

Management and Outcomes of Congenital Anomalies in Low-, Middle- and High-Income Countries: A Multi-centre, International, Prospective Cohort Study



Global PaedSurg Research Collaboration: A multi-centre research collaboration comprising surgeons, anaesthetists, paediatricians, nurses and allied health professionals working with neonates and children requiring surgery across the world.



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Study Protocol v7

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Protocol to be registered on [ClinicalTrials.gov](https://clinicaltrials.gov)

The protocol is available in other languages

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Abstract

Background: Congenital anomalies have risen to become the 5th leading cause of death in children under 5-years of age globally, yet limited literature exists, particularly from low- and middle-income countries (LMICs) where most of these deaths occur.

Aim: To undertake a multi-centre prospective cohort study of congenital anomalies to compare outcomes between LMICs and high-income countries (HICs) globally.

Methods: The Global PaedSurg Research Collaboration will be established consisting of children's surgical care providers from around the world to participate in the study; collaborators will be co-authors of resulting presentations and publication(s). Data will be collected on patients presenting primarily with seven congenital anomalies (oesophageal atresia, congenital diaphragmatic hernia, intestinal atresia, gastroschisis, exomphalos, anorectal malformation and Hirschsprung's disease) for a minimum of one month between Oct 2018 – April 2019. Anonymous data will be collected on patient demographics, clinical status, interventions and outcome. Data will be captured using the secure, online data collection tool REDCap.

The primary outcome will be all-cause in-hospital mortality and the secondary outcomes will be occurrence of post-operative complications. Chi-squared analysis will be used to compare mortality between LMICs and HICs. Multilevel, multivariate logistic regression analysis will be undertaken to identify patient level and hospital level factors affecting outcomes with adjustment for confounding factors. $P < 0.05$ will be deemed significant. Study approval will be sought from all participating centres. Funding has been granted by the Wellcome Trust.

Outcomes: The study aims to be the first large-scale, geographically comprehensive, multi-centre prospective cohort study of a selection of common congenital anomalies to define current management and outcomes globally. Results will be used to aid advocacy and global health prioritisation and inform future interventional studies aimed at improving outcomes.

Introduction

Research Collaboratives

The Global PaedSurg Research Collaboration aims to create a network of surgeons, anaesthetists, paediatricians, neonatologists and allied health professionals involved in the management of neonates and children requiring surgical care across the world - an area heavily neglected in global health prioritisation. Such research collaboratives are being increasingly utilised as a highly effective and efficient method of collecting large series prospective data in a short period of time. Utilising a similar methodology, GlobalSurg-1 united surgical teams from 375 centres around the world to collect data on 10,745 patients, highlighting the feasibility of this study.¹

There are a number of benefits to participating in the study.

For collaborators:

- Opportunity to participate in a high impact international research study.
- Co-authorship on all international presentations and publications, and the opportunity to present the study locally, nationally, regionally and internationally.
- Development of skills including applying for local study approval, patient identification, protocol application, data collection, and use of REDCap for data upload and analysis.
- Following the study, the opportunity to participate in online training to develop and undertake your own project using REDCap.
- Option of undertaking a research training fellowship alongside the main study.
- Participation in the Global PaedSurg Research Collaboration with the opportunity for ongoing collaborative research and interventional studies aimed at improving outcomes.

For patients in the future:

- Development of large population prospective data on congenital anomalies in order to advocate for enhanced neonatal surgical services at a national and international level. Such data is vital to inform advocacy efforts and global health prioritisation.
- Identification of factors affecting outcomes in low-, middle- and high-income countries, which can be modified to improve patient care.
- The opportunity for centres across the world to learn from each other to improve patient care and outcomes.

Congenital Anomalies in the Global Context

In 2015, the Global Burden of Disease study highlighted that congenital anomalies have risen to become the 5th leading cause of death in children under 5-years of age globally.²

Almost a third of infant deaths worldwide are attributed to congenital anomalies.³⁻⁶ This equates to approximately half a million deaths from congenital anomalies each year, 97% of which are in low- and middle-income countries (LMICs).^{7,8} This is likely to be an underestimation of the actual number of deaths due to under-diagnosis of neonates with congenital anomalies who die in the community and a lack of death certification in many LMICs.⁶ The prevalence of congenital anomalies is higher in LMICs than high-income countries (HICs), estimated at 3-6% of births, due to poor maternal nutrition and/ or increased exposure to infections and teratogens.^{7,8} The incidence of congenital anomalies is also greater due to a higher birth rate and limited antenatal diagnosis and hence fewer terminations in LMICs.^{6,7}

Despite the majority of deaths from congenital anomalies being in LMICs, the majority of data on these conditions is from HICs. Most congenital anomaly registries are situated in American and European regions.⁷ The International Clearing House for Birth Defects does include a few LMIC sites in Central and South America and the Middle and Far East, however there are no African sites yet highlighted on their site map⁹. Mastroiacovo et al have recently run workshops in a number of sites in sub-Saharan Africa (SSA) on how to develop and maintain a congenital anomaly registry, but we are yet to see if these will come to fruition.⁷ The focus of such registries is often epidemiology and prevention rather than management and outcomes. There are also limited research studies from LMICs. Through charitable organisations, data has been collected on some congenital anomalies such as cleft lip & palate, club foot, neural tube defects and congenital heart defects.¹⁰⁻¹⁹ Very little data is available on congenital anomalies involving the gastrointestinal tract. The latter have received less global attention, possibly due to the difficulty of raising awareness and charitable funds in the public domain without the use of images, which would be inappropriate for these conditions²⁰.

The seven conditions included in this study constitute a selection of the commonest life-threatening congenital anomalies at birth: oesophageal atresia, congenital diaphragmatic hernia, intestinal atresia, gastroschisis, exomphalos, anorectal malformation and Hirschsprung's disease. All have an incidence between 1/2000 – 1/5000 live births.^{21,22} These conditions typically require emergency surgical care within the first few days of life, which can form up to 40% of neonatal surgery.²³ Mortality from these conditions can be in excess of 50% in LMICS in contrast to other major congenital anomalies such as spina bifida, which is associated with less than 3% mortality in LMICs, but considerable morbidity.²⁴ Disparities in outcomes globally can be stark; for example the mortality from gastroschisis is 75-100% in many LMICs compared to 4% or less in HICs.²⁵⁻²⁷ Reasons for poor outcomes include a lack of antenatal diagnosis, delayed presentation, inadequate resources, a dearth of trained support personnel, and a lack of neonatal intensive care (NIC).^{24,28,29} In Uganda, it was calculated that only 3.5% of the need for neonatal surgery was met by the healthcare system.²³

In 2010, the World Health Assembly passed a resolution on congenital anomalies recommending 'prevention whenever possible, to implement screening programmes and to provide care and ongoing support to children with birth defects and their families'.⁷ Following on from that, the second target of the Sustainable Development Goal 3 is to end preventable deaths of newborn babies and children under the age of 5-years by 2030.³⁰ Clearly this will not be possible without a shift in global prioritisation towards provision of surgical care for neonates and children, which is estimated to prevent up to two-thirds of the deaths and disability from congenital anomalies.^{21,31} Currently surgical care for neonates and children is low priority as evidenced by UNICEF who have no funds earmarked for surgical care yet have a budget of over \$100 million for HIV, which results in considerably fewer deaths and less disability.²⁰ Commonly

surgical care is misconceived as being too expensive for global health initiatives, yet paediatric surgical provision has been shown to be cheaper than condom distribution in terms of disability-adjusted life years (DALYs) saved.²⁰

Lack of global data on congenital anomalies, particularly from LMICs, is preventing their elevation on the global health agenda. This study aims to create the first large-scale, geographically comprehensive, multi-centre prospective cohort study of a selection of common congenital anomalies to define current management and outcomes globally. This is vital to aid advocacy and global health prioritisation and inform future interventional studies aimed at improving outcomes.

The Seven Study Conditions in the Global Context

Oesophageal Atresia:

Oesophageal atresia (OA) is defined as complete interruption of the normal continuity of the oesophagus.³² Ninety percent of cases are associated with a tracheo-oesophageal fistula (TOF).³² Gross has classified OA into 5 types: A) without a TOF, B) proximal TOF, distal OA, C) distal TOF with proximal OA, D) proximal and distal TOF, E) H-type TOF without OA.³² The majority of cases are type C.³² Associated anomalies are common: 29-39% have a cardiovascular anomaly, 11-18% anorectal malformation, 16-22% musculoskeletal anomaly, 4-26% genito-urinary anomaly, 3-4% duodenal atresia and 3-6% Down Syndrome.^{33,34} Just under half of associated anomalies are categorised as part of the VACTERL association; a non-random co-occurrence of anomalies (Vertebral, Anorectal, Cardiac, Tracheo-oesophageal, Renal and Limb).³³ Neonates with OA are commonly small for gestational age weighing 500-1000g less than normal infants.³⁵

Management in HICs typically consists of stabilisation at birth in a NIC unit, followed by ligation of the TOF if present and oesophageal anastomosis either via thoracotomy or thoracoscopy.^{32,36} Approximately 90% of patients require post-operative ventilation for a median of 3-days.³² Median time to first oral feed is 5-days.³² In LMICs, patients tend to present late at which point half to two-thirds will have developed a chest infection and up to half are hypothermic.³⁷⁻³⁹ Poor clinical condition and a lack of resources, facilities and trained personnel for neonatal surgery result in many patients being managed with a gastrostomy, oesophagostomy and ligation of a TOF or transabdominal occlusion of the distal oesophagus, followed by reconstructive surgery when older if they survive.⁴⁰ Mortality rates in HICs are currently under 3%, compared to 42% in MICs and 79% in HICs according to the limited data available for the latter.^{21,37-50}

Congenital Diaphragmatic Hernia:

Congenital diaphragmatic hernia (CDH) is defined as any developmental defect of the diaphragm present at birth that permits herniation of the abdominal contents into the chest.⁵¹ CDH represents a spectrum of abnormalities ranging from a small defect in the diaphragm to a major disturbance of thoracic development resulting in severe lung hypoplasia and persisting pulmonary hypertension.^{51,52} Twenty-eight percent are associated with another anomaly.⁵¹ In HICs, 61% of live-born patients are diagnosed antenatally.⁵¹ Of all cases detected antenatally, 25-50% are terminated.⁵³ Patients who are diagnosed antenatally are five times more likely to die before surgery reflecting a greater disease severity in this group.⁵¹

There have been great advancements in NIC provision in HICs in recent decades; 90% of neonates with CDH receive ventilation, 61% inotropes, 96% nitric oxide and 36%

pulmonary vasodilators.^{51,54} Significant reductions in mortality were seen in HICs from the 1970's to 2000 from 50% to 20%, respectively.⁵⁴ However, mortality rates since then have remained static.^{51,54,55} Mortality in middle-income countries (MICs) has remained around 50% amongst the limited number of studies available.⁵⁶⁻⁶² The one study identified from a low-income country (LIC) is incomparable because it mainly included 'late presenters', which are a sub-group with low disease severity and typically up to 100% survival.^{63,64} Indeed some MIC studies also include a high proportion of patients born outside the hospital who survive to presentation and hence must be interpreted carefully.^{65,66} It can be hypothesised that many neonates with CDH in LICs and some MICs, particularly those with more severe disease, do not survive to present at a tertiary healthcare facility.

Intestinal atresia:

Intestinal atresia is responsible for a third of neonatal intestinal obstruction.⁶⁷⁻⁶⁹ It includes duodenal atresia (DA), jejuno-ileal atresia (JIA) and colonic atresia (CA). They are classified into four types: 1) complete intra-luminal web with a continuous muscular layer, 2) atretic segment without mesenteric defect, 3) atretic segment with mesenteric defect, 4) multiple atretic segments.^{68,70} In JIA type 3 is separated into 3a) atretic segment with mesenteric defect and 3b) apple-peel (bowel wrapped around a single artery).⁷⁰ All are associated with other anomalies, particularly Down's Syndrome in DA (25-40% of cases) and cystic fibrosis in JIA (11% cases).⁷⁰⁻⁷³ Burjonrappa's review of 130 cases provides a useful overview of the three conditions from a HIC perspective (Table 1).⁶⁷

Table 1: Descriptive data and outcomes of duodenal atresia (DA), jejuno-ileal atresia (JIA) and colonic atresia (CA)⁶⁷

Variable	DA (n=59)	JIA (n=63)	CA (n=8)
Antenatal diagnosis	46%	41%	12.5%
Mean birth weight (kg)	2.4	2.8	3.2
Gestational age	36	37	37
Associated anomalies	76%	52%	38%
Mean time to full feeds (days)	18	20	16
Incidence of re-operation	13.5%	25%	25%
Mean length of hospital stay (days)	33	41	44
Mortality	0%	10%	0%

Whereas overall mortality in HICs is typically less than 3%, it remains around 40% in LMICs.^{67,70,72,74-82} In HICs management consists of primary repair via laparotomy, laparoscopy or endoscopy.⁷⁰ However in LMICs primary stoma formation with closure/anastomosis at a later date when older and more stable is often required; the stoma can be related to considerable morbidity.⁷⁸ In Uganda, the mean time from birth to presentation is 7-days and hence neonates are typically very sick on arrival.⁷⁶ Common causes of death in LMICs include: aspiration, sepsis, electrolyte disturbance, fluid imbalance, anastomotic leak and short gut.^{72,75,76,78}

Gastroschisis:

Gastroschisis is a condition where the intestines and sometimes other intra-abdominal organs protrude through a defect in the abdominal wall adjacent to the umbilicus. There is no covering sac, unlike exomphalos. Gastroschisis is classified into simple (intact, non-obstructed bowel) and complex (with associated atresia, necrosis or perforation). In HICs, approximately 10% are complex, however a multi-centre study in sub-Saharan Africa has shown up to 25% are complex likely due to additional postnatal bowel damage before presentation at a tertiary healthcare facility.^{26,27,83} An estimated 10-15% of neonates with gastroschisis have an extra-intestinal congenital anomaly (cardiac,

genito-urological, musculoskeletal and neurological); these findings are consistent in studies across the globe including both HICs and LMICs.⁸⁴⁻⁹⁰ In HICs, the majority of cases are diagnosed antenatally and delivered in a tertiary paediatric surgery centre. However, in LMICs, few are antenatally diagnosed and hence are born in the community and by the time they arrive at a tertiary paediatric surgery centre are often already septic, hypothermic and hypovolaemic.^{25,26,91-93}

In all settings, the methods for reducing the bowel and closing the defect vary widely. In HICs, the two most commonly utilised techniques are primarily closure in the operating room (OR) under general anaesthetic (GA) within a few hours of birth or cotside application of a preformed silo, gradual reduction over a few days and closure of the defect either at the cotside without GA or in the OR. A randomised controlled trial, systematic reviews and meta-analyses have shown the two techniques to be equivalent in terms of clinical outcomes, but with a greater need for NIC unit resources such as ventilation in those managed with primary closure.⁹⁴⁻⁹⁷ In LMICs, NIC unit facilities are often unavailable and hence use of a preformed silo could potentially result in improved clinical outcomes in these settings.²⁵ However, preformed silos are not routinely used in LMICs due to cost, limited availability and lack of training and interventional studies trialling their use in the low-resource setting have yet to be undertaken. In HICs, neonates with simple gastroschisis receive a median of 23-days of parenteral nutrition until enteral feeding is established; this resource is commonly lacking in LMICs.^{25,27} There is a huge disparity in outcomes globally, with less than 4% mortality in HICs, compared to 75-100% mortality in many tertiary paediatric surgery centres across sub-Saharan Africa.^{25,27}

Exomphalos:

Exomphalos (also known as omphalocele) is defined as herniation of the abdominal contents into the umbilical cord. It is categorised into major (>50% of the liver in the exomphalos sac and abdominal wall defect >5cm) and minor (infants with smaller defects).²² Both major and minor sub-types are associated with anomalies in 50-70% of cases, including: chromosome abnormalities (commonly trisomy 13,14,15,18,21), and cardiac defects.⁹⁸⁻¹⁰¹ Beckwith-Weidemann syndrome occurs in 10% of cases and presents with macroglossia, organomegaly and early hypoglycaemia related to pancreatic hypertrophy.⁹⁸ In HICs, between 83-99% of cases are antenatally diagnosed and of those approximately a third are terminated, primarily those with associated chromosomal abnormalities.¹⁰²⁻¹⁰⁴ In LMICs, few women receive an antenatal ultrasound scan and, even if they do, diagnostic accuracy varies considerably.¹⁰⁵ In Cote d'Ivoire 6/80 cases of exomphalos received a maternal ultrasound scan, but only 2 cases were correctly diagnosed.¹⁰⁵

In HICs, most cases of exomphalos minor are managed operatively, however equipoise still exists regarding the optimal management for exomphalos major: staged operative closure or conservative management with a topical treatment to the exomphalos sac until epithelialisation occurs followed by delayed abdominal wall reconstruction.^{106,107} In LMICs, many have adopted conservative treatment for all patients with exomphalos with improved survival.¹⁰⁸⁻¹¹⁰ The major problem remains with cases where the exomphalos sac ruptures, which can result in up to 90% mortality in LMIC settings due to a lack of resources for operative management or treatment of resulting sepsis.^{108,110,111} In HICs, the overall mortality is estimated at 12.7% and in LMICs 30.1%, with the majority of deaths occurring in those with exomphalos major, associated anomalies and ruptured sac.^{21,22,85,90,100,104,105,110,112-118} Limited literature exists in all settings, particularly LMICs.

Anorectal malformation:

Anorectal malformation (ARM) comprises a wide spectrum of diseases involving failure of the normal development of the anal opening and deformities of the urinary and genital tracts.¹¹⁹ The multiple variants have been defined by the Krickenbeck international classification.^{120,121} Patients with no perineal fistula are commonly grouped under 'high malformations' and those with a perineal fistula as a 'low malformation'.¹²² Up to 70% of patients have an associated anomaly.¹²³⁻¹²⁵ Management is dependent on the type of anomaly and has been defined by a Krickenbeck list of surgical procedures for ARM.¹²¹ Low malformations are often treated with a primary anoplasty and high malformations with a posterior sagittal anorectoplasty (PSARP) either undertaken primarily or at a later date following primary stoma formation.

Mortality in HICs has fallen from 23% in the 1940's to approximately 3% today.^{122,126} Studies from MICs and LICs suggest a mortality of 18% and 26% respectively.^{21,26,50,127-134} Late presentation, which is more common in LMICs, can result in considerable morbidity and poorer long-term outcomes.¹³⁰ This can have a significant psycho-social impact, for example in a girl who is incontinent of stool via the vagina and is excluded from school and society. Similarly, neonates who receive a stoma at birth, but then experience significant delays or indeed no reconstructive surgery can suffer considerable morbidity, stigma and social exclusion.³¹

Hirschsprung's Disease:

Hirschsprung's Disease (HD) is the absence of ganglion cells in the distal bowel, beginning at the anal sphincter and extending proximally to varying degrees.¹³⁵ This results in functional obstruction due to a lack of peristalsis in the affected segment.¹³⁵ Up to a quarter have an associated anomaly; 10% have Down's Syndrome.^{27,136} Most cases are not diagnosed antenatally across all settings.^{136,137} In HICs, 90% of patient's present within the neonatal period typically with delayed passage of meconium (>24hours), abdominal distension and bilious vomiting.^{135,138} In LMICs, few patients present within the neonatal period and instead often present later with complete obstruction.^{137,139,140} Delayed diagnosis not only results in considerable morbidity prior to presentation, since most patients are symptomatic from birth, it also increases the risk of enterocolitis, which can be fatal, and renders corrective surgery more difficult with poorer long-term outcomes.^{135,140}

Diagnosis in HICs is commonly made using a rectal suction biopsy that can be undertaken at the cotside without anaesthesia in infants. However, in LMICs, a full thickness rectal biopsy under general anaesthesia is more commonly practiced likely due to the older age of the patients and lack of equipment/ facilities.^{139,141} In HICs, most surgeons aim to undertake definitive surgery before 3-months of age, with use of rectal washouts to maintain decompression pre-operatively rather than a stoma where possible.^{138,142} In LMICs, patients often receive a stoma initially and definite surgery at a later date.^{141,143,144} One article recommends the use of a trans-anal posterior anorectal myectomy in patients with ultra-short segment HD in low-resource settings.¹⁴⁵ The overall mortality in HICs is currently less than 3% compared to an estimated 18% in LMICs.^{21,127,137,138,146-153}

Aim

To undertake the first large-scale, geographically comprehensive multi-centre, prospective cohort study comparing the management and outcomes of a selection of common congenital anomalies in low-, middle-, and high-income countries across the globe.

Objectives

- 1) To compare the mortality and post-intervention complications of a selection of common congenital anomalies in LMICs and HICs globally.
- 2) To identify patient level and hospital level factors affecting outcomes that may be modifiable to improve care.
- 3) To establish a research collaboration consisting of children's surgical care providers across the world to help enhance research capacity and to create a platform for ongoing collaborative research and intervention studies aimed at improving outcomes.
- 4) To raise awareness and provide advocacy for neonatal and paediatric surgical care within global health prioritisation, planning, policy and funding.

Methodology

Study design:

This is an international, multi-centre prospective cohort study. It will involve data collection from children's surgical care providers (collaborators) from across the globe.

Collaborator recruitment:

Collaborators will be invited to participate in the study through a number of routes:

- Personal contacts
- Organisations focused on global surgery, global anaesthesia, children's surgery, regional or global research, trainee and professional networks
- Conference presentations
- Social media, including Twitter, Facebook and LinkedIn
- Professional websites
- A bespoke website designed specifically for the Global PaedSurg Research Collaboration, www.globalpaedsurg.com
- Allocation of continent, regional and country leads to invite collaborators from throughout their regions to participate in the study

Authorship:

Publishing journal(s) will be asked to make all collaborators PubMed citable co-authors. The authorship on the front page of the article will read 'Global PaedSurg Research Collaboration' with all authors' names listed in full at the end of the article. This methodology is based on an equal partnership model previously described in The Lancet and utilised by a number of national and international collaboratives.^{1,154-157} Similarly, all collaborators will have their names listed as an author on all resulting oral international conference presentations. On international poster presentations 'Global PaedSurg Research Collaboration' will be utilised to encompass all collaborators due to space restrictions.

In publication(s), authors will be listed according to their role in the study with details of what was involved (Appendix 1):

- Local collaborators
- Continent, regional and country leads
- Lead investigators
- Lead organisers
- Steering committee

Each individual collaborator can participate in more than one role in the study and this will be represented in the authorship list accordingly.

Collaborator and hospital inclusion criteria:

Any healthcare professional caring for neonates and children presenting with one of the study conditions can participate as a collaborator in the study. This includes surgeons, anaesthetists, paediatricians, neonatologists, nurses and allied health professionals. Collaborators can range from medical student to consultant level. Students and junior doctors, nurses and allied health professionals should gain permission from the senior surgeon or physician who oversees the care of the children to be included in the study in order to participate. This senior healthcare professional should be included as a collaborator within the team and will hold the responsibility of ensuring data collected is accurate, complete and without duplicates.

All hospitals providing care for neonates and children presenting for the first time with one or more of the study conditions can be included.

Team structure:

There can be up to three collaborators in a team. Data collection can be undertaken by just one team for up to seven months duration (between October 2018 to April 2019) or by multiple teams (of up to three collaborators per team) each collecting data over a different one-month period. This allows for more than three collaborators to participate from an institution. The maximum number of collaborators participating from one institution is twenty-one. The minimum length of data collection for participation in the study is one-month.

Conditions to be studied:

The seven congenital anomalies to be included in the study are:

- 1) Oesophageal atresia +/- tracheo-oesophageal atresia.
- 2) Congenital diaphragmatic hernia.
- 3) Intestinal atresia.
- 4) Gastroschisis.
- 5) Exomphalos (also known as omphalocele).
- 6) Anorectal Malformation.
- 7) Hirschsprung's Disease.

These represent a selection of the commonest congenital anomalies involving the gastrointestinal tract. They commonly require a similar package of emergency neonatal surgical care within a few hours or days of life to avoid death although some less severe forms can present later. In HICs and some LMICs, these conditions are primarily managed by the general paediatric surgery and neonatology teams, although in some LMICs adult surgical teams may also care for these children. They are a particularly understudied group of congenital anomalies in LMICs and indeed there remains a lot to be learned in HICs too.

Other life threatening congenital anomalies at birth involving other organ systems such as cardiac and genito-urinary anomalies have not been included since they may be managed by other surgical or medical teams and often require a different package of neonatal surgical care. Hence, there is a risk that some collaborators collecting data in the study would not be the primary care givers to these patients, which could result in patients being missed or inadequate data being collected.

Patient inclusion and exclusion criteria:

Inclusion criteria

Any neonate, infant or child under the age of 16-years, presenting for the first time, with one of the study conditions can be included in the study. This only includes children who have NOT previously received any surgery for their condition (surgery includes patients who have previously received a stoma). Children who have received basic resuscitative and supportive care for their condition at a different healthcare facility and then been transferred to the study centre can be included.

If a patient presents with more than one of the study conditions (for example oesophageal atresia and ARM), the details of each condition can be included within the study. However, only those conditions presenting within the study period should be included. For example, if a patient has previously had a duodenal atresia repair and then presents with Hirschsprung's disease during the study period, only the latter should be included in terms of management and outcomes.

Patients presenting primarily with one of the study conditions who receive palliative care or no care must be included within the study to reflect true outcomes.

Exclusion criteria

Any neonate, infant or child with one of the study conditions who has previously received surgery for their condition. If they have recently received surgery for their

condition, were discharged and then represented with a complication of the surgery during the study period they should NOT be included in the study. Only patients who present for the first time within the study period should be included.

Time period:

The data collection period for the study is from the 1st October 2018 to the 30th April 2019 (inclusive), with a 30-day post-primary intervention follow-up period (see Appendix 2 for a definition of primary intervention). This only includes patients receiving a primary intervention within the first 30-days of hospital admission. Hence, primary data collection will be complete by the end of June 2019. Data validation will be undertaken in July and August 2019.

In order to participate in the study collaborators must contribute data for a minimum period of 1-month. This is to allow those collaborators under significant time restraints to participate. However, we encourage all collaborators with the time and capacity to contribute data for as many months during the data collection period as possible (maximum 7-months) to optimise the number of patients included in the study and hence the impact of the results.

To standardise data collection, each month of data collection must start on the 1st day of the month and end on the last day of the month. The month of data collection will be recorded for each patient entered into the study.

During the data collection period, all patients fulfilling the inclusion criteria must be included within the study in order to provide accurate data on mortality and morbidity rates. For example, if 4 patients present with gastroschisis during the data collection period and 2 die, all 4 must be included in the study to provide an accurate result of 50% mortality. If only the 2 that survive are included the result will falsely show 100% survival. If only the 2 who died are included the result will falsely show 100% mortality.

Methods for identifying consecutive patients:

Methods for identifying all patients to include in the study are as follows:

- Daily ward rounds – on neonatal units, paediatric wards and any other sites where neonates and children with the study conditions may present.
- Handovers.
- Multi-disciplinary team meetings.
- Patient admission records.
- Operating room logbooks.
- Regular communication with colleagues and members of the team caring for neonates and children with the study conditions.
- Ensure all staff members caring for neonates and children with the study conditions are aware that the study is in progress and to alert a member of the study team if any patient presents who should be included in the study.

Methods to avoid duplicate patient entry into the study:

In order to avoid including the same patient more than once in the study a

contemporaneous list of all patients included in the study must be maintained by the team lead and utilised by all collaborators on the team. The list should include the patient's name, date of birth and hospital number alongside their REDCap ID (this is created when the patient's data is entered onto REDCap). At study sign-up the team will be emailed a spreadsheet for this purpose.

Outcome measures and patient data collection:

Primary outcome: all-cause, in-hospital mortality.

This will include all patients in the study, both those who did not receive an intervention and those that did.

For patient's hospitalised for over 30-days following primary intervention, a 30-day post-primary intervention mortality rate will be utilised. The definition of primary intervention for each study condition is provided in Appendix 2.

For patients who do not receive a primary intervention (conservative generic ward care only) but remain alive and hospitalised at 30-days following primary admission will have this time point used for recording their mortality status for the primary outcome.

Secondary outcomes: complications occurring within 30-days of primary intervention including:

- Surgical site-infection
- Wound dehiscence
- Need for re-intervention
- Condition specific complications (Appendix 2/3).
- Condition specific outcome variables (Appendix 2/3).
- Length of hospital stay (time from admission to death in patients who do not survive)
- 30-day post primary intervention mortality.

For definitions see Appendix 2.

Secondary outcomes will not be collected on patients who do not receive a primary intervention within 30-days of hospital admission, with the exception of length of hospital stay or time from admission to death.

Data will be collected on:

- Patient demographics
- Antenatal care/ diagnosis
- Pre-hospital care
- Time from birth to primary presentation at the study centre
- Time from admission to receiving primary intervention
- Clinical condition
- Peri-operative (or peri-primary intervention) resuscitation and care
- Surgical intervention
- Outcomes

Appendix 3 details the data collection form.

Outcomes and variables have been chosen using published core outcomes sets,

commonly collected outcomes in systematic reviews and meta-analyses, data collected within international registries and international classifications.^{51,52,67,89,95,96,119-121,138,158-163}

Data collection tool:

Data will be collected utilising the secure, user-friendly data collection tool REDCap.¹⁶⁴ This will be free of charge to participating collaborators. Data can be uploaded directly onto the REDCap system or collaborators can collect data on a printed data collection form and upload it at a later date onto REDCap. There is also a Smartphone App that allows offline data collection. Collaborators should not enter any patient identifying information into REDCap. Upon submission of data for a patient, a unique REDCap ID will be created for that patient. Collaborators should maintain a confidential list of patients included in the study along with their REDCap IDs so that patients can be identified at a later date for follow-up and validation if required. This list should be stored in line with local data protection laws.¹⁶⁵

Once approval for study participation has been provided at a centre, evidence should be emailed to the principal investigator, Naomi Wright (on paedsurg.research@gmail.com). The REDCap team at King's College London will then email the collaborator(s) with login details. A step-by-step guide on how to upload data to REDCap will be provided to all collaborators. REDCap will contain a pre-designed data collection tool with tick boxes and drop-down menus for easy and quick data entry.

Institutional data collection:

A short survey will be undertaken by research collaborators at the time of project sign up regarding the facilities and resources available for neonatal and paediatric surgical care at their institution (Appendix 4). To optimise accuracy and to permit data validation the survey should be completed independently by at least two qualified healthcare professionals, one of whom should ideally be the study lead, senior surgeon or anaesthetist. Students should not complete the survey. Data will be used to evaluate associations between availability of resources and facilities and patient outcomes. No individual collaborator, institution or country will be independently identifiable in the results.

Data validation:

Patient data:

Ten percent (10%) of collaborating centres will be selected at random for data validation. This will involve identifying an additional independent research collaborator at each validation centre to determine the number of patients eligible for study inclusion within the data collection period, to check if any were missed, and to collect a selection of the data again to be checked for accuracy. The independent collaborator will be identified and invited to participate by the study lead at the allocated centre. They must be a healthcare professional within the team who cares for neonates and/ or children with the study conditions, but who was not involved in the initial data collection. They will also be included as a co-author on resulting presentations and publication(s).

The validation data will be collected on a separate REDCap validation database and the inputted data will be cross-checked with that entered into the main database to assess for accuracy. The selection of validation data will include seven variables for each patient included in the study from 1-month of data collection at the validating institution. The variables that have been chosen for validation should be available retrospectively via admission records and operating room logbooks; details of ward management from patient notes will not be requested since this could be more inaccurate retrospectively than the original prospective data collection. The validation data collection form will be provided to validation centres if selected for this role.

Validating questions will also be built into the data collection tool. For example, if a patient died prior to primary intervention they should have 'not applicable' entered for type of anaesthesia at the time of primary intervention. Similarly, patients who died during their primary admission in hospital should not have data entered for post-discharge follow-up. At least 90% of the primary and secondary outcomes should be completed for each patient. Data can be initially uploaded and completed at a later date. Collaborators will be emailed with a reminder to complete any datasets with missing data.

All collaborators at the validating centres will be asked to complete a brief survey regarding their experience with collecting the data in order to identify any potential areas for error and to aid with data interpretation (Appendix 5/6).

Institutional data:

The survey data regarding the institutional resources and facilities for neonatal and paediatric surgery will be validated by evaluating the level of agreement between surveys completed independently by different collaborators at the same centre. One of these collaborators should be the study lead (senior surgeon, physician or nurse) and the other another member of the study team.

Sample Size Calculation:

A sample size calculation was undertaken using Stata/IC 15.0 based on Bonferroni correction for multiple testing, assuming 80% power and an overall type 1 error of 5%. Table 2 illustrates the required sample size for each condition. This has been calculated for the primary outcome of mortality in LMICs compared to HICs and also low, middle and high-income countries (LM&HICs) separately. Mortality estimations utilised in the calculation are based on pooled data from published studies of these conditions in low-, middle- and high-income countries respectively as referenced in the first column.

Table 2: Estimated mortality and sample sizes for low, middle and high-income countries and the mean number of cases per month per institution globally

Condition	Mortality LIC (%, n)	Mortality MIC (%, n)	Mortality LMIC combined (%, n)	Mortality HIC (%, n)	Sample size for LIC	Sample size for MIC	Sample size for HIC	Sample size for LMIC vs HIC (per group)	Mean no. cases/ month/ institution (L,M&HIC combined)
OA +/- TOF 21,32,36-50,166	79.5% (62/78)	41.8% (623/1488)	43.7% (685/1566)	2.7% (6/221)	34	34	23	21	1.02
CDH* 51,55-62	-	47.4% (130/274)	47.4% (130/274)	20.4% (201/982)	-	-	-	63	0.54
IA 67,72,74-82	42.9% (42/98)	40.0% (97/241)	41.0% (139/339)	2.9% (12/407)	6014	6014	25	24	0.63
Gastroschisis 21,26,27,85,91- 94,108,167-174	83.1% (211/254)	42.6% (205/481)	56.6% (416/735)	3.7% (28/748)	29	29	24	15	0.85
Exomphalos 21,22,85,90,104,105,110, 112-118	25.5% (41/161)	31.9% (132/414)	30.1% (173/575)	12.7% (40/316)	1040	1040	196	115	0.63
ARM 21,26,50,122,126-134	26.3% (26/99)	17.5% (243/1391)	18.1% (269/1490)	3% (14/462)	460	460	90	85	1.34
Hirschsprung's Disease 138,146-148	19.1% (33/173)	16.8% (55/328)	17.6% (88/501)	2.3% (43/1897)	5802	5802	85	79	2.21

* Representative data on the mortality from CDH in LICs is not currently available.

Based on the patient numbers included in the previously undertaken PaedSurg Africa study, which utilised a similar study design, the estimated sample sizes to detect a significant difference between LMICs and HICs in this study are achievable.²⁶ During the PaedSurg Africa study, data was collected by 220 collaborators across 76 hospitals in 23-countries in sub-Saharan Africa for the same time period as this study and included 188 patients with anorectal malformation and 111 with gastroschisis.²⁶ Since this study is global rather than limited to sub-Saharan Africa we would expect the patient numbers to exceed this.

Based on the limited data available from LMICs, it does not appear to be feasible to detect significant differences between low and middle-income countries for IA, exomphalos, ARM and Hirschsprung's; CDH is unknown since there is no reliable data from LICs at present. Hence, the primary data analysis will be a comparison of mortality for each condition between LMICs and HICs. We will attempt a secondary data analysis comparing mortality in LICs, MICs and HICs if possible, however the study is only powered to do this for oesophageal atresia and gastroschisis.

Estimated study population:

The mean number of cases presenting to an institution per month for each study condition was estimated from published studies across all income settings as detailed in Table 2 above. On average most institutions caring for patients with these conditions receive 1-2 new cases per month. Hence, each participating institution would expect to have approximately 7-14 cases to include in the study per month (although some institutions may have considerably more or less). There is no minimum number of cases required to participate in the study. Not all institutions will receive patients with all seven of the study conditions during their data collection period.

We aim to include a minimum of 365 months of data; 183 months from LMICs and 183

months from HICs. This should ensure enough cases of exomphalos to determine a significant difference between LMICs and HICs; fewer months of data are required to determine significant differences in mortality for the other study conditions. This could involve data collection by 365 institutions for 1-month each or data collection by 52 institutions for 7-months each or a variant in between (i.e 100 institutions for 3-4 months each). An up-to-date total of the patient numbers included within the study will be maintained on the study website (www.globalpaedsurg.com) so that all collaborators can work together towards this target.

Pilot study:

A pilot study of the patient data collection form, institutional survey, validation data collection form and validation surveys will be undertaken by lead investigators in multiple languages and continents to optimise their design prior to use in the study and to address any feasibility or other barriers to effective data collection and study completion across participating sites.

Data Analysis:

Patient and institutional data:

Data will be analysed using Stata and SAS 9.4 (Cary, NC; USA). Duplicates will be removed if present. Missing data for the covariates will be analysed to determine whether it is related to the outcome and either complete-case analyses or multiple imputation techniques will be used for analyses accordingly.

Significant differences in mortality between LMICs and HICs will be determined for each of the study conditions using Chi-Squared analysis, or Fisher's exact test if either group contains less than 10 patients. World Bank classification of low-, middle- and high-income countries during the fiscal year 2018 will be utilised.¹⁷⁵

Univariate logistic regression analyses will be conducted between covariates and the primary outcome of mortality. Based on the results, covariates with a p-value of <0.10 will be included in the multivariate model. The final multi-level multivariate logistic model will be determined using stepwise, backward elimination to interventions and peri-operative factors affecting outcomes. Results will be presented as odds ratios with corresponding 95% confidence intervals. Data will be adjusted for confounding factors and effect modifiers. Potential confounders include: gestational age at birth, weight, time from birth to presentation and American Society of Anesthesiologists (ASA) score at the time of primary intervention. Potential effect modifiers include: administration of peri-operative antibiotics, fluid resuscitation, thermal control and provision of other condition specific neonatal care such as parenteral nutrition in neonates with gastroschisis.

Multi-level, multivariate logistic regression analysis will also be undertaken to identify institutional factors affecting mortality with adjustment for confounders. $P < 0.05$ will be deemed significant.

Data validation:

A weighted kappa statistic will be utilised to determine the level of agreement between

the study patient data and the validation patient data. This will be presented as a proportion of agreement for each variable being validated.

For institutions where two or more collaborators have independently completed the survey on availability of resources and facilities for neonatal and paediatric surgery, a weighted kappa statistic will be utilised to determine the level of agreement between responses.

Data storage, governance and sharing:

All data will be stored on the secure, password protected, REDCap database.¹⁶⁴ This will be backed-up daily on the King's College London server by the REDCap team. The principal investigator will also back-up the data on a weekly basis on two encrypted, password protected memory sticks. All data will be governed by a data management plan that will be overseen by the data management team at King's College London and updated on a 3-monthly basis throughout the duration of the study. The full dataset will be stored securely long-term, for a minimum of 10-years following the study.

Individual collaborators will be able to access their institutional data at all times. It can be downloaded and analysed using REDCap. The principal investigator, will be able to access the full dataset in order to oversee data collection throughout the study and to undertake the subsequent data analysis. Access to the full dataset will be provided to study team members on an individual basis as required. This will include a statistician to assist with the data analysis. This may include members of the steering committee to oversee data collection. It may include members of the organising committee in order to contact collaborators to complete datasets with missing data.

Following publication of the main study results, the full anonymised dataset will be shared with all collaborators and made publicly available. At no time during presentation or publication of the study will individual collaborators, institutions or countries be independently identifiable. For the main study publication, all data within low, middle and high-income countries will be pooled for analysis. Following publication of the main study, collaborators from within a country can undertake a sub-analysis of the data from their country, but only if all collaborators who have contributed data from that country agree. Individual country names will not be identifiable on the dataset made publicly available – each country will be represented by a random number. The publicly available anonymised data will be identifiable by continent allowing for continental sub-analyses to be undertaken.

Local study approval/ ethical considerations:

According to King's College London Research Ethics Committee guidelines, this study is classified as an audit and hence does not require ethical approval (Appendices 7, 8 & 9).

The study fulfils the audit criteria as follows:

- All data collected measures current practice. The study does not involve any changes to normal patient management.
- Current practice and outcomes in low, middle and high-income countries will be compared to published standards in the literature. Table 2 details the current mortality standards for each of the seven study conditions in high-income countries.
- All the study data is routinely collected information which should be known to the

- study team without asking any additional questions to the patient/ parents.
- All data to be entered into REDCap is entirely anonymous, with no patient identifiable information.
- No individual collaborator, institution or country will be independently identifiable in the study results.
- All data will be stored securely and will be governed by a regularly updated and regulated data protection plan by King's College London data protection team.

Additional advice has been sought from King's College Hospital Research Ethics Department with respect to NHS patients. Confirmation has been provided that since the study is classified as an audit it does not require ethical approval. Local audit approval must be sought accordingly (Appendix 10).

Research collaborators will be required to gain local approval for the study at their institution according to local regulations. In some centres the study may be deemed an audit, however in others full ethical approval may be required. Evidence of local study approval, sent via email to the principal investigator, will be required to gain login access to the REDCap data collection tool.

If no formal ethics or audit committee exists, collaborators must seek approval from the Director of the Hospital or Head of the Surgery, Paediatric or Neonatology Unit in order to participate. In these circumstances please email a signed letter confirming the latter to the principal investigator.

For clinical audits collecting routine, anonymous, de-identified data, patient consent is not usually required. However, collaborators should check their local regulations regarding this and follow them accordingly.

Funding:

Funding has been provided by the Wellcome Trust to cover the costs of the REDCap data collection tool and supporting REDCap administration team and data protection team (£4032) and the website design, development and maintenance (£850).

In line with other continent-wide and global collaborative, prospective, observational cohort studies such as this, funding is not available for individual ethical applications and payments will not be made to collaborators participating in the study.^{1,26,154-156,176}

Collaborators will collect anonymous data regarding their own patients, they will maintain ownership of their data throughout the study and will be able to download and analyse the data for local audit and improvement purposes. All collaborators will be a co-author on resulting publications and the study will provide additional opportunities and benefits to the collaborator, team and future patients as highlighted on page 4. In many institutions, audit and/ or ethical approval does not incur a fee. In sites where this is required, ethical review boards may consider this to be a locally driven collaborative project rather than a formal international study for fee purposes.

Funding is not available for patient follow-up. Please follow-up patients to 30-days post primary intervention as best you can within the capacity of your current service. There is an option to document when follow-up is not possible on the data collection form.

The Wellcome Trust has had no input into the content of the study protocol other than

to recommend open-access publication of the results in a peer-reviewed journal and to make the full anonymised dataset publicly available following publication.

Limitations:

- This study will only capture the management and outcomes of those neonates and children who reach an institution in order to be included in the study. Some children with these conditions, particularly in LMICs, may never reach a centre capable of providing the required surgical care resulting in either death or life-long disability in the community. Hence, results are likely to represent an underestimation of the true mortality and morbidity from these conditions in LMICs.
- Participating institutions will be recruited through convenience sampling with snowballing. Institutions with the networks and capability to participate in the study may represent a proportion of centres with higher neonatal and paediatric surgical care capacity and hence better outcomes. The healthcare level of the participating centres will be recorded according to WHO classification to assess for this. However, in practice it is unlikely that centres other than tertiary care facilities would be able to provide definitive surgical care for the neonates presenting with the congenital anomalies represented in this study. The study could miss patients receiving life-saving, temporising surgery in a district hospital such as a stoma for anorectal malformation, rectal washouts or stoma for patients with Hirschsprung's disease or conservative management of exomphalos.
- Follow-up will be limited to 30-days post-primary intervention. Hence, the study will capture patients' acute management and outcomes, but not their longer-term outcomes, which are also important for patients with congenital anomalies in terms of long-term disability and quality of life.

Research Capacity Building:

Participation in the study will provide collaborators with experience of undertaking research including gaining local study approval, using a protocol to identify patients and collect data, use of the REDCap data collection tool, the process of data validation and an example of data analysis, interpretation and write-up. An online training session on how to set up a project using REDCap will be offered to all collaborators who are interested in undertaking their own study using this software. Through this process we hope to support the enhancement of research capacity amongst the collaborating team, which in turn aims to encourage further research into neonatal and paediatric surgery globally.

The establishment of the Global PaedSurg Research Collaboration during this study will create a platform for ongoing collaborative work and interventional studies aimed at improving outcomes in the future. An example of this is the multi-centre interventional study aimed at improving survival in neonates born with gastroschisis across sub-Saharan Africa that has been funded by the Wellcome Trust using the results of the PaedSurg Africa multi-center prospective cohort study undertaken in 2016/17.

Research Training Fellowship:

In addition to above, collaborators will have the opportunity to undertake an optional research training fellowship alongside the main study. During this fellowship the aim

will be for collaborators to develop and undertake their own local research project. Monthly research webinars will be provided covering the following topics:

1. Generation of a research question and hypothesis
2. Types of study design
3. Protocol writing
4. Ethical considerations and study approval
5. Data collection
6. Data cleaning and analysis
7. Data interpretation
8. Preparing an abstract for submission to a conference for presentation
9. Writing a manuscript
10. Choosing a journal and submitting for publication

In total there will be 10 online sessions over 1-year starting in October 2018. Each session will last between 1-2 hours. Each stage of the development and undertaking of the main Global PaedSurg study will be used as a working example during the sessions. Webinars will be undertaken in English, but a summary of each session will be provided in multiple languages as required. In conjunction with the webinars, a mentoring scheme will be established where collaborators are partnered with an academic (who speaks the same language) to provide one-on-one advice and support throughout the development, undertaking and write-up of their study.

The aim will be for each participant to produce their own abstract for submission to a conference for publication. Mentors will also support participants to write-up their results for publication. All participants will receive a certificate to confirm completion of the research training fellowship. Following abstract selection, 10 participants will be invited to present their research findings via online teleconference to the wider Global PaedSurg collaboration, with the top three winning a prize.

There will be an opportunity for a group of collaborators who are not undertaking the research training fellowship to design and undertake a pre- and post-fellowship evaluation of research capacity building with the opportunity to present and publish results as first authors. This will require separate ethical approval to the main study. Collaborators with research experience will be invited to volunteer as a mentor.

Dissemination:

Presentations:

Initially the study concept and design will be presented at international conferences focused on children's surgery, global surgery, global health, child health and congenital anomalies around the world in order to recruit collaborators to participate in the study. This process will not only facilitate study participation, but will also help to raise awareness of the need to consider congenital anomalies within the global health agenda. Following study completion, the results will be presented at local, regional, national and international conferences globally. Both the promotional presentations of the study protocol and the study results will be presented by study collaborators of all levels of training, disciplines and regions of the world. This often provides collaborators from LMICs the opportunity to gain a travel scholarship through the conference organisation to attend and present at the conference. This not only assists in the dissemination of the study results, but also creates opportunities for children's surgical care providers to

attend, present and network at international meetings.

All collaborators will be encouraged to present the results locally, regionally and nationally to raise awareness within their community. A standard PowerPoint presentation and poster will be provided in multiple languages for this purpose. All presentations will be co-ordinated by the principal investigator and organising committee to avoid duplications and to ensure all conference regulations are fulfilled.

Publications:

The study protocol will be registered on ClinicalTrials.gov and the study protocol will be submitted for peer-reviewed publication. Following completion of the study, one or more teleconferences will be held to share and discuss the data analysis undertaken and the study results amongst collaborators. The final manuscript will be shared with all collaborators for approval prior to submission. The main results paper will be submitted for open access publication in a peer reviewed journal. We shall request that all collaborators are listed as PubMed citable co-authors.

Following publication:

Following publication, the manuscript can be shared by collaborators with their local ethics committees and teams to feedback the study results and to consider areas for improved patient care. The study results can be compared to the locally collected data, which can be downloaded by collaborators at any time during the study and requested from the principal investigator following study completion. The full anonymised dataset will be made publicly available.

Collaborators will have the opportunity to undertake sub-analyses of the data for their country (if all collaborators from that country agree), region or continent. All local collaborators providing data for that region, the country/ regional/ continent leads for that region, the lead investigators, lead organisers and steering committee will be listed as co-authors.

Outcome:

This study aims to define, for the first time to our knowledge, the management and outcomes of a selection of common life-threatening congenital anomalies across the globe. This will help to raise awareness of the unacceptable disparities in outcomes between low-, middle- and high-income countries and the need to focus on improving both antenatal diagnosis and surgical care for neonates with congenital anomalies within the global health agenda. Despite congenital anomalies rising to become the 5th leading cause of death in under 5-year old's globally, surgical care for neonates has yet to gain gravitas within organisations such as UNICEF and the WHO. This may be due to the dearth of research on congenital anomalies, particularly those that involve the gastrointestinal tract, in LMICs. This study will provide the large-series, geographically comprehensive dataset that it required for such advocacy. This will provide local surgical teams with the evidence to support the incorporation of neonatal surgical care into National Surgical Plans being produced and will provide advocates of global surgical care with the data to support global change. This is vital if the sustainable development goal 3.2 is to be met with no neonate or child under 5-years of age dying of a preventable cause by 2030.

Appendices

1. Collaborator roles

There are many ways in which to participate in this study:

1) **As a local collaborator:**

This involves:

- discussing the study with relevant members of your team who care for children with the study conditions and creating a team (or more than one team) to participate in the data collection. Data collection can be undertaken by just one team for up to seven months duration (between October 2018 to April 2019) or by multiple teams each collecting data over a different one-month period. There can be up to three collaborators in a team.
- using the study protocol to apply for and gain approval for the study at your institution.
- using the criteria set in the protocol to identify patients to include in the study.
- collecting prospective data using the pre-designed data collection forms.
- uploading anonymised data onto REDCap.
- maintaining a confidential list of all patients included within the study along with their REDCap IDs in order to avoid duplications and to be able to identify them at a later date for follow-up and validation if required.

Collaborators will have the opportunity to present the study at meetings and conferences across the globe - initially the study concept to recruit collaborators and then subsequently the study results once it is complete. This will be co-ordinated by the principal investigator and the organising committee to avoid duplications and to ensure all conference regulations are complied with.

2) **As a Country-Lead:**

In addition to the roles of a local collaborator, a country lead helps to recruit other collaborators to participate in the study from across their country. They also help to trouble-shoot with questions from local collaborators and may help to provide support with gaining local study approval. Another role may be to help translate the study literature into the local language of the country if required.

3) **As a Continent or Regional Lead:**

In addition to the roles of a local collaborator, a continent or regional lead will help to recruit country leads. They will act as a first port of call for country leads who have questions regarding the study. They will encourage and co-ordinate presentations of the study protocol at national and international meetings and conferences within their region or continent to help recruit collaborators. Following such presentations, they will help to direct interested collaborators to the appropriate country lead for further advice.

4) **As a Lead Organiser:**

Roles of a lead organiser may include one or more of the following activities:

- **Developing a logo** for the study.

- **Developing and maintaining a 'Global PaedSurg' website.**
- **Co-ordinating a blog** on the website with contributions from collaborators from around the world.
- **Translation** of study documents, the REDCap data collection tool and the website to optimise inclusivity into the study of all countries around the world.
- **Development of the REDCap data collection tool.**
- Running the **Global PaedSurg Twitter account.**
- Initiating and running a **Global PaedSurg Facebook account.**
- As above for **other social media outlets.**
- There will be an opportunity for a group of collaborators to **write up the study protocol** for publication in advance of data collection.
- Registration of the protocol on ClinicalTrials.gov.
- Maintenance of **the collaborator database.**
- **Communication with collaborators.**

5) As a Lead Investigator:

Roles of a lead investigator may include one or more of the following activities:

- Participation in the **pilot study** and provision of feedback on how to optimise the data collection forms and study prior to study launch in October 2018.
- Participation in the pilot study and design of the **data validation process.**
- **Translation** of study documents, the REDCap data collection tool and the website to optimise inclusivity into the study of all countries around the world.
- There will be an opportunity for a group of collaborators to **write up the study protocol** for publication in advance of data collection.
- **Registration** of the protocol on ClinicalTrials.gov.
- Opportunity to participate in the **writing committee** for the main results manuscript.

5) As a Member of the Steering Committee:

- Participation in the study design and protocol development.
- Participation in the ethical application for the study at King's College London.
- Participation in the writing and revising of the study protocol for publication.
- Participation in the data analysis, write-up and revisions of the results manuscript for publication.
- Oversight and decisions regarding the study.

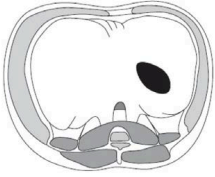
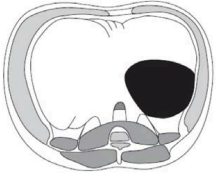
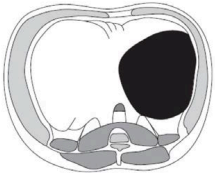
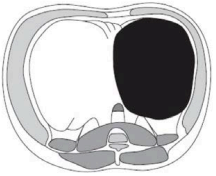
The **Principal Investigator** for the study is Ms Naomi Wright MBChB (Hons) BSc (Hons) MRCS DCH, Paediatric Surgery Registrar and Wellcome Trust Clinical PhD Fellow at King's Centre for Global Health and Health Partnerships, King's College London, UK. Email: paedsurg.research@gmail.com. Tel: 0044 7824468954.

***** All collaborators will be co-authors of resulting presentations and will be PubMed Citable co-authors of the resulting publication(s).**

2. Glossary of terms used on the data collection form

Term	Definition
Gestational age at birth	Number of weeks from the first day of the women's last menstrual cycle until birth.
Primary intervention: definition for each study condition	<ul style="list-style-type: none"> • Oesophageal atresia: surgery, either temporising or definitive, to manage the oesophageal atresia and/ or tracheo-oesophageal fistula. • Congenital diaphragmatic hernia: surgery to reduce the hernia and close the defect. • Intestinal atresia: surgery, either temporising or definitive, to manage the obstruction including stoma formation and primary anastomosis. • Gastroschisis: any procedure to either cover or reduce the bowel and/ or close the defect. This includes application of a silo (regardless of whether or not they go on to require surgery). It excludes initial covering of the bowel in a plastic covering (bag or cling film) prior to intervention. • Exomphalos: surgery or application of topical treatment to the sac in patients managed conservatively (regardless of whether or not they go on to require surgery). • Hirschsprung's disease: surgery, either temporising or definitive, or rectal/ distal bowel irrigation, laxatives or digital stimulation in patients managed conservatively. This does not include pre-operative washouts. If the patient does receive surgery during their primary admission then the primary intervention is defined as the surgery. • Anorectal malformation: surgery, either temporising or definitive, or anal/ fistula dilatation in patients with a low anorectal malformation managed conservatively. If anal/ fistula dilatation fails and the patient goes on to require surgery during their primary admission then the primary intervention is defined as the surgery. <p>Please include surgical interventions regardless of whether an anaesthetic was used or not and regardless of the location – the intervention does not have to have occurred in the operating theatre to be included.</p> <p>Primary intervention excludes:</p> <ul style="list-style-type: none"> • Surgical procedures not directly related to the temporising or definitive management of the congenital anomaly. For example, it excludes chest drain placement, abdominal drain placement and central line placement.
American Society of Anesthesiologists (ASA) score	1. Healthy person, 2. Mild systematic disease, 3. Severe systematic disease, 4. Severe systemic disease that is a constant threat to life, 5. A moribund patient who is not expected to survive without the operation.
Follow-up	This can include all reliable communication with the patient/ patient's family including in person, via telephone and other.
Duration of hospital stay	This includes the day of admission and the day of discharge. For example, a patient who presented on the 5 th October and was discharged on the 10 th of October had a hospital stay of 6-days. If the patient died, please record the number of days until death. Only include the duration of the primary admission, not the subsequent admission if the patient re-presented after discharge.
Surgical site infection (SSI)	<p>This is defined by the Centre for Disease Control¹⁷⁷ as including one or more of the following within 30-days of surgery:</p> <p>1) purulent drainage from the superficial or deep (fascia or muscle) incision, but not within the organ/ space component of the surgical site</p> <p>OR 2) at least two of: pain or tenderness; localised swelling; redness; heat; fever; AND the incision is opened deliberately to manage infection, spontaneously dehisces or the clinician diagnoses a SSI (negative culture swab excludes this criterion)</p> <p>OR 3) there is an abscess within the wound (clinically or radiologically detected).</p>

Wound dehiscence	All layers of the wound open post-operatively
Sepsis	Sepsis is SIRS (Systemic Inflammatory Response Syndrome) with a suspected or confirmed bacterial, viral, or fungal cause. SIRS is a response to a stimulus, which results in two or more of the following: temperature > 38.5°C or < 36°C, tachycardia*, bradycardia* in children < 1 year old, tachypnoea*, leukopenia or leucocytosis*, hyperglycaemia*, altered mental status, hyperlactaemia*, increased central capillary refill time >2 seconds. *Variables are defined as values outside the normal range for age.
Appropriate antibiotics	Antibiotics that are either broad spectrum covering gram negative, gram positive and anaerobic bacteria OR antibiotics that are the standard empirical treatment for that condition according to local guidelines OR are based on sensitivities provided by a microbiology sample.
Hypothermia	Defined as <36.5 degrees Celsius core temperature.
Hypovolaemia	Criteria for diagnosis include at least one of the following: prolonged central capillary refill time > 2 seconds, *tachycardia, mottled skin, *reduced urine output, cyanosis, impaired consciousness, *hypotension. *Variables are defined as values outside the normal range for age.
First enteral feed	The first day that the patient received any enteral intake, via any route
Full enteral feeds	The patient is tolerating the full volume and content of enteral intake as required for their age AND they are not reliant on any other source of nutrition
Type of OA +/- TOF (Gross classification)	A: without a fistula, B: proximal TOF, distal OA, C: distal TOF with proximal OA, D: proximal and distal TOF, E: H-type TOF without OA.
Long gap OA	A gap of 4 vertebral bodies or more. Anatomically cases either have no TOF or a gap of over 4 vertebral bodies following division of the distal fistula making primary repair unfeasible.
Short gap OA	A gap of less than 4 vertebral bodies. Primary anastomosis typically feasible.
Pneumonia	Lung inflammation typically caused by bacterial or viral infection, in which the air sacs fill with pus and may become solid.
CDH Study Group (SG) Classification ^{54,178,179}	<p>Defect A: smallest defect, usually “intramuscular” defect with >90% of the hemi-diaphragm present; this defect involves <10% of the circumference of the chest wall.</p> <p>Defect B: 50-75% hemi-diaphragm present; this defect involves <50% of the chest wall.</p> <p>Defect C: <50% hemi-diaphragm present; this defect involves >50% of the chest wall.</p> <p>Defect D: largest defect (previously known as “agenesis”); complete or near complete absence of the diaphragm with <10% hemi-diaphragm present; this defect involves >90% of the chest wall. Surgically, it is an absent posterior rim beyond the spine, absent posterior-lateral rim, and an anterior/anterior-medial rim which is miniscule. As it is truly unusual to have zero tissue at all, this is the CDHSG member consensus. “D” defects should all require a patch (or muscle flap) for repair.</p> <p>Diagram of the CDHSG Staging System: A left diaphragmatic defect is shown as viewed from the peritoneal cavity looking toward the hemi-thorax.</p>

	<div style="display: flex; flex-wrap: wrap; justify-content: space-around;"> <div style="text-align: center;">Defect A </div> <div style="text-align: center;">Defect B </div> <div style="text-align: center;">Defect C </div> <div style="text-align: center;">Defect D </div> </div> <p>There is no defect diagram for right-sided defects so the CDHSG recommends applying the above descriptions and reversing (mirror-image) the diagrams to determine the size of a right-sided defect.</p>
Pulmonary hypertension	Persistent pulmonary hypertension of the newborn (PPHN) is defined as the failure of the normal circulatory transition that occurs after birth. It is a syndrome characterised by marked pulmonary hypertension that causes hypoxemia secondary to right-to-left extrapulmonary shunting of deoxygenated blood. It should be suspected whenever the level of hypoxemia is out of proportion to the level of pulmonary disease. Echocardiography plays a major role in screening and assisting in making the diagnosis of PPHN.
Classification of atresia	1) intraluminal web with continuity of the muscular layer, 2) atretic segment without a mesenteric defect, 3) atretic segment with mesenteric defect, 4) multiple atresias = string of sausages appearance. Jejunio-ileal atresia has a further sub-division of type 3: 3a) atretic segment with mesenteric defect, 3b) apple-peel (bowel wrapped around a single artery).
Abdominal compartment syndrome (ACS)	Respiratory insufficiency secondary to compromised tidal volumes, decreased urine output caused by falling renal perfusion or any other organ dysfunction caused by increased intra-abdominal pressure.
Exomphalos major	>50% of the liver in the exomphalos sac and abdominal wall defect >5cm
Exomphalos minor	Infants with defects less than 5cm
Hypoglycaemia	Blood glucose levels below 4 mmol/L (72mg/dL)
Hirschsprung's associated enterocolitis (HAEC)	Inflammation of the small and or large bowel in patient's born with Hirschsprung's disease.
Peña stimulator	Muscle locating stimulator commonly used to identify the anal sphincter muscles whilst undertaking a PSARP for patients with ARM

3. Data collection form

See Appendix 2 for the glossary of terms used in the data collection form. Of note, on the REDCap data collection system the terms in the glossary will be incorporated within the data collection form to ensure definitions are readily available next to each data point. Below they have been separated for clarity.

Generic data points:

These data points are required for all patients in the study.

Generic questions	Answers
Demographics	
Gestational age (GA) at birth	22-44, unknown
Age at presentation	In days (include the day of birth and the day of presentation)
Gender	Male, female, ambiguous, unknown
Weight	In kilograms on the day of presentation.
Does the patient have another anomaly in addition to the study condition? (select all that apply)	Yes: cardiovascular, yes: respiratory, yes: gastrointestinal, yes: neurological, yes: genito-urinary, yes: musculoskeletal, yes: Down syndrome, yes: Beckwith-Wiedemann syndrome, yes: cystic fibrosis, yes: chromosomal other, yes: other, no
Distance from the patient's home to the study centre	In kilometres
Clinical condition and patient care	
Antenatal ultrasound undertaken? *If the condition was diagnosed antenatally, at what GA?	Yes: study condition diagnosed*, Yes: problem identified but study condition not diagnosed, yes: no problem identified, No
Mode of transport to hospital	Ambulance, other transport provided by the health service, patient's own transport, born within the hospital
Type of delivery	Vaginal (spontaneous), vaginal (induced), caesarean section (elective), caesarean section (urgent/ non-elective)
Was the patient septic on arrival? If yes, were appropriate antibiotics administered within 2-hours of arrival?	Yes, no Yes, no
Was the patient hypovolaemic on arrival? If yes, was an intravenous fluid bolus given within 2-hours of arrival?	Yes, no Yes: 10mls – 20mls/kg, Yes: more than 20mls/kg, no.
Was the patient hypothermic on arrival? If yes, was the patient warmed to normal temperature within 2-hours of arrival?	Yes, no Yes, no
Did the patient receive central venous access? If yes, did the patient acquire central line sepsis during their primary admission?	Yes: umbilical catheter, Yes: peripherally inserted central catheter (PICC), Yes: percutaneously inserted central line with ultrasound guidance, Yes: percutaneously inserted central line without ultrasound guidance, Yes: surgically placed central line (open insertion), No Yes: diagnosed clinically, yes: confirmed on microbiology, no
Time from arrival at the hospital to primary intervention	In hours (enter 0 if no intervention was undertaken)
ASA score at the time of primary intervention	1-5, not applicable (no intervention)
Type of anaesthesia used for the primary intervention	General anaesthesia with endotracheal tube, general anaesthesia with laryngeal airway, ketamine anaesthesia, spinal/ caudal anaesthesia, local anaesthesia, no anaesthesia/ just analgesia, no anaesthesia/ no analgesia, not applicable – no surgery or intervention undertaken.

Who undertook the anaesthetic for the primary intervention?	Anaesthetic doctor, anaesthetic nurse, medical officer, surgeon, other healthcare professional (if other, please specify), no anaesthesia undertaken.
Was a surgical safety checklist used at primary intervention?	Yes, no: but it was available, no: it was not available
Total duration of antibiotics post-surgery (or gastroschisis closure)	In days (including the day of surgery and the day antibiotics were stopped. Include intravenous and oral antibiotics).
Did the patient receive a blood transfusion during their primary admission?	No: not required, no: it was required but was not available, yes: not cross-matched, yes: cross-matched.
Did the patient require ventilation? If yes, for how long did the patient remain on ventilation?	Yes and it was available, yes but it was not available, no In days (only include the first episode on ventilation if the patient was weaned off then relapsed requiring further ventilation).
Time to first enteral feed (post-primary intervention)	In days (include the day of primary intervention and the day of first enteral feed in the calculation)
Time to full enteral feeds (post-primary intervention)	In days (enter 0 if the patient died before reaching full enteral feeds or 30 if the patient had not reached full enteral feeds at 30-days post primary intervention)
Did the patient require parenteral nutrition (PN)? If yes, for how long did the patient receive PN?	Yes and it was available, yes and it was sometimes available but less than required, yes but it was not available, no In days (only include the first episode on PN if the patient was weaned off then relapsed requiring further PN. Include all days when the patient received PN regardless of the volume given)
Outcomes	
Did the patient survive to discharge? If yes, was the patient still alive at 30-days post primary intervention? If no, cause of death:	Yes, no (select yes if the patient was still alive in your hospital 30-days after primary intervention or if the patient was still alive 30-days following admission if the patient did not receive an intervention). Yes, no, not followed-up after discharge, not followed-up to 30-days post primary intervention. Sepsis, aspiration pneumonia, respiratory failure, cardiac failure, malnutrition, electrolyte disturbance, haemorrhage, lack of intravenous access, hypoglycaemia, condition specific (recurrent tracheo-oesophageal fistula, recurrent diaphragmatic hernia, anastomotic leak, ischaemic bowel, ruptured exomphalos sac, enterocolitis), other (please specify)
Duration of hospital stay	In days
Did the patient have a surgical site infection?	Yes/ no
Did the patient have a full thickness wound dehiscence?	Yes/ no
Did the patient require a further intervention within 30-days of primary intervention?	No, yes: percutaneous intervention, yes: surgical intervention (this does not include the routine reduction and closure of the defect in neonates with gastroschisis receiving a preformed silo).
Was the patient followed-up to 30-days post primary intervention to assess for complications?	No: data is based on in-patient observations only, no: follow-up was done but prior to 30-days, yes: reviewed in person, yes: via telephone consultant, yes: via other means, yes: still an in-patient at 30-days.
If the patient had a complication, when was it diagnosed?	During primary admission, as an emergency re-attender, at routine follow-up as an out-patient, not applicable (no complications)
Study condition (select all that apply)	Oesophageal atresia, CDH, IA, gastroschisis, exomphalos, ARM, Hirschsprung's Disease.

Condition specific data points:

These data points will only be required for the condition or conditions that the patient has as selected in the previous section.

Oesophageal atresia (OA)

Question	Answers
Type of OA +/- TOF (Gross classification)	A-E
Long or short gap	Long, short
Pneumonia at presentation?	Yes: diagnosed clinically, yes: diagnosed radiologically, yes: other means of diagnosis, no: patient born in the study centre, no: patients born outside the study centre but no evidence of pneumonia on arrival
Primary intervention (select all that apply) If the patient had a primary oesophageal anastomosis, was a post-operative oesophagogram undertaken? If yes, routine or clinically indicated? If yes, when? If yes, what was the result? For patients diagnosed with a leak radiologically, was it associated with clinical symptoms? For patient's not receiving a primary oesophageal anastomosis, at what age is definitive surgery planned? What is the future planned procedure? (select all that apply)	TOF ligation*, oesophageal anastomosis*, oesophagostomy, gastrostomy, ligation of the distal oesophagus, gastro-oesophageal disconnection, Foker technique, fundoplication, other (please specify), palliative care Yes, no Routine, clinically indicated Number of days after primary surgery Leak, no leak Yes, no In months Gap assessment, primary oesophageal anastomosis if possible, gastric pull-up, jejunal interposition or colonic interposition (if primary oesophageal anastomosis not possible), other (please specify)
Surgical approach Converted to open?	Thoracotomy muscle cutting, thoracotomy muscle splitting, thoracoscopy*, laparotomy, laparoscopy*, limited local incision, other (please specify) Yes, no
Time to first oral feed post-operatively	In days
Time to full oral feeds	In days (enter 0 if the patient died before reaching full oral feeds or 30 if the patient had not reached full oral feeds at 30-days post primary intervention)
Did the patient have a condition specific complication within 30-days of primary intervention? (select all that apply)	Pneumonia, mediastinitis, pneumothorax, chylothorax, haemothorax, anastomotic leak, anastomotic stricture, recurrent TOF, other (please specify), none
Did the patient have tracheomalacia? If yes, was an intervention required?	Yes: diagnosed clinically, yes: diagnosed on bronchoscopy, yes: diagnosed on CT, yes: diagnosed on bronchogram, yes: other method of diagnosis, no Yes: aortopexy, yes: tracheostomy, yes: tracheal stent, yes: supportive management (oxygen +/- ventilation) only, yes: other treatment (specify), no

Congenital diaphragmatic hernia

Question	Answers
Type of CDH Type of Bochdalek CDH (CDH Study Group Classification ^{54,178})	Left posteriolateral (Bochdalek)*, right posteriolateral (Bochdalek)*, bilateral posteriolateral (Bochdalek)*, central, anterior (Morgagni), other, unknown A-D, other (specify), unknown (this will be asked separately for left and right for those with a bilateral CDH)
If antenatally diagnosed, what was the lung-to-head ratio (LHR)?	Enter zero if not undertaken/ not known

Was foetal tracheal occlusion (FETO) undertaken? If yes, at what gestational age was it inserted? If yes, at what gestational age was it removed?	Yes, no
Liver position	Chest, abdomen
Did the patient have pulmonary hypertension (at any stage)? If yes, treatment given?	Yes: diagnosed clinically, yes: diagnosis confirmed on echocardiography, yes: other method of confirming diagnosis, no, unsure Nitric oxide, sildenafil, endothelial receptor blockade, prostacyclin, alprostadil, milrinone, other (please specify), none: not required, none: required but not available
Did the patient receive extracorporeal membrane oxygenation (ECMO)? If yes, for how long?	Yes, no In days
Primary intervention *If patch repair, material used? Other procedures undertaken at the same time (select all that apply):	Primary repair (absorbable sutures), primary repair (non-absorbable sutures), patch repair* Permacol, PTFE, alloderm, dacron, mesh plug, muscle flap, surgisis, other (please specify) Chest drain insertion, abdominal wall patch, fundoplication, correction of malrotation, appendicectomy, other (specify), none
Surgical approach *Conversion to open?	Laparotomy, laparoscopy*, thoracotomy, thoracoscopy*, other (please specify) Yes, no
Condition specific complication within 30-days of primary surgery? (Select all that apply).	Air leak (not just redundant space in the pleural cavity which is common), chylothorax, recurrence, adhesional obstruction

Intestinal atresia

Question	Answers
Type of intestinal atresia	Duodenal, jejuno-ileal, colonic
Classification of atresia	1,2,3a,3b,4
Primary intervention For those with a primary anastomosis, was a covering stoma placed? Was the distal bowel flushed to check for patency?	Laparotomy (Kimura's diamond shaped anastomosis, side-to-side anastomosis, end-to-end anastomosis, primary loop stoma, primary divided stoma, primary Bishop-Koop stoma, Santulli stoma, other) Yes, no Yes, no
Condition specific complications within 30-days of primary intervention (select all that apply)	Anastomotic leak/ stenosis, short-gut, missed additional atresia, adhesive bowel obstruction

Gastroschisis

Question	Answers
Type of gastroschisis	Simple, complex: associated with atresia, complex: associated with necrosis, complex: associated with perforation.
Method of gastroschisis closure *If staged closure was undertaken, what method was used for closure? *Which type of silo was used?	Primary closure in the operating room (OR), primary closure at the bedside, *staged closure using a preformed silo, *staged closure using a surgical silo (including sterile improvised silo), other method (please specify), not applicable: palliative care. Sutureless closure without general anaesthetic (GA), sutureless closure with GA, sutured closure without GA, sutured closure with GA Preformed silo, spring-loaded silo, Alexis wound

	protector and retractor, surgical silo, improvised silo, female condom, other
On what day following admission was abdominal wall closure achieved?	In days
Did the neonate have any of these complications within 30-days of primary intervention? (select all that apply) If the patient had ACS, was the abdomen re-opened?	Ischaemic bowel, abdominal compartment syndrome* (ACS), necrotising enterocolitis. Yes, no

Exomphalos

Question	Answers
Type of exomphalos	Minor, major
Hypoglycaemic on arrival?	Yes, no, blood glucose not measured
Primary intervention If conservative management, was a topical treatment applied to the exomphalos sac?	Primary operative closure, staged closure, conservative management Yes: silver sulfadiazine, yes: betadine, yes: honey, yes: merbromide tannage, yes: other (please specify), no
What is the plan for future management?	No further surgery planned, delayed closure at this hospital, delayed closure at another hospital, other (please specify)

Anorectal malformation (ARM)

Question	Answers
Type of anorectal malformation (Krickenbeck classification) ^{120,121}	Low ARM: Perineal (cutaneous) fistula High ARM: Rectourethral fistula (prostatic, bulbar), Rectovesical fistula, Vestibular fistula, Cloaca, No fistula, Anal stenosis, High ARM: but type unknown at present, Rare variant (pouch colon, rectal atresia/ stenosis, rectovaginal fistula, H fistula, other)
Did the patient have pre-operative bowel perforation	Yes, no
What primary intervention was undertaken? (select all that apply) If primary anorectal reconstruction was undertaken, was a Peña stimulator or equivalent used to identify the position of the muscle complex intra-operatively?	Fistula dilatation: no surgery, loop sigmoid colostomy, divided sigmoid colostomy, loop transverse colostomy, divided transverse colostomy, other stoma, anoplasty, posterior sagittal anorectoplasty (PSARP), abdominosacroperineal pull-through, abdominoperineal pull-through, laparoscopic-assisted pull-through, palliative care, other (please specify) Yes, no: equipment was not available, no: the equipment was available but not used
Did the patient have any of the following complications within 30-days of primary intervention? (select all that apply)	Electrolyte disturbance, high stoma output (over 20mls/kg/day), stoma prolapse/ retraction/ herniation, peri-stoma skin breakdown (or perianal if primary reconstructive surgery was undertaken without a covering stoma), anal stenosis (if primary reconstructive surgery was undertaken without a covering stoma)
What is the plan for future management? (select all that apply)	No further operative management, anoplasty/ pull-through at your hospital, anoplasty/ pull-through planned at another hospital, stoma closure planned at your hospital, stoma closure planned at another hospital, other (please specify).

Hirschsprung's disease

Question	Answers
Time to first passage of meconium after birth	Less than 24 hours, 24-48 hours, over 48 hours, unknown
Features at presentation (select all that apply)	Abdominal distension, bilious vomiting, non-bilious vomiting, poor feeding, suspected enterocolitis, perforation, other

Source of diagnosis of Hirschsprung's disease (select all that apply) *If on biopsy, what was the method of histology staining (select all that apply)	Genetic, mucosal biopsy*, full thickness biopsy*, anorectal manometry, barium enema, not confirmed: suspected only, other Hemotoxilin and Eosin (H&E), acetylcholinesterase, calretinin, other (please specify)
Length of aganglionosis	Rectal, recto-sigmoid, to the descending colon, to the transverse colon, to the ascending colon, involving the small bowel, unknown at present
Primary intervention If primary pull-through undertaken, did the patient have a covering stoma? Was it laparoscopic assisted?	Conservative: no treatment, conservative: digital stimulation, conservative: laxatives only, conservative: regular rectal washouts/ enemas, initial rectal washouts/ enemas followed by a stoma during the same hospital admission, primary stoma (less than three prior rectal washouts/ enemas), primary pull-through (Swenson, Duhamel, Soave, other), transanal posterior anorectal myectomy, palliative care. Yes, no Yes, no
Did the patient have any condition specific complications within 30-days of primary intervention? (select all that apply)	Enterocolitis, electrolyte disturbance, high stoma output (over 20mls/kg/day), stoma prolapse/ retraction/ herniation, peri-stoma skin breakdown (or perianal if primary pull-through was undertaken without a covering stoma), anal stenosis or post-operative obstruction or anastomotic leak (if primary pull-through was undertaken without a covering stoma)

Branching logic will be utilised so that subsequent questions appearing within the same box in the tables above, will only appear if relevant to the patient. This will minimise the time to complete the data collection form.

Where the number of days is requested please include the first day and the last day in the calculation. For example, a patient who presented on the 1st Oct 2018 and was discharged on the 5th October 2018 had a length of hospital stay of 5-days. Similarly, where the number of hours is requested include the first hour and the last hour in the calculation. For example, if a patient presents at 08:00 and undergoes primary intervention at 15:00, then the time from admission to primary intervention is 8-hours.

4. Institutional survey

Dear Global PaedSurg Research Collaborator,

Please kindly complete this brief survey on the facilities and resources available at your institution. Please note that no individual collaborator, institution or country will be independently identifiable in future results, presentations or publications.

Please provide an answer in every box. The survey only takes a few minutes to complete.

Thank you for your time and participation.

Kindest regards,

Dr Naomi Wright
Principal Investigator, Global PaedSurg Research Collaboration

Title:

Professor
Dr
Mr
Mrs
Miss
Ms
Other

Surname/ Last Name:

First name:

Professional position:

Professor
Consultant
Registrar
Intern/ house officer/ senior house officer
Medical officer
Medical Student
Nurse
Other

Specialty:

General Surgery (adult and paediatric)
Paediatric Surgery
Anaesthetics
Paediatrics
Neonatology
Nursing
Not specialised yet
Other

Full name of institution:

Address of institution:

Type of institution (WHO classification):

Specialised children's hospital (Provides highly specialised care dedicated to children).
Referral hospital (WHO defined tertiary healthcare. Includes academic, university, teaching,

national, central and specialised mission hospitals. Can provide specialised surgical services). District hospital (WHO defined secondary healthcare. Includes provincial, general, general mission or regional hospitals. Has general anaesthesia and can provide general surgical care). Health centre (WHO defined primary healthcare. No general anaesthesia, can do minor local procedures, wound management, triage and referral).

Institution classification: government, non-government; not for profit, for profit

Country:

Population served by your institution:
(in millions, including children and adults)

Personnel:

Number of Consultant Paediatric Surgeons undertaking general paediatric surgery at your institution:
(excluding trainees)

Number of Consultant Paediatric Surgeons undertaking neonatal surgery at your institution:
(excluding trainees)

Number of Consultant General Surgeons (covering adults and children) undertaking general paediatric surgery at your institution:
(excluding trainees)

Number of Consultant General Surgeons (covering adults and children) undertaking neonatal surgery at your institution:
(excluding trainees)

Number of medical officers undertaking paediatric surgery independently at your institution:
(without a consultant surgeon present at the time of surgery)

Number of medical officers undertaking neonatal surgery independently at your institution:
(without a consultant surgeon present at the time of surgery)

Infrastructure:

Please state whether the following facilities are available at your institution when required. (Each field requires an answer – Always, Sometimes or Never).

- Running water
- Electricity
- Electricity generator back-up
- Laboratory for biochemistry
- Laboratory for haematology
- Blood bank
- Neonatal ventilation outside the operating room
- Paediatric ventilation outside the operating room
- Neonatal intensive care unit for surgical neonates pre- and post-operatively (including if a stoma is present)
- Paediatric intensive care unit for surgical paediatric patients pre- and post-operatively if required
- Extracorporeal membrane oxygenation (ECMO)
- Parenteral nutrition for adults and older children
- Parenteral nutrition for neonates

- Sterile gloves and gown
- Autoclave for sterilising surgical equipment
- Peña stimulator or equivalent device to identify the muscle complex during anorectal reconstruction
- Suction rectal biopsy gun to investigate for Hirschsprung's disease

Procedures:

Please state whether the following procedures are available at your institution when clinically appropriate/ required.

(Each field requires an answer – Always, Sometimes or Never).

- Neonatal thoracotomy
- Neonatal thoracoscopy
- Neonatal laparotomy
- Neonatal laparoscopy
- Foetal tracheal occlusion (FETO) for CDH
- Bedside primary reduction and closure of gastroschisis (Bianchi technique)
- Preformed silo application, reduction and closure of gastroschisis
- Surgical silo application, reduction and closure of gastroschisis
- Primary closure of gastroschisis in the operating room
- Sigmoid colostomy
- Posterior Sagittal AnorectoPlasty (PSARP) for anorectal malformation
- Pull-through for Hirschsprung's disease
- Neonatal central line insertion
- Umbilical vein catheterisation
- Paediatric central line insertion

Anaesthesia and resuscitation:

Please state whether the following facilities are available at your institution when required.

(Each field requires an answer – Always, Sometimes or Never)

- Neonatal bag, valve and mask
- Paediatric bag, valve and mask
- Bottled oxygen
- Piped oxygen
- Oxygen saturation monitor
- Apnoea monitor
- Multi-parameter intra-operative monitoring
- Anaesthetic machine for neonates
- Anaesthetic machine for children
- Ketamine anaesthesia for neonates
- Ketamine anaesthesia for children
- Spinal/ caudal anaesthesia for neonates
- Spinal/ caudal anaesthesia for children
- Anaesthetic doctor competent to perform neonatal anaesthesia
- Anaesthetic doctor competent to perform paediatric anaesthesia
- Anaesthetic nurse competent to perform neonatal anaesthesia
- Anaesthetic nurse competent to perform paediatric anaesthesia

Does your country have at least one children's hospital that can provide neonatal and paediatric surgery? Yes/ No

Any other comments: _____

5. Validation survey to be completed by the collaborators who undertook the original data collection

Global PaedSurg Validation Survey

Dear Global PaedSurg Collaborator,

Your centre has been randomly selected for data validation. In order to assist this process please can you kindly complete this brief survey on the validity of the data collected from your centre?

Please note that your participation in the validation process will remain entirely anonymous and at no point will either yourself or your team be identified as one of the centres participating in data validation. Hence, please be honest and open with your answers. It is likely that there may have been difficulty collecting some of the data points or identifying some of the patients. It is important to identify this to help with interpretation of the data from this study and also to help improve the design of future studies.

Thank you very much for your time and participation in this vital component of the study.

The survey should only take a few minutes to complete.

Kindest regards,

Dr Naomi Wright
Principal Investigator, Global PaedSurg Research Collaboration

What is the name of your hospital?

(Please note that this will be anonymous in all presentations and publications).

Do you think your team managed to identify all patients eligible for the study during the data collection period?

Yes

No

Unsure

If you answered no or unsure, what problems did you experience with identifying patients?

Free text box

Could any patients have been missed from study inclusion?

Yes

No

Unsure

(Please answer yes or unsure if any patients with one of the 7 study conditions may have been managed by adult colleagues or other specialties at your hospital and not included in the study).

If you answered yes or unsure, how might patients have been missed from study inclusion?

Free text box

Are there any study conditions that were more likely to have been missed from study inclusion?

Oesophageal atresia

CDH

IA

Gastroschisis

Exomphalos

ARM

Hirschsprung's disease

If you selected any of the above conditions, why was this the case?

Free text box

How did you identify patients to include in the study?

Ward round

Handover

Operating room logbook

Planned operation lists

Ward patient lists

Word of mouth

Personal knowledge of patients

Other

If other, please provide further detail:

If you and the other collaborators at your centre were not present at the hospital for one or more of the days during the data collection period, were you able to identify all the patients to be included in the study on those days?

Yes

No

Unsure

Not applicable

How did you identify patients to be included in the study on days when you and the other collaborators were not present at the hospital?

Ward round

Handover

Operating room logbook

Planned operation lists

Ward patient lists

Word of mouth

Personal knowledge of patients

Other

If other, please provide further detail:

Do you have any concerns regarding the accuracy of the data collected on the patients included in the study?

Yes

No

Unsure

If yes or unsure, what data points might be inaccurate and what were the challenges for collecting this data?

Free text box

If you had problems with any of the data points, did you manage to overcome these problems and how?

Free text box

Any other comments:

Free text box

6. Validation Survey to be undertaken by the Independent Validating Collaborators

Global PaedSurg Validation Survey (for Validators)

What is the name of your hospital?

(Please note that this will be anonymous on all presentations and publications).

What month of patient data are you validating?

Please enter the total number of patients who presented with one or more of the study conditions during that month:

Please enter the number of patients presenting with oesophageal atresia during this time period:

Please enter the number of patients presenting with CDH during this time period:

Please enter the number of patients presenting with IA during this time period:

Please enter the number of patients presenting with gastroschisis during this time period:

Please enter the number of patients presenting with exomphalos during this time period:

Please enter the number of patients presenting with ARM during this time period:

Please enter the number of patients presenting with Hirschsprung's disease during this time period:

Do you think your team managed to identify all patients eligible for the study during the data collection period?

Yes

No

Unsure

If you answered no or unsure, what problems might they have experienced when trying to identify patients?

Free text box

Have you managed to identify any additional patients that were eligible for the study, but were not included?

Yes

No

If yes, through what sources were you able to identify additional patients?

Admission records

Operating room logbook

Elective operation lists

Ward patient lists

Word of mouth/ discussion with colleagues

Personal knowledge of patients
Other
If other, please provide further detail:

Why do you think these patients might have been missed from study inclusion?

Are there any study conditions that were more likely to have been missed from study inclusion?

Oesophageal atresia
CDH
IA
Gastroschisis
Exomphalos
ARM
Hirschsprung's disease

If you selected any of the above conditions, why might this have been the case?

Free text box

What sources did you utilise to check whether all patients had been included in the study?

Admission records
Operating room logbook
Elective operation lists
Ward patient lists
Word of mouth/ discussion with colleagues
Personal knowledge of patients
Other
If other, please provide further detail:

If the collaborators at your centre were not present at the hospital for one or more of the days during the data collection period, do you think they were able to identify all the patients to be included in the study on those days?

Yes
No
Unsure

How would they identify patients to be included in the study on days when they were not present at the hospital?

Admission records
Operating room logbook
Elective operation lists
Ward patient lists
Word of mouth/ discussion with colleagues
Personal knowledge of patients
Other
If other, please provide further detail:

Do you have any concerns regarding the accuracy of the data collected on the patients included in the study?

Yes
No
Unsure

If yes or unsure, what data points might be inaccurate and what were the challenges for collecting this data?

Free text box

Did you have problems collecting any of the data points?

If so, did you manage to overcome these problems and how?

Any other comments:

7. King's College London Research Ethics Office Guidelines (June 2016, Version 1).

Is my project Research, Service Evaluation or Audit?

	RESEARCH (Primary data)	RESEARCH (Secondary data)	SERVICE EVALUATION	AUDIT
What will the project determine?	Practice that could or should be done, generally determined by project specific objectives or testing of a hypothesis.	Practice that could or should be done, generally determined by project specific objectives or testing of a hypothesis.	How effective the current practice is.	If the practice is of the standard expected.
What is the purpose?	To derive generalizable new knowledge.	To derive generalizable new knowledge.	The generation of non-generalisable knowledge, concerning a specific service, <i>without</i> reference to a standard.	The generation of non-generalisable knowledge, concerning a specific service/setting, <i>with</i> reference to a standard.
What data will be used?	Primary data collection solely for purposes of research i.e. not routinely collected data.	Secondary data collection from a previously conducted project. No primary data collection.	Usually involves the analysis of information which has been routinely collected as part of the service (teaching activity, clinical service etc) or information on a specific aspect of a service, but may include the administration of interview or questionnaire.	Usually involves the analysis of information which has been routinely collected as part of the practice, but can include the administration of interview or questionnaire.
What methodology will be used?	May involve a broad range of methods including interventions, randomisation, and treatments, samples or investigations outside of routine practice. Will often test a hypothesis.	Retrospective analysis only. No collection of new data.	Descriptive methodologies only. Will not involve intervention or randomisation. Evaluates an already current* service**.	Descriptive methodologies only. Will not involve intervention or randomisation. Audits an already current practice.
Is Ethical Approval Required?	Yes.	Yes if the data is identifiable. No if the data is anonymous.	No (but follow basic ethical principles).	No (but follow basic ethical principles).

Please note: It is the responsibility of the researcher to ensure all other required local approvals (i.e. HRA approval) are in place prior to conducting any project.

*The service must either be already available or already be planned at the time that the evaluation is conducted.

**If you wish to evaluate a service which has been generated as part of a research project, you should seek approval to evaluate this service as part of the ethical approval for the research element of your project.

8. Letter from the Study Steering Committee confirming audit status

Faculty of Life Sciences
& Medicine

School of Population Health
And Environmental Science

King's Centre for Global Health
& Health Partnerships

Professor Charles Wolfe
MD FFPH FRCOG FRCP
Head of Division

Mr Andy Leather
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25th May 2018

To whom it may concern,

Re: 'Management and Outcomes of Congenital Anomalies in Low-, Middle- and High-Income Countries: A Multi-Centre, International, Prospective Cohort Study'

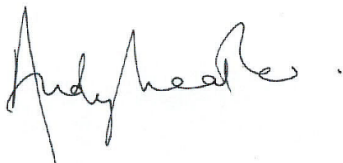
We have reviewed the above study protocol and can confirm that it is an audit based on the following King's College London Research Ethics criteria:

- All data collected measures current practice. The study does not involve any changes to normal patient management.
- Current practice and outcomes in low, middle and high-income countries will be compared to published standards in the literature.
- The study data is routinely collected information which should be known to the study team without asking any additional questions to the patient/ parents.
- All data to be entered into REDCap is entirely anonymous, with no patient identifiable information.
- No individual collaborator, institution or country will be independently identifiable in the study results.
- All data will be stored securely and will be governed by a regularly updated and regulated data protection plan by King's College London data protection team.

We have received confirmation from the ethical committee that because the study is an audit it does not require ethical clearance at King's College London.

Local institutional approval will be required to participate in the study from each collaborating institution. Local institutional regulations should be followed regarding what approval is required to participate.

Yours sincerely,



Andy Leather MBBS MS FRCS, on Behalf of the Global PaedSurg Steering Committee
Senior Lecturer in Global Health and Surgery,
Director, King's Centre for Global Health and Health Partnerships,
School of Population Health and Environmental Science
Faculty of Life Sciences & Medicine, King's College London.

9. Letter from King's College London Research Ethics Committee



Research Ethics Office
King's College London
Rm 5.11 FWB (Waterloo Bridge Wing)
London
SE1 9NH

Dr Naomi Wright
King's Centre for Global Health and Health Partnerships
Weston Education Centre,
Cutcombe Road,
London
SE5 9RJ

23 May 2018

Dear Naomi

Study Title: *'Management and outcomes of congenital anomalies in low-, middle-, and high-income countries: protocol for a multi-centre, international, prospective cohort study.'*

I can confirm that as the team have decided the above study is an audit rather than a piece of research, ethical clearance from Kings College London is not required.

Please note it is the responsibility of the Principal Investigator to ensure all other approvals, including NHS ethical review if applicable, are in place prior to commencing this work.

Please do not hesitate to contact the Research Ethics Team at rec@kcl.ac.uk should you have any queries.

Kind regards,

A handwritten signature in black ink, appearing to read 'Laura Stackpoole'.

Ms Laura Stackpoole

Senior Research Ethics Officer

10. Letter from King's College Hospital NHS Foundation Trust

29 – May - 2018

King's College Hospital 
NHS Foundation Trust

Naomi Wright
Paediatric Surgery Registrar
King's College Hospital

King's College Hospital NHS Foundation Trust
King's College Hospital
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London SE5 9RS

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Dear Naomi,

SUBJECT: Management and outcomes of congenital anomalies in low-, middle-, and high-income countries - Audit

Further to your enquiry about the above referenced project.

As this is an audit it does not come under the remit of the Research & Innovation office and does not require NHS ethics or HRA approval.

The guidance on http://kweb/kwiki/Clinical_Audit_Research_or_Service_Review confirms the process for gaining Trust approval is as follows:

- Clinical audits must comply with the Trust Clinical Audit Standards - see Appendix 1 of the **Clinical Audit Policy** in the link above.
- Clinical audits must be registered with the appropriate Care Group Patient Outcomes Lead – you can find the relevant one for your area under the **Patient Outcomes Lead** in the link above.

Best wishes



Kirsty Hedditch

Research Facilitator
Research & Innovation Office
1st Floor, 161 Denmark Hill
King's College Hospital NHS Foundation Trust
London SE5 8EF

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