morbidity between GS and Exomphalos - GI symptoms and scar concerns were common • QOL of group as a whole (GS & E) comparable with general Finnish population of same age
Henrich 2008 Erlangen, Germany SI RC	1-10 yrs Median 6.3 yrs	22/40 born with gastroschisis	• Neurodevelopment • Cosmesis • Quality of life.	• Clinical follow-up • Bespoke questionnaire	• Cosmetic concerns in some • GI symptoms uncommon • Developmental delays initially but then made up for in most

Key: SI- Single Institution PC- prospective cohort RC- Retrospective Cohort
 BMI- Body Mass Index GS – Gastroschisis ‡ Height and Weight Compared to Swedish standards
 QOL – Quality of Life BDI- Becks Depression Inventory Test
 RSE- Rosenbergs Self-Esteem scale CTM- Cohen’s Test for Life Management
 SF-36 – 36 Item Short Form Health Survey

Example of a data-sheet provided to centres to help identification of children

[‡]Example data

Appendix 12

Invitation letter to parents



AIMES GS Study
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Oxford, OX3 7LF
Email: baps-cass@npeu.ox.ac.uk

Dear Parent

Invitation to take part in a research study of children born with gastroschisis

We have asked the surgical doctors who treated your child to send you this letter. We would like to invite you and your child to take part in a research study. The study is looking at how well children born with gastroschisis are at 7-9 years of age. We hope that the study will improve the care of children born with gastroschisis in the future and help to give parents of gastroschisis babies a good idea of what the future holds.

You will find enclosed with this letter, an information leaflet. The leaflet tells you more about the study. Please take time to read it and consider whether you would like to know more about being involved.

In the enclosed envelope is a questionnaire for you and one for your child. If you do not want to open this, you can send it back to us unopened and we will know that you do not wish to take part. If you would like to take part then please fill in the questionnaire(s) and the contact details form and send these back to us in the envelope.

If you would like to complete the questionnaire over the telephone or with the help of a Language Line Interpreter, please telephone this number: 01865 289714.

Thank you for your time

Prof Marian Knight
Study Lead Investigator

Dr Anna-May Long
Study Researcher

Appendix 13

Parent information leaflet



AIMES^{GS}



Assessing the Impact of Early Surgical Care
in **Gastro**schisis
Learning about Gastroschisis from Parents and Children

Parent Information Leaflet

You and your child are being invited to take part in a research study. The study is looking at how well children born with gastroschisis are at 7-9 yrs of age.

Before you decide it is important for you to understand why the research is being done and what it will involve. Please take the time to carefully read this leaflet. Talk to others about the study if you wish.

Ask us anything that is not clear or if you would like more information

Who are we?

We are a group of research doctors and children's surgeons who are carrying out research into children born with an abdominal wall defect called gastroschisis. We are looking for ways to improve treatment and provide better information about gastroschisis for families. We would like to invite you and your child to help us find out how to do this by joining in with an important research study.

Why are we contacting you?

Your surgical doctor has told us that you had a child born with gastroschisis between October 2006 and April 2008. At the moment we don't have your contact details. We will only have these if you decide to give them to us.

There is still so much about gastroschisis that we don't know. **As a parent, you know more about your child's care, health, growth and development than anyone else.** By asking you about your child we can get the very best information about how your child is as they grow. If most parents' who had a baby born during this time, agree to take part in the studies, we can get accurate information about babies born in the UK and Ireland which can be used to improve treatment for future babies born with gastroschisis.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do decide to take part, you can withdraw at any time, without giving a reason.

What would taking part in the research involve?

In the sealed envelope in this pack there are 2 questionnaires, one for you and one for your child to fill in. These contain questions about your child's health and wellbeing. There are questions about symptoms they may or may not be having and about whether they have been to the doctors or to hospital recently. There are also some general questions about how they feel in themselves, questions about how their tummy looks and how you and they feel about it and questions on the impact that having a child with gastroschisis has had on you and your family.

The questions are very general and many have been used in other studies involving children. Although some questions may not seem to be related to children with gastroschisis, we have to include them because that is the way the questions have been designed for these other studies. You may find some of them sensitive or upsetting. **It is absolutely fine to only answer some, but not all of the questions.** Please just complete the questions you are happy to answer. You will have our direct contact details and if you are upset or distressed by anything you are asked you may wish to talk to someone from our research team.

We would also like to contact your child's teacher to ask some questions about how your child gets on at school. If you do not wish for us to do this, we can still include the information you and/or your child provide through returning the questionnaires.

What do I need to do?

If you decide you would like to fill in the questionnaires, please do so and send them back with the consent and assent forms to us in the FREEPOST envelope provided. If you would like to, you can also give us your contact details so that we can send you the results of the study and contact you about further studies in the future.

You can also complete the questions over the telephone or with a translator if you would prefer. Should you prefer to do this, please call 01865 289714 during normal office hours.

You do not have to open the questionnaire envelope if you don't want to. If you would rather not look at them, you are welcome to send back the envelope to us unopened and we will ask your doctor not to contact you again.

We would also like you to speak with your child's teacher to see if they would be happy for us to contact them to ask some questions about how your child gets on at school. If they are happy, please fill in the teacher's contact details on the form provided and return this to the research team with the completed questionnaires.

The care of your child will not be affected by your decision. The hospital won't know if you've joined the study.

What will happen to the information I give?

All the information you tell us will be kept strictly confidential and will be stored securely, including your contact details. These will not be shared with any other organisations and will be stored

securely for contact reasons only. Access to your information will be restricted to the research team, but responsible members of the University of Oxford or the local NHS Trust may be given access to information for checking the study to ensure we are meeting regulations.

Where can I find the results of the study?

The results of the study will be published in a journal and on our website (www.npeu.ox.ac.uk/baps-cass). If you take part and give us your contact details we will also send you the results of the study. There will be no information in anything we write that will be able to be traced to any individual parents or children.

Can I get some more information about the studies?

If you would like to know more information, we would be delighted to talk to you about the study. Please call us on 01865 289714 during normal office hours and ask to speak to Melanie O'Connor, Anna Long or Marian Knight or email baps-cass@npeu.ox.ac.uk.

Who is organising and funding the study?

The study is organised by researchers at the National Perinatal Epidemiology Unit, University of Oxford jointly with the British Association of Paediatric Surgeons. It will be led by Professor Marian Knight. The National Institute for Health Research (NIHR) has funded the study.

What if I have a complaint?

If you wish to complain about any aspect of this study, at any time you should contact Professor Marian Knight using the details at the bottom of this page. Or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or the head of CTRG, email CTRG@admin.ox.ac.uk

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in the study.

What should I do if I have further questions or concerns?

Please contact us. If you would prefer someone from our research team to get in touch with you, please fill out your contact details on the form enclosed. You may also want to discuss any concerns with your family doctor. Overleaf are the names of some support groups for parents of children born with gastroschisis. You may also feel you would like to talk to other parents through these groups.

This work is supported by:



Exomphalos and Gastroschisis Group

Our contact information:

Professor Marian Knight
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Oxford, OX3 7LF

Email: baps-cass@npeu.ox.ac.uk

Telephone: 01865 289714

Usually staffed 8.30am-5pm, Monday-Friday

Thank you very much for reading this leaflet



Appendix 14

Parent consent form



Consent Form

I have read the information about the parent study and I am happy to take part ☐

I have read the information about the children's study and have explained this to my child and we are happy for them to take part ☐

Signature _____

Print Name _____ DD / MM / YY

Relationship to child with Gastroschisis

Mother ☐
Father ☐
Mother's Partner ☐
Other ☐

If Other, please specify (eg Grandmother) _____

If you would like to receive a copy of the study results and/or be contacted about future studies, please complete the section below. You do not have to complete this section for your child to be included in the study

Address _____

_____ Postcode

Email Address _____

Contact Telephone Number

Home _____ Mobile _____

Please place this form with the questionnaires in the FREEPOST envelope provided and send it back to us.

Thank-You

Our ref:

Appendix 15

Parent questionnaire



Assessing the Impact of Early Surgical Care
in **Gastroschisis**

Learning about Gastroschisis from Parents and Children

PARENT QUESTIONNAIRE

We have sent you this questionnaire as the parent or main caregiver of a child born with gastroschisis.

There is still so much about gastroschisis that we don't know. Our aim is to learn from the experiences of children and parents so that children born with this condition get the very best possible care.

By telling us about you and your child as they are now, we can use this information to help these children and their families.

This questionnaire covers things to do with your child and you that we know are important in some children and their families affected by the condition.

Please answer the questions as completely as you can. If you have any queries, please call 01865 289 714 and ask to speak to Anna Long or Melanie O'Connor.

If you would prefer to complete the questionnaire over the telephone or with the help of a Language Line interpreter, please telephone this number 01865 289 714.

All of the information you give us will be treated in the strictest confidence.

Your Child's Name: _____

Your Child's Date of Birth: _____

/ /

This questionnaire is completed by: (Name) _____

MOTHER ☐ **FATHER** ☐ **MOTHER's PARTNER** ☐ **OTHER** ☐
(please tick as appropriate)

If Other, please specify (e.g. Grandmother) _____

Today's Date: _____

/ /



Our Ref:



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Section 1: Your Child's Development

In this section we would like to ask you some questions about how your child is in general

1.1 Your Child's Physical Ability

a) Was your child walking at 2 years of age? Yes ☐ No ☐

b) Please tick which box best describes your child's ability to get around now

Please tick one box only

- ☐ Walks well without help
- ☐ Has an unsteady walk but doesn't need help
- ☐ Unable to walk without help
- ☐ Unable to walk even with help

1.2 Your Child's Vision

a) Does your child wear glasses? Yes ☐ No ☐

b) Please tick the box that best describes your child's ability to see (with glasses if worn)

Please tick one box only

- ☐ Sees well
- ☐ Has some difficulty but sees well enough for everyday activities
- ☐ Has considerable difficulty but can see objects if near
- ☐ Is only able to see light or has no vision

c) Please describe below the reason for your child's problems with vision if known

1.3 Your Child's Hearing

a) Please tick the box that best describes your child's ability to hear

Please tick one box only

- ☐ Hears well
- ☐ Has some hearing problems but does NOT need a hearing aid
- ☐ Hears well or with only a little difficulty WITH a hearing aid
- ☐ Has hearing difficulty even with a hearing aid or hearing is not helped with an aid

b) Is the hearing problem due to recurrent ear infections or 'glue' ear?

Yes ☐ No ☐ Don't know ☐

c) Please describe the reason for your child's hearing problems if you know

Section 2: Your Child's Feeding

We would now like to ask you some questions about your child's feeding

2.1 Nutrition

- a) From the time when your child was born, up to now, have you ever been told that your child was **not** able to take milk that was made from cows milk? Yes ☐ No ☐

If Yes, please give the reason if you know

If Yes, is your child able to take cows milk now? Yes ☐ No ☐

If Yes, at what age were they able to start taking cows milk? years

- b) Is your child on **parenteral nutrition** at the moment?
(Parenteral nutrition is given into a vein through a special IV line) Yes ☐ No ☐

- c) Does your child have a tube to feed them into their tummy? Yes ☐ No ☐

If Yes, please tick what type of tube this is

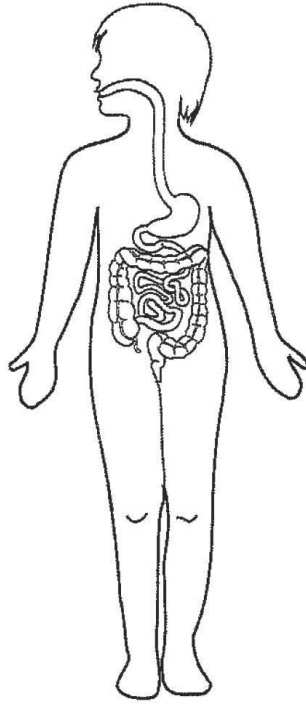
- ☐ A nasogastric tube
☐ A gastrostomy
☐ A feeding jejunostomy

- d) Does your child have a stoma? Yes ☐ No ☐

- e) Have you ever been told your child has 'short gut'? Yes ☐ No ☐

If Yes, please add any details if you would like about this

Section 3: Your Child's Digestive System



The next questions are about your child's digestive system (oesophagus, stomach, small intestine and colon) and problems they may have with it.

Certain problems may apply to your child, others will not.

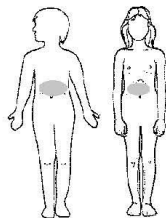
Please try to answer *all* of the questions. If it is *impossible* for you to answer a particular question, please answer "I don't know" where indicated.

We know that some children born with gastroschisis don't have a belly button. Some of the questions that follow refer to the belly button area. If your child does not have a belly button, the diagrams are there to show you where this area is.

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3.1 Pain and Uncomfortable Feelings in the Upper Abdomen above the Belly Button Area

The shaded area in the pictures below shows an area ABOVE your child's belly button area where children sometimes hurt, feel pain or have an uncomfortable feeling. Some words for these feelings are stomach ache, nausea, bloating, a feeling of fullness or not hungry after eating very little



Above the Belly Button Area

The questions in this section are about pain and uncomfortable feelings ABOVE the belly button area that your child may have had in the last 2 months. Children can have pain and uncomfortable feelings in more than one area of the belly.

In a different section of the questionnaire, you will be asked about areas around or below your child's belly button.

a) In the last 2 months, how often did your child have pain or an uncomfortable feeling in the upper abdomen *above the belly button area*?

- ☐ Never
- ☐ 1-3 times a month
- ☐ Once a week
- ☐ Several times a week
- ☐ Every day

If your child has not had ANY pain or uncomfortable feelings above the belly button in the last 2 months, please go to 3.2

b) Which of the following feelings did your child have above the belly button area? You may tick one or more than one.

- | | | |
|---|------------------------------|-----------------------------|
| Pain | Yes ☐ | No ☐ |
| Nausea | Yes ☐ | No ☐ |
| Bloating | Yes ☐ | No ☐ |
| Feeling of Fullness | Yes ☐ | No ☐ |
| Not being hungry after eating very little | Yes ☐ | No ☐ |

c) In the last 2 months, how much did your child hurt or feel uncomfortable *above the belly button area*?

- ☐ A little
- ☐ Some (between a little and a lot)
- ☐ A lot
- ☐ A great deal
- ☐ I don't know

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d) When your child hurt or felt uncomfortable *above the belly button area* for how long did it last?

- ☐ Less than an hour
☐ 1-2 hours
☐ 2-3 hours
☐ Most of the day
☐ All of the time

e) For how long has your child had pain or an uncomfortable feeling *above the belly button area*?

- ☐ 1m or less
☐ 2 months
☐ 3 months
☐ 4 - 11 months
☐ 1 year or longer

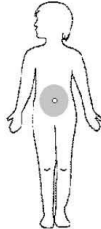
f) Circle a number for your answer to each question below, thanks

In the last 2 months, when your child hurt or felt uncomfortable above the belly button area, how often...	Never	Once in a while	Some times	Most of the time	Always	I don't know (please tick box)
Did the hurt or uncomfortable feeling get better after your child had a poo?	0	1	2	3	4	☐
Were your child's poos harder or lumpier than usual?	0	1	2	3	4	☐
Were your child's poos softer and more mushy or watery than usual?	0	1	2	3	4	☐
Did your child have more poos than usual?	0	1	2	3	4	☐
Did your child feel bloated in the belly?	0	1	2	3	4	☐
Did your child have a headache?	0	1	2	3	4	☐
Did your child have difficulty sleeping?	0	1	2	3	4	☐
Did your child have pain in the arms, legs, or back?	0	1	2	3	4	☐
Did your child faint or feel dizzy?	0	1	2	3	4	☐
Did your child miss school or stop activities?	0	1	2	3	4	☐

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3.2 Belly Aches and Abdominal Pain Around and Below the Belly Button Area

The questions in this section are about pain and uncomfortable feelings AROUND and BELOW the belly button area. These areas are shown in the shaded picture below. Children sometime have belly ache in these areas. Belly aches are sometimes milder than pain. Some children call their belly aches “stomach aches” or “tummy aches”.



**Around the
Belly Button Area**



**Below the Belly
Button Area**

a) In the last 2 months, how often did you child have pain or an uncomfortable feeling *in the area around or below the belly button*?

- ☐ Never
- ☐ 1-3 times a month
- ☐ Once a week
- ☐ Several times a week
- ☐ Every day

If your child has not had ANY belly aches or pain in the areas around or below the belly button in the past 2 months, please go to 3.3

b) In the last 2 months, how much did your child hurt or feel uncomfortable *in the area around or below the belly button*?

- ☐ A little
- ☐ Some (between a little and a lot)
- ☐ A lot
- ☐ A great deal
- ☐ I don't know

c) When your child hurt or felt uncomfortable *around or below the belly button area* for how long did it last?

- ☐ Less than an hour
- ☐ 1-2 hours
- ☐ 2-3 hours
- ☐ Most of the day
- ☐ All of the time

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d) For how long has your child had pain or an uncomfortable feeling *around or below the belly button area*?

- ☐ 1m or less
☐ 2 months
☐ 3 months
☐ 4 - 11 months
☐ 1 year or longer

e) Circle a number for your answer to each question below, thanks

In the last 2 months, when your child hurt or felt uncomfortable around or below the belly button, how often...	Never	Once in a while	Some times	Most of the time	Always	I don't know (please tick box)
Did it get better after your child had a poo?	0	1	2	3	4	☐
Were your child's poos softer and more mushy or watery than usual?	0	1	2	3	4	☐
Were your child's poos harder or lumpier than usual?	0	1	2	3	4	☐
Did your child have more poos than usual?	0	1	2	3	4	☐
Did your child have fewer poos than usual?	0	1	2	3	4	☐
Did your child feel bloated in the belly?	0	1	2	3	4	☐
Did your child have a headache?	0	1	2	3	4	☐
Did your child have difficulty sleeping?	0	1	2	3	4	☐
Did your child have pain in the arms, legs, or back?	0	1	2	3	4	☐
Did your child pain or feel dizzy?	0	1	2	3	4	☐
Did your child miss school or stop activities?	0	1	2	3	4	☐

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3.3 Bowel Movements (“Poo”, “Stool”, “ Number 2”)

This section is about your child's bowel movements. There are many words for bowel movements, such as “poo”, “stool” and “going to the toilet for a number 2”. Your family may use another special word when they talk about poos.

a) In the last 2 months, how often did your child usually have a poo?

- ☐ 2 times a week or less often
- ☐ 3-6 times a week
- ☐ Once a day
- ☐ 2-3 times a day
- ☐ More than 3 times a day
- ☐ I don't know

b) In the last 2 months, what was your child's poo usually like?

- ☐ Very hard
- ☐ Hard
- ☐ Not too hard and not too soft
- ☐ Very soft or mushy
- ☐ Watery
- ☐ It depends (his/ her poos are not always the same)
- ☐ I don't know

bi) If your child's poos are usually hard, for how long have they been hard?

- ☐ Less than 1 month
- ☐ 1 month
- ☐ 2 months
- ☐ 3 or more months

c) In the last 2 months, did it hurt when your child had a poo?

Yes ☐ No ☐ I don't know ☐

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d) Circle a number for your answer to each question below, thanks

In the last 2 months, how often...	Never	Once in a while	Some times	Most of the time	Always	I don't know (please tick box)
Did your child have to rush to the toilet to poo?	0	1	2	3	4	☐
Did your child have to strain (push hard) to make the poo come out?	0	1	2	3	4	☐
Did your child pass mucus or phlegm (white, yellowish, stringy or slimy material) during a poo?	0	1	2	3	4	☐
Did your child have a feeling of not being finished after a poo (like there was more that wouldn't come out)?	0	1	2	3	4	☐

e) In the last 2 months, did your child have a poo that was so big it clogged the toilet?
Yes ☐ No ☐

f) Some children hold their poo even when a toilet is available. They may do this by stiffening their bodies or crossing their legs. In the last 2 months, while at home, how often did your child try to hold a poo?
☐ Never
☐ 1-3 times a month
☐ Once a week
☐ Several times a week
☐ Every day

g) Did a doctor or nurse ever examine your child and say that your child had a huge poo inside?
Yes ☐ No ☐

h) In the last 2 months, how often was your child's underwear stained or soiled with poo? *(If never, please go to question 3.4)*
☐ Never
☐ Less than once a month
☐ 1-3 times a month
☐ Once a week
☐ Several times a week
☐ Every day

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hi) When your child had stained or soiled underwear, how much was it stained or soiled?

- ☐ Underwear was stained (no poo)
- ☐ Large amount of poo in underwear (less than a whole poo)
- ☐ Large amount of poo in underwear (a whole poo)

hii) For how long has your child had stained or soiled underwear?

- ☐ Less than 1 month
- ☐ 2 months
- ☐ 3 months
- ☐ 3 or more months
- ☐ 4 - 11 months
- ☐ 1 year or longer

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3.4 Feelings of Sickness/ Vomiting

In the **past week** has your child *Please tick all that apply*

- | | | |
|--|------------------------------|-----------------------------|
| Thrown up or been sick? | Yes ☐ | No ☐ |
| Felt like throwing up or felt nauseous? | Yes ☐ | No ☐ |
| Had a burning or painful feeling in the middle of the chest? | Yes ☐ | No ☐ |
| Had stomach ache? | Yes ☐ | No ☐ |
| Had a stomach ache above the belly button? | Yes ☐ | No ☐ |
| Had a sour taste, like the taste of vomit, in the mouth? | Yes ☐ | No ☐ |
| Found that it hurt to swallow food or drink? | Yes ☐ | No ☐ |

From: Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based study.
Pediatric Practice Research Group. Nelson SP, Chen EH, Syniar GM, Christoffel KK.
Arch. Pediatr Adolesc Med. 2000 Feb;154(2):150-4.

Section 4: Your Child's Health

4.1 What is your child's current weight . Kg **OR** Stone Pounds

Please ask your child to stand up against a flat surface with no shoes on, make a little mark at the top of their head and then measure the distance from the floor to the mark using the tape-measure in this pack

4.2 What is your child's current height cms **OR** Feet inches

4.3 Medicines

a) In the last 6 months has your child been on regular medicines? Yes ☐ No ☐

If Yes, please give details:

Name of Medicine	Treatment has stopped	Treatment is continuing
	☐	☐
	☐	☐
	☐	☐
	☐	☐
	☐	☐

4.4 Hospital Admissions

a) In the last 12 months, has your child been admitted to hospital for any reason, including surgery? Yes ☐ No ☐

If Yes, please complete the following:

Month/Year	Reason for Admission	Name of Hospital	Approx stay (days)

- b) Please could you mark with a circle which, if any, of the following people your child has seen **in the last 6 months** and then estimate how many times your child has seen that professional.

Community Professional		Total Number of times
GP/Family Doctor	Yes ☐ No ☐	
Practice Nurse	Yes ☐ No ☐	
Community Nurse	Yes ☐ No ☐	
Community Paediatrician	Yes ☐ No ☐	
Optician	Yes ☐ No ☐	
Physiotherapist	Yes ☐ No ☐	
Speech Therapist	Yes ☐ No ☐	
Hearing Specialist	Yes ☐ No ☐	
Social Worker	Yes ☐ No ☐	
Home Visitor/Volunteer	Yes ☐ No ☐	
Dietician	Yes ☐ No ☐	
Other (specify) _____	Yes ☐ No ☐	

- c) Does your child have any other long-term illness not mentioned so far? Yes ☐ No ☐

If Yes, please give details:

Section 5: You and Your Family

Having a baby born with gastroschisis can affect you and your family in many ways. In the questions below we would like to ask you about this.

Has this been a problem before and is it still a problem?

Please answer the questions as fully as you can, but if you would rather not answer the questions then just leave them blank.

5.1 Please tick a box on each line

	Having a child born with gastroschisis...		Not at all	Only a little	Quite a lot
Work	...meant/ means that I changed my choices about working (eg. whether you were able to work at all, worked less or changed jobs or job plans)	In the Past	☐	☐	☐
		Now	☐	☐	☐
Friends	...affected/ affects my relationships with my friends	In the Past	☐	☐	☐
		Now	☐	☐	☐
Childcare	...affected/ affects my childcare choices (eg. if it was difficult to find someone to look after your child or to find a nursery for your child)	In the Past	☐	☐	☐
		Now	☐	☐	☐
Leisure	...affected/ affects my/our ability to enjoy family leisure time (eg. if family trips or holiday choices were affected)	In the Past	☐	☐	☐
		Now	☐	☐	☐
Relationship with partner	...affected/ affects my relationship with my partner	In the Past	☐	☐	☐
		Now	☐	☐	☐
Any other children	...affected/ affects my other children	In the Past	☐	☐	☐
		Now	☐	☐	☐
Mood and energy	...has meant/ means I feel low or have little energy	In the Past	☐	☐	☐
		Now	☐	☐	☐
Personal Attitude	...affected/ affects the way I feel about myself in a positive way (ie. do you feel stronger as a person)	In the Past	☐	☐	☐
		Now	☐	☐	☐

5.2 Please add any comments on anything in the table above about the impact of having a child born with gastroschisis on you and your family if you would like to.

5.3 Are you still in a relationship with the same partner you were with when your child with gastroschisis was born?

- ☐ Yes we are still together
- ☐ No we are not together, I am on my own
- ☐ No we are not together, I have a new partner

5.4 Have you had another pregnancy since having your baby with gastroschisis?

Yes ☐ No ☐

If Yes, how many other children have you had since having your baby with gastroschisis?

Section 6: How Your Child's Tummy Looks Now

6.1 Your child's belly button area

Please tick which box best describes your child's belly button area

- ☐ It looks like a normal belly button
- ☐ It looks very near to normal
- ☐ It looks quite abnormal
- ☐ It looks very abnormal

6.2 Belly button hernia

A belly button hernia happens when a hole in the belly button allows things inside the tummy to bulge through. You may have noticed a bulge inside your child's belly button that may come and go with straining or be there all of the time

Please tick which best applies to your child

- ☐ My child has never had a belly button hernia
- ☐ My child currently has a belly button hernia and is waiting for an operation to fix it
- ☐ My child has a belly button hernia and is not waiting for an operation to fix it
- ☐ My child had a belly button hernia and had an operation to fix it
- ☐ My child had a belly button hernia but it got better by itself.

6.3 Other scars outside the belly button area

a) Does your child have any scars outside of the belly button area? Yes ☐ No ☐

b) If Yes, please describe or draw the scar/s on the diagram below



6.4 How you feel about how your child's tummy looks...

These questions are about how you feel – in later questions we will ask how your child feels

Please tick one box on each line

	When	Yes	No
Do you worry about the appearance of your child's belly button area ?	I am worried at the moment	☐	☐
	I am worried it may cause them problems in the future	☐	☐
Do you worry about the appearance of your child's other tummy scars ? (leave blank if they don't have any)	I am worried at the moment	☐	☐
	I am worried it may cause them problems in the future	☐	☐

a) Do you ever worry about people seeing your child's tummy, for example, when they are changing, swimming or on the beach? Yes ☐ No ☐

b) Have you ever been distressed by any comments made by other people (children or adults) about your child's belly button or scars? Yes ☐ No ☐

c) Has your child ever had an operation to improve the appearance of their belly button or scars (other than to repair a hernia)? Yes ☐ No ☐

If Yes, what age was this operation done? years

If Yes, was this for their belly button or other scars or both?

Belly Button ☐ Other Scars ☐ Both ☐

If No, have you ever *considered* your child having an operation to improve the appearance of their belly button or scars? Yes ☐ No ☐

Was this for the way their belly button looked or their other scars or both

Belly Button ☐ Other Scars ☐ Both ☐

Have you discussed this with a surgeon? Yes ☐ No ☐

d) Would you like to let us know anything more about how you feel about how your child's tummy looks or any experiences you have had related to this?

6.5 How your child feels about how their tummy looks...

Please tick one box on each line

	When	Yes	No
Does your child worry about the appearance of their belly button area ?	Are they worried at the moment	☐	☐
	Are they worried it may cause them problems in the future	☐	☐
Does your child worry about the appearance of their other tummy scars ? (leave blank if they don't have any)	Are they worried at the moment	☐	☐
	Are they worried it may cause them problems in the future	☐	☐

a) Does your child ever worry about people seeing their tummy, for example, when they are changing, swimming or on the beach? Yes ☐ No ☐

b) Has your child ever been distressed by any comments made by other people (children or adults) about their belly button or scars? Yes ☐ No ☐

c) Please tell us anything else you would like to about the way your child feels about how their tummy looks or any experiences they have had related to this

Section 7: Your Child in General

We would like to ask you a few questions about how your child is in general

These questions ask about how your child is **today**. For each question, read all the choices and decide which one is most like your child **today**.

*Only tick **one** box for each question.*

Example

Today my child feels quite upset so I will tick this box.

Upset

- ☐ My child doesn't feel upset today
- ☐ My child feels a little bit upset today
- ☐ My child feels a bit upset today
- ☒ My child feels quite upset today
- ☐ My child feels very upset today

Now please think about and answer the rest of the questions below

7.1 Worried

- ☐ My child doesn't feel worried today
- ☐ My child feels a little bit worried today
- ☐ My child feels a bit worried today
- ☐ My child feels quite worried today
- ☐ My child feels very worried today

7.2 Sad

- ☐ My child doesn't feel sad today
- ☐ My child feels a little bit sad today
- ☐ My child feels a bit sad today
- ☐ My child feels quite sad today
- ☐ My child feels very sad today

7.3 Pain

- ☐ My child doesn't have any pain today
- ☐ My child has a little bit of pain today
- ☐ My child has a bit of pain today
- ☐ My child has quite a lot of pain today
- ☐ My child has a lot of pain today

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7.4 Tired

- ☐ My child doesn't feel tired today
- ☐ My child feels a little bit tired today
- ☐ My child feels a bit tired today
- ☐ My child feels quite tired today
- ☐ My child feels very tired today

7.5 Annoyed

- ☐ My child doesn't feel annoyed today
- ☐ My child feels a little bit annoyed today
- ☐ My child feels a bit annoyed today
- ☐ My child feels quite annoyed today
- ☐ My child feels very annoyed today

7.6 School Work/Homework (such as reading, writing, doing lessons)

- ☐ My child has no problems with their schoolwork/homework today
- ☐ My child has a few problems with their schoolwork/homework today
- ☐ My child has some problems with their schoolwork/homework today
- ☐ My child has many problems with their schoolwork/homework today
- ☐ My child can't do their schoolwork/homework today

7.7 Sleep

- ☐ Last night my child had no problems sleeping
- ☐ Last night my child had a few problems sleeping
- ☐ Last night my child had some problems sleeping
- ☐ Last night my child had many problems sleeping
- ☐ Last night my child couldn't sleep at all

7.8 Daily routine (things like eating, having a bath/shower, getting dressed)

- ☐ My child has no problems with their daily routine today
- ☐ My child has a few problems with their daily routine today
- ☐ My child has some problems with their daily routine today
- ☐ My child has many problems with their daily routine today
- ☐ My child can't do their daily routine today

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7.9 Able to join in activities (things like playing out with their friends, doing sports, joining in things)

- ☐ My child can join in with any activities today
- ☐ My child can join in with most activities today
- ☐ My child can join in with some activities today
- ☐ My child can join in with a few activities today
- ☐ My child can join in with no activities today

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7.10 Please describe any concerns you may have about your child

7.11 Please describe the best things about your child:

Section 8: Your Child's School

8.1 When did your child start full-time infant or primary school?

Please give the month and year

M	M	/	Y	Y
---	---	---	---	---

If not started yet, please give the reason:

8.2 Does your child currently receive any special needs support in school? Yes ☐ No ☐

8.3 Does your child have a health-care plan being used by his/ her school? Yes ☐ No ☐

8.4 Would you be happy for us to contact your child's teacher to ask more about how your child is getting on at school? Yes ☐ No ☐

If Yes, please complete the form at the back of this booklet and write your child's teacher's name and the address of their school

Section 9: You and Your Household

Please answer as many of these questions as you can. This will help us describe the children and families taking part in this survey and show whether their treatment and experiences are the same regardless of their background or circumstances

9.1 How old are you now?

years

9.2 How old were you when you left full-time education?

- ☐ 16 years or less
- ☐ 17-18 years
- ☐ 19 years or over
- ☐ Still in full time education

9.3 Which of the following people live with you? Please tick all that apply

- ☐ Your children
- ☐ Your spouse or partner
- ☐ Same sex partner
- ☐ Other family members
- ☐ Other people in your household

9.4 To which of these ethnic groups would you say you belong?

White:

- English/ Welsh/ Scottish/ Northern Irish/ British ☐
Irish ☐
Gypsy or Irish Traveller ☐
Any other White background ☐

If Other, please specify: _____

Black or Black British:

- African ☐
Caribbean ☐
Any other Black/ African/ Caribbean ☐

If Other, please specify: _____

Mixed:

- White & Black Caribbean ☐
White & Black African ☐
White & Asian ☐

Any other mixed/ multiple ethnic background ☐

If Other, please specify: _____

Other Ethnic Group:

- Arab ☐
Any other ethnic group ☐

If Other, please specify: _____

Asian or Asian British:

- Indian ☐
Pakistani ☐
Bangladeshi ☐
Chinese ☐
Any other Asian background ☐

If Other, please specify: _____

9.5 Do you need any help understanding English?

Yes ☐ No ☐

9.6 Which of these best describes your current situation?

- ☐ In paid work (full-time or part-time)
☐ On maternity leave
☐ Looking after my family, home or dependants
☐ In education
☐ Unemployed
☐ Unable to work because of disability or ill health
☐ Other *Please give details* _____

9.7 Do you have a long-standing physical problem or disability?

Yes ☐ No ☐ Don't know / Not sure ☐

9.8 Do you have a long-standing mental health problem or learning disability?

Yes ☐ No ☐

9.9 Do any of these problems or disabilities affect your day-to-day activities?

Yes, definitely ☐ Yes, to some extent ☐ No ☐ Not applicable ☐

9.10 If you have a health problem or disability, would you mind telling us what it is?

Please give details

9.11 If there is anything you would like to tell us about you and your child that has or has not been covered in the other parts of this form, please add your comments here or use the back page.

[illegible]

Thank you very much for your time and help in completing this questionnaire.

If this has raised any issues or questions of concern you may wish to contact your family doctor (GP)

Please return the questionnaire in the envelope provided. If you would like to know any more about the research or discuss any aspect of it with us please contact call 01865 289 714 or email baps-cass@npeu.ox.ac.uk.

If you are happy for us to contact your child's teacher, please complete the form on the next page

I am happy for my child's teacher to be contacted for information about how my child is getting on at school. I have discussed it with him/her and he/she is happy for me to provide her contact details.

Signed: _____ Name: _____

Please write your child's teacher's contact details here

Mr/ Miss/ Mrs: _____ *(Please give their surname)*

School Name: _____

School Address

This form will be detached from the questionnaire and stored separately

Our Ref:

--	--	--	--	--



Appendix 16

Children's assent form



Assent Form for Children

Please circle the answers you agree with

Has your Mum, Dad or guardian explained this project to you?	Yes ☐	No ☐
Do you understand what this project is about?	Yes ☐	No ☐
Have you asked all the questions you want?	Yes ☐	No ☐
Have you had your questions answered in a way you understand?	Yes ☐	No ☐
Are you happy to answer the questions on the questionnaire?	Yes ☐	No ☐

If any answers are "no", don't sign your name!

If you are happy to answer the questions on the questionnaire, you can write your name below

Your name _____

Date

<table><tr><td>D</td><td>D</td></tr></table>	D	D	/	<table><tr><td>M</td><td>M</td></tr></table>	M	M	/	<table><tr><td>Y</td><td>Y</td></tr></table>	Y	Y
D	D									
M	M									
Y	Y									

Please place this form with the questionnaires in the **FREEPOST** envelope provided and send it back to us.

Thank-You

Our ref:

--	--	--	--	--

Appendix 17

Child questionnaire

Our Ref:


AIMES^{GS}
Assessing the Impact of Early Surgical Care
in **Gastroschisis**
Learning about Gastroschisis from Parents and Children

QUESTIONNAIRE FOR CHILDREN

This part is for your child to complete once you have explained to them about the study and they have agreed to take part.

Your child may or may not ask for your help filling in this questionnaire. It is fine for you to do this if they would like you to.

For Children to Read

We need to learn more about what happens to children who were born with gastroschisis when they are older.

The best people who can tell us about this is you! We would like to ask you some questions about how you are doing. These questions have been asked of lots of other boys and girls of your age before.

You don't have to answer the questions, but if you do you could help other children born with gastroschisis.

Your name will not be joined up to anything that you tell us.

Please write Today's Date: / /



This page is blank

Section 1:

Instructions

These questions ask about how you are **today**. For each question, read all the choices and decide which one is most like you **today**.

Then put a tick in the box next to it like this ☒. Only tick **one** box for each question.

Example

Today I feel quite upset so I will tick this box.

Upset

- ☐ I don't feel upset today
- ☐ I feel a little bit upset today
- ☐ I feel a bit upset today
- ☐ I feel quite upset today
- ☒ I feel very upset today

Now think about and answer the rest of the questions below

1.1 Worried

- ☐ I don't feel worried today
- ☐ I feel a little bit worried today
- ☐ I feel a bit worried today
- ☐ I feel quite worried today
- ☐ I feel very worried today

1.2 Sad

- ☐ I don't feel sad today
- ☐ I feel a little bit sad today
- ☐ I feel a bit sad today
- ☐ I feel quite sad today
- ☐ I feel very sad today

1.3 Pain

- ☐ I don't have any pain today
- ☐ I have a little bit of pain today
- ☐ I have a bit of pain today
- ☐ I have quite a lot of pain today
- ☐ I have a lot of pain today

1.4 Tired

- ☐ I don't feel tired today
- ☐ I feel a little bit tired today
- ☐ I feel a bit tired today
- ☐ I feel quite tired today
- ☐ I feel very tired today

1.5 Annoyed

- ☐ I don't feel annoyed today
- ☐ I feel a little bit annoyed today
- ☐ I feel a bit annoyed today
- ☐ I feel quite annoyed today
- ☐ I feel very annoyed today

1.6 School Work/Homework (such as reading, writing, doing lessons)

- ☐ I have no problems with my schoolwork/homework today
- ☐ I have a few problems with my schoolwork/homework today
- ☐ I have some problems with my schoolwork/homework today
- ☐ I have many problems with my schoolwork/homework today
- ☐ I can't do my schoolwork/homework today

1.7 Sleep

- ☐ Last night I had no problems sleeping
- ☐ Last night I had a few problems sleeping
- ☐ Last night I had some problems sleeping
- ☐ Last night I had many problems sleeping
- ☐ Last night I couldn't sleep at all

1.8 Daily routine (things like eating, having a bath/shower, getting dressed)

- ☐ I have no problems with my daily routine today
- ☐ I have a few problems with my daily routine today
- ☐ I have some problems with my daily routine today
- ☐ I have many problems with my daily routine today
- ☐ I can't do my daily routine today

1.9 Able to join in activities (things like playing out with your friends, doing sports, joining in things)

- ☐ I can join in with any activities today
- ☐ I can join in with most activities today
- ☐ I can join in with some activities today
- ☐ I can join in with a few activities today
- ☐ I can join in with no activities today

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Please carry on with the questions on the next page

Section 2:

Instructions

These questions ask about how you have been **in the last week**. We would like you to tell us how you feel.

Please read every question carefully. What answer comes to your mind first? Choose the box that fits your answer then tick it.

Remember: This is not a test so there are no wrong answers. It is important that you answer all of the questions and also that we can see your marks clearly. When you think of your answer please try to remember the last week.

You do not have to show your answers to anybody. Also, nobody who knows you will look at your questionnaire once you have posted it.

Physical Activities and Health

1. In general how would you say your health is?

- ☐ excellent
- ☐ very good
- ☐ good
- ☐ fair
- ☐ poor

Thinking about the last week ...

	not at all	slightly	moderately	very	extremely
2. Have you felt fit and well?	☐	☐	☐	☐	☐
3. Have you been physically active (e.g. running, climbing, biking)?	☐	☐	☐	☐	☐
4. Have you been able to run well?	☐	☐	☐	☐	☐

Thinking about the last week ...

	never	seldom	quite often	very often	always
5. Have you felt full of energy?	☐	☐	☐	☐	☐

Feelings

Thinking about the last week ...

	not at all	slightly	moderately	very	extremely
1. Has your life been enjoyable?	☐	☐	☐	☐	☐
2. Have you felt pleased that you are alive?	☐	☐	☐	☐	☐
3. Have you felt satisfied with your life?	☐	☐	☐	☐	☐

Thinking about the last week ...

	never	seldom	quite often	very often	always
4. Have you been in a good mood?	☐	☐	☐	☐	☐
5. Have you felt cheerful?	☐	☐	☐	☐	☐
6. Have you had fun?	☐	☐	☐	☐	☐

General Mood

Thinking about the last week ...

	never	seldom	quite often	very often	always
1. Have you felt that you do everything badly?	☐	☐	☐	☐	☐
2. Have you felt sad?	☐	☐	☐	☐	☐
3. Have you felt so bad that you didn't want to do anything?	☐	☐	☐	☐	☐
4. Have you felt that everything in your life goes wrong?	☐	☐	☐	☐	☐
5. Have you felt fed up?	☐	☐	☐	☐	☐
6. Have you felt lonely?	☐	☐	☐	☐	☐

About Yourself

Thinking about the last week ...

	never	seldom	quite often	very often	always
1. Have you been happy with the way you are?	☐	☐	☐	☐	☐
2. Have you been happy with your clothes?	☐	☐	☐	☐	☐
3. Have you been worried about the way you look?	☐	☐	☐	☐	☐
4. Have you felt jealous about the way other girls and boys look?	☐	☐	☐	☐	☐
5. Would you like to change something about your body?	☐	☐	☐	☐	☐

Free Time

Thinking about the last week ...

	never	seldom	quite often	very often	always
1. Have you had enough time for yourself?	☐	☐	☐	☐	☐
2. Have you been able to do the things that you want to do in your free time?	☐	☐	☐	☐	☐
3. Have you had enough opportunity to be outside?	☐	☐	☐	☐	☐
4. Have you had enough time to meet friends?	☐	☐	☐	☐	☐
5. Have you been able to choose what to do in your free time?	☐	☐	☐	☐	☐

Family and Home Life

Thinking about the last week ...

	not at all	slightly	moderately	very	extremely
1. Have your parent(s) understood you?	☐	☐	☐	☐	☐
2. Have you felt loved by your parent(s)?	☐	☐	☐	☐	☐

Thinking about the last week ...

	never	seldom	quite often	very often	always
3. Have you been happy at home?	☐	☐	☐	☐	☐
4. Have your parent(s) had enough time for you?	☐	☐	☐	☐	☐
5. Have your parent(s) treated you fairly?	☐	☐	☐	☐	☐
6. Have you had been able to talk to your parent(s) when you wanted to?	☐	☐	☐	☐	☐

Money Matters

Thinking about the last week ...

	never	seldom	quite often	very often	always
1. Have you had enough money to do the same things as your friends?	☐	☐	☐	☐	☐
2. Have you had enough money for your expenses?	☐	☐	☐	☐	☐

Thinking about the last week ...

	not at all	slightly	moderately	very	extremely
3. Do you have enough money to do things with your friends?	☐	☐	☐	☐	☐

Friends

Thinking about the last week ...

	never	seldom	quite often	very often	always
1. Have you spent time with your friends?	☐	☐	☐	☐	☐
2. Have you done things with other girls and boys?	☐	☐	☐	☐	☐
3. Have you had fun with your friends?	☐	☐	☐	☐	☐
4. Have you and your friends helped each other?	☐	☐	☐	☐	☐
5. Have you been able to talk about everything with your friends?	☐	☐	☐	☐	☐
6. Have you been able to rely on your friends?	☐	☐	☐	☐	☐

School and Learning

Thinking about the last week ...

	not at all	slightly	moderately	very	extremely
1. Have you been happy at school?	☐	☐	☐	☐	☐
2. Have you got on well at school?	☐	☐	☐	☐	☐
3. Have you been satisfied with your teachers?	☐	☐	☐	☐	☐

Thinking about the last week ...

	never	seldom	quite often	very often	always
4. Have you been able to pay attention?	☐	☐	☐	☐	☐
5. Have you enjoyed going to school?	☐	☐	☐	☐	☐
6. Have you got along well with your teachers?	☐	☐	☐	☐	☐

Bullying

Thinking about the last week ...

	never	seldom	quite often	very often	always
1. Have you been afraid of other girls and boys?	☐	☐	☐	☐	☐
2. Have other girls and boys made fun of you?	☐	☐	☐	☐	☐
3. Have other girls and boys bullied you?	☐	☐	☐	☐	☐

Thank you for giving your time to fill in these questions



Appendix 18

Number of parents contacted by each centre and response rate

Centre Code	N [‡]	Died ≤1yr [*]	Died >1yr ^α	Identified children sent packs	Packs returned	RTS	Parent Q complet ^d	Child Q complet ^d	Resp ^{se} rate ^β (%)
1	16	0	0	16	7	0	6	6	44
2	23	2	1	20	2	0	2	2	10
3	21	0	0	21	0	0	0	0	0
4	18	0	0	18	5	0	5	5	28
5	9	0	0	8	0	0	0	0	0
6	14	0	0	13	3	0	3	3	23
7	13	0	0	13	0	0	0	0	0
8	6	0	0	6	0	0	0	0	0
9	6	0	0	0	0	0	0	0	NA
10	13	3	0	10	2	0	2	1	20
11	14	1	0	11	0	0	0	0	0
12	21	0	0	0	0	0	0	0	NA
13	12	0	2	10	3	0	3	3	30
14	7	0	1	6	2	0	2	2	33
15	7	NK	NK	0	0	0	0	0	NA
16	21	1	0	20	4	0	3	3	25
17	3	0	0	3	2	0	2	2	66
18	3	0	0	0	0	0	0	0	NA
19	7	1	1	5	0	0	0	0	0
20	6	0	0	6	0	0	0	0	0
21	27	1	1	22	0	1	0	0	0
22	37	1	0	34	8	0	7	5	24
23	24	1	0	19	1	3	1	1	6
24	21	0	0	21	2	0	2	2	10
25	4	0	0	4	1	0	1	1	25
26	5	0	0	5	2	1	2	2	50
27	17	0	0	17	2	1	2	2	13
TOTAL	369	11	5	308	46	6	43	40	15

N[‡] Number reported in original cohort *Known deaths before one year

^α Known deaths after one year ^βResponse rate

Appendix 19

Data collection form for the gastroschisis long-term study

ID Number:

British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS)

Gastroschisis

Data Collection Form - Long-Term Clinical Outcomes

NB for the purposes of this Data Collection Form one-year refers to 1 year from the date of first surgical intervention.

Case Definition:

A congenital malformation characterised by visceral herniation through an abdominal wall defect lateral to an intact umbilical cord and not covered by a membrane.

Exclude:

- Aplasia or hypoplasia of abdominal muscles
- Skin covered umbilical hernia, exomphalos or omphalocele
- All infants born with gastroschisis within the time period not included in the original BAPS-CASS cohort

Instructions

1. Please do not enter any personally identifiable information (e.g. name, address or hospital number) on this form.
2. Fill in the form using the information available in the child's case notes.
3. Tick the boxes as appropriate. If you require any additional space to answer a question please use the space provided in section 8.
4. Please complete all dates in the format DD/MM/YY, and all times using the 24hr clock e.g. 18:37.
5. **If you do not know the answers to some questions, please indicate this in section 8.**
6. If you encounter any problems with completing the form please contact the Study Administrator or use the space in section 8.

Please return the completed form to:



BAPS-CASS
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Oxford
OX3 7LF
Fax: 01865 617775
Phone: 01865 289714



Case reported in: _____

Section 1:

1.1 Mother's first language _____ Not known ☐

Section 2: Details of Hospital Admissions

2.1 Date of first discharge from hospital or first transfer / /

2.2 Has this child ever had any episodes of bowel obstruction from any cause? Yes ☐ No ☐

If Yes, please give details below:

Date of admission	Cause (Please state if not known)	Surgical (S) or conservative (C) management?	Operation(s) Performed (if Surgically managed)	Complications (Please state if none)
/ /		S ☐ C ☐		
/ /		S ☐ C ☐		
/ /		S ☐ C ☐		

Please continue in section 8 if there is insufficient space

2.3 Has this child had other surgical procedures after primary closure in your centre? (include umbilical hernia repair, operations for undescended testes, central lines etc.) Yes ☐ No ☐

If Yes, please give details below:

Please be as accurate as possible when recording the operation type

Indication	Exact Procedure (incl. side if appropriate)	Date	Complications (Please state if none)
		/ /	
		/ /	
		/ /	
		/ /	
		/ /	

Please continue in section 8 if there is insufficient space

2.4 Has this child had any other operations performed in another centre?

Yes ☐ No ☐ Not known ☐

If Yes, please give details below:

Indication	Exact Procedure (incl. side if appropriate)	Date	Centre	Complications (Please state if none)
		DD / MM / YY		
		DD / MM / YY		
		DD / MM / YY		
		DD / MM / YY		
		DD / MM / YY		

Please continue in section 8 if there is insufficient space

2.5 Has this child had an operation to improve the appearance of their umbilicus or scars (excluding hernia repair)?

Yes ☐ No ☐

If Yes, was this performed either with or by a plastic surgeon?

Yes ☐ No ☐ Not known ☐

2.6 Has this child had any other hospital admissions (not documented above) after their initial discharge?

Yes ☐ No ☐

If Yes, please give details below:

Admission Date	Discharge Date	Indication for Admission	Management
DD / MM / YY	DD / MM / YY		
DD / MM / YY	DD / MM / YY		
DD / MM / YY	DD / MM / YY		
DD / MM / YY	DD / MM / YY		
DD / MM / YY	DD / MM / YY		

Please continue in section 8 if there is insufficient space

Section 3: GI and Nutrition

3.1 What type of milk was this child on at first discharge from hospital? _____

3.2 Has this child ever been diagnosed with cows milk protein intolerance? Yes ☐ No ☐ Not known ☐

3.3 Was this child still receiving parenteral nutrition (PN) at 1 yr of age? Yes ☐ No ☐

3.4 Did this child receive any PN after 1 yr of age? Yes ☐ No ☐

If Yes, are they currently receiving PN? Yes ☐ No ☐

If No, did they have any episodes of PN lasting ≥ 28 days after 1 year of age? Yes ☐ No ☐

If Yes, please give the date that the last episode of PN use ≥ 28 days terminated
DD/MM/YY

If Yes, please give the indication for this course of PN _____

3.5 Has the child ever have evidence of liver disease associated with PN use*?
(*raised serum alkaline phosphatase and gamma glutamyl transferase
1.5 x above the normal reference range for more than 6 weeks) Yes ☐ No ☐

3.6 Has the child ever been diagnosed with a nutritional deficiency requiring supplementation (e.g. Iron, B12, folate, Zinc/other trace element etc.)? Yes ☐ No ☐

If Yes, is the child currently receiving treatment for nutritional deficiency? Yes ☐ No ☐

If No, please give the date that the last episode of treatment commenced
DD/MM/YY OR Not known ☐

3.7 Has this child ever been diagnosed with gastrointestinal bacterial overgrowth requiring treatment?
(N.B. this does not include prophylaxis) Yes ☐ No ☐

If Yes, please indicate the method of diagnosis e.g. clinical suspicion, H breath test, serum d-lactate etc. _____ Not known ☐

If Yes, is the child currently receiving treatment for bacterial overgrowth? Yes ☐ No ☐

If No, please give the date that the last episode of treatment commenced
DD/MM/YY OR Not known ☐

3.8 Has the child ever been diagnosed with renal calculi or nephrocalcinosis? Yes ☐ No ☐ Not known ☐

3.9 After 1 year of age, has this child ever been on medication for gastro-oesophageal reflux(GOR)?

Yes ☐ No ☐ Not known ☐

If Yes, is the child currently on medication for GOR?

Yes ☐ No ☐ Not known ☐

If No, please give the approximate date the child stopped any medical treatment for GOR

/ / **OR** Not known ☐

3.10 After 1 year of age, has this child ever been on medication for constipation?

Yes ☐ No ☐ Not known ☐

If Yes, is the child currently on medication for constipation?

Yes ☐ No ☐ Not known ☐

If No, please give the approximate date the child stopped any medical treatment for constipation

/ / **OR** Not known ☐

3.11 Has this child ever complained of abdominal pain when in outpatient follow-up?

Yes ☐ No ☐

If Yes, please give details below:

Date first reported	Management	Has this now resolved? Yes / No	Approx. Date Resolved
/ /		Y ☐ N ☐	/ /
/ /		Y ☐ N ☐	/ /
/ /		Y ☐ N ☐	/ /

Please continue in section 8 if there is insufficient space

Section 4: Neurological Impairment

4.1 Has the child ever been diagnosed with any of the following?

	Yes/ No/ Unknown	Aids Used* (Yes / No)	Cause (if known)
Hearing Impairment	Y ☐ N ☐ U ☐	Y ☐ N ☐	
Visual Impairment	Y ☐ N ☐ U ☐	Y ☐ N ☐	
Motor Impairment	Y ☐ N ☐ U ☐	Y ☐ N ☐	
Developmental Delay	Y ☐ N ☐ U ☐	N/A	

*E.g. glasses, hearing aids, wheelchair

Please continue in section 8 if there is insufficient space

Section 5: Growth

5.1 Did this child have length/height or weight measurements recorded at first discharge or transfer?

Yes ☐ No ☐

If Yes, please specify

Weight . kg Date / /

Length/Height cm Date / /

5.2 Did this child have any other documented height or weight measurements?

Yes ☐ No ☐

If Yes, please document height or weight measurements that fit into the age brackets given

Age Measured	Weight (kg)	Height (cms)	Date
Age 6M - 1 yr	.		/ /
Age 1-2 yrs	.		/ /
Age 4-5yrs	.		/ /
Last recorded measurements >5yrs	.		/ /

Section 6: Outpatient Services

6.1 Was this child followed up by paediatric surgeons after first discharge from hospital?

Yes ☐ No ☐

If No, please give the reason e.g. DNA: _____ Not known ☐

If Yes, please give the dates of all paediatric surgical outpatient follow-up periods. If discharged from routine follow-up then re-referred please give the reasons for re-referral in the first column titled 'Indication'; e.g. if developed new symptoms such as abdominal pain or a new surgical problem (eg. a hernia)

Indication	Management (Please state if none)	Date From	Still in follow-up Yes / No	If No, date period of follow-up terminated
Following first discharge (Routine)		/ /	Y ☐ N ☐	/ /
		/ /	Y ☐ N ☐	/ /
		/ /	Y ☐ N ☐	/ /

Please continue in section 8 if there is insufficient space

6.2 Has this child ever been seen by a gastroenterologist as an outpatient?

Yes ☐ No ☐ Not known ☐

If Yes, please give details below:

Date From	Discharged from gastro follow up? Yes / No	If Yes, date discharged from follow-up	Indication for Gastroenterology Involvement	Management
DD/MM/YY	Y ☐ N ☐	DD/MM/YY		
DD/MM/YY	Y ☐ N ☐	DD/MM/YY		
DD/MM/YY	Y ☐ N ☐	DD/MM/YY		

Please continue in section 8 if there is insufficient space

6.3 Has the child ever seen another specialist at the tertiary centre?

Yes ☐ No ☐

If Yes, please give details of the specialist and dates of follow-up periods

Speciality	Discharged from follow up? Yes / No	If Yes, date discharged from follow-up	Indication
	Y ☐ N ☐	DD/MM/YY	
	Y ☐ N ☐	DD/MM/YY	
	Y ☐ N ☐	DD/MM/YY	
	Y ☐ N ☐	DD/MM/YY	

Section 7: Other Outcomes

7.1 Did this child die?*

Yes ☐ No ☐

If Yes, please specify date of death*

DD/MM/YY

What was the primary cause of death? _____

**N.B. if the date of death is not available in the hospital record please ask the assistance of a medical secretary to try to identify it from the patient's electronic record e.g. the NHS Spine.*

Section 8:

Please use this space to enter any other information you feel may be important

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Section 9:

Name of person completing the form _____

Designation _____

Today's date

You may find it useful in the case of queries to keep a copy of this form.

