The qualitative and quantitative outcomes of children with Hirschsprung's Disease and Anorectal Malformations

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Abstract

Introduction: Hirschsprung's disease (HSCR) is a rare disease and has a range of different aetiologies. HSCR can be classified according to the length of aganglionosis of the bowel, with the most common type being recto-sigmoid HSCR. Patients require histological analysis to confirm the absence of ganglion cells and will eventually require surgery to remove the aganglionic portion of bowel. This is a pull-through procedure in most cases. Anorectal malformations (ARM) are also rare diseases which can also be classified according to anatomy and the position of the fistula. The majority of these patients require anal reconstruction to correct the malformation and restore normal anatomy. Both of these conditions can lead to poor patient outcomes, such as faecal incontinence or constipation, however outcome reporting for these conditions has been limited and variable. The HSCR core outcome set (COS) consists of 10 core outcome measures and was produced to improve outcome reporting. The aim of this study is to investigate outcomes in infants with either HSCR or ARM, according to the HSCR COS.

Methods: A systematic review was completed to identify all studies reporting outcomes of patients with HSCR. Three electronic databases were searched (PubMed, MEDLINE and Scopus) and any study reporting outcomes of patients with histologically diagnosed HSCR was included. A retrospective cohort study was also carried out with the aim to assess the outcomes of children with either HSCR or ARM. Children were identified from hospital databases and clinic visits and those who were eligible were included. Clinician reported outcomes, such as unplanned reoperation and permanent stoma formation, were collected and consent forms were distributed to all eligible children, with patient reported outcomes, such as bowel function and quality of life scores, collected from children who returned the questionnaires after consenting.

Results: The systematic review identified 751 unique studies, with 188 of these being eligible for inclusion in the study. Of the 188 studies, only 4 reported the full HSCR COS, with only one of these studies using the correct outcome measures to report these outcomes. Of the 107 studies published after the publication of the HSCR COS, 3 failed to report any core

outcomes, with the remaining 104 studies reporting at least 1 core outcome. The increase in reporting a few core outcomes, such as death with cause specified an objective score of quality of life had a statistically significant increase after the publication of the HSCR COS. The cohort study included 106 HSCR and 140 ARM patients, from which clinician reported outcomes could be collected from. Of these patients, 14 HSCR and 16 ARM patients returned questionnaires and therefore provided patient reported outcomes. 20.8% of HSCR patients required at least one unplanned reoperation and 15.1% required permanent stoma formation. 24.3% of ARM patients required at least one unplanned reoperation and 10% underwent permanent stoma formation. Outcomes also varied between the classifications of each condition. 8 patients met the criteria for constipation and 13 for impaired continence according to bowel function scores in both the HSCR and ARM patient cohort.

Conclusion: Children with HSCR or ARM have variable outcomes, which can also depend on the form of the condition they have. Outcomes for these conditions have been assessed by a number of studies, however variability in outcome reporting has made comparisons difficult. Following the HSCR COS would improve the quality of outcome reporting and could lead to the identification of factors affecting outcomes in these children. Future studies could assess the longer-term outcomes of children with HSCR and ARM and include more patient reported outcomes to get a more accurate measure of bowel function and quality of life in these patients.

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ACE	Antegrade continence enema
ARM	Anorectal malformation
ASD	Atrial septal defect
CCK	Cholecystokinin
CLM	Conjoined longitudinal muscle
COS	Core outcome set
EAS	External anal sphincter
ECHO	Echocardiogram
ECM	Extracellular matrix
EDNRB	Endothelin receptor type B gene
EPR	Electronic patient records
FGF10	Fibroblast growth factor 10
GDNF	Glial cell line-derived neurotrophic factor
GIQLI	Gastrointestinal quality of life index
HAEC	Hirschsprung-associated enterocolitis
HSCR	Hirschsprung's disease
H&E	Haematoxylin and Eosin
IAS	Internal anal sphincter
IASA	Internal anal sphincter achalasia
ICC	Interstitial cells of Cajal
IND	Intestinal neuronal dysplasia
LS	Long-segment
MCUG	Micturating cystourethrography
MeSH	Medical sub-headings
MEN	Multiple endocrine neoplasia
MMIHS	Megacystis-microcolon intestinal hypoperistalsis syndrome
NCCs	Neural crest cells
OR	Odds ratio
PedsQL	Pediatric quality of life
PHOX2B	Paired-like homeobox 2b

PICS	Paediatric incontinence and constipation score
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSARP	Posterior sagittal anorectoplasty
RA	Retinoic acid
RAIR	Recto-anal inhibitory reflex
RET	Receptor tyrosine kinase RET proto-oncogene
RSI	Recto-sigmoid index
SHH	Sonic Hedgehog
SS	Short-segment
TAP	Transanal proctoplasty
TCA	Total colonic aganglionosis
TIA	Total intestinal aganglionosis
VSD	Ventricular septal defect
VUR	Vesicoureteric reflux
WS	Waardenburg syndrome
ZFHX1B	Zinc finger homeobox 1b

1. Introduction

1.1. Aims and Objectives

1.1.1. Research question

What are the long-term qualitative and quantitative outcomes in children with Hirschsprung's Disease and Anorectal Malformations using the core outcome set?

1.1.2. Objectives

The main objectives of this thesis are:

1. To explain the current available knowledge on Hirschsprung's Disease (HSCR) and Anorectal Malformations (ARM's)
2. To summarize the development process of the HSCR core outcome set and describe which outcomes make up this outcome set
3. To systematically review the current literature reporting outcomes of patients with HSCR to establish whether the publication of the HSCR core outcome set has changed the outcomes being reported
4. To describe the outcomes of patients with HSCR and ARM's using clinician reported outcomes and patient reported outcomes from a single institution

1.2.The Intestinal Tract

1.2.1. Embryology of the intestinal tract

The embryo begins development of the gastrointestinal tract by the end of the first month after conception with the endoderm forming the primitive gut through cephalocaudal and lateral folding. The cephalic and caudal sections of the primitive gut form the foregut and hindgut, respectively, with the middle part making up the midgut.(1) During the fifth week, the foregut divides into the pharynx, oesophagus, stoma and proximal duodenum. Diverticula grow from the caudal duodenum forming the liver, pancreas, gallbladder and cystic duct. The proximal two thirds of the transverse colon, ascending colon, caecum, ileum, jejunum and distal duodenum are all formed from the midgut and the hindgut gives

rise to the proximal two thirds of the anorectal canal, the sigmoid and descending colon and the distal third of the transverse colon.(2)

The concentration gradient of retinoic acid (RA), which is highest in the colon, determines which transcription factors are expressed in different areas of the primitive gut. Specification of the gut therefore happens due to SOX2 in the oesophagus and stoma, PDX1 in the duodenum, CDXC in the small intestine and CDXA in the large intestine. Sonic Hedgehog (SHH) expression in the endoderm begins epithelial-mesenchymal interaction.(1) Induction of mesodermal differentiation of interstitial cells of Cajal (ICC) and intestinal smooth muscle cells due to SHH expression results in dependency of organogenesis and regional differentiation within the gut tube on the restriction of SHH expression.(3)

A short mesentery suspends the midgut from the dorsal abdominal wall. Rapid elongation of the gut and mesentery results in the production of the primary intestinal loop comprising of the cephalic and caudal limbs developing into the small intestine and proximal large intestine, respectively. Intestinal loops enter the umbilical cord in week six of embryonic development due to rapid growth. Rotation of the gut occurs during this time (90 degrees) and again when the intestinal loops return into the abdomen (180 degrees). The first part to return to the abdominal cavity is the jejunum which lies on the left, with the caecal bud, appearing in week six and eventually forming the appendix, being the last part to return. The caecal bud initially lies underneath the liver however, it then descends into the right iliac fossa pushing the ascending colon towards the right of the abdomen.(1)

During the development of the hindgut, the cloaca is divided into the anterior urogenital system and the posterior anorectal system by the urorectal septum during week six.(4) The cloaca is a cavity lined by endoderm and ventrally covered by ectoderm with the cloacal membrane being the boundary between the two. By week seven, a ventral opening for the urogenital sinus and anal opening of the hindgut form due to rupture of the cloacal membrane. The perineal body is created by the tip of the urorectal septum.(1) Failure of these processes could lead to the development of an anorectal malformation.

1.2.2. Innervation of the intestinal tract

The intestinal tract is innervated by a number of different nerves including extrinsic neurons in parasympathetic and sympathetic ganglia, sensory ganglia and intrinsic neurons in the enteric nervous system.(2) The parasympathetic nervous system innervates the intestinal

tract via two different pathways. The vagus nerve innervates up to the proximal third of the transverse colon whereas the distal two-thirds of the transverse colon to the rectum is innervated by pelvic splanchnic nerves originating as preganglionic fibres from sacral roots S2 to S4.(1) Sympathetic chain ganglia produce postganglionic sympathetic fibres which innervate the intestinal tract wall. By week four of embryonic development, neural crest cells (NCCs), which produce glia and vagal neurons, have commenced colonisation at the cranial end and by week seven, will have spread throughout the length of the gut.(2) There are a number of transcription factors involved in neural crest cell specification including SOX10, Foxd3 and Pax3, with a loss in these factors causing defects in the enteric nervous system.(5, 6) In the vagal neural crest, receptor tyrosine kinase RET proto-oncogene (RET) is a target of Pax3 promoting proliferation and migration survival in a variety of cells including neuronal germ cells. Loss of function mutations in the RET gene can led to HSCR, with the distal gut being void of enteric innervation.(7)

1.2.3. Structure and function of the intestinal tract

1.2.3.1. Small intestine

The small intestine is formed by three regions: the duodenum, the jejunum and the ileum. The duodenum is retroperitoneal and is divided into four sections according to their locations: superior, descending, inferior and ascending sections. The jejunum is characterised by prominent plicae circulares and a long vasa recta contrasting to the ileum which is characterised by less prominent plicae circulares and a shorter vasa recta.(8) The blood supply of the small intestine comes from branches of the aorta including the celiac artery, which supply the duodenum, and superior mesenteric artery, which supplies the remainder of the small intestine.(9)

The walls of the small intestine are composed of mucosa, submucosa, muscularis and serosa layers, with the mucosa layer containing the epithelium, lamina propria and muscularis mucosae layers. Within the small intestine there are deep crevices, lined with glandular epithelium which form the intestinal glands. These intestinal glands contain cells which produce intestinal juice containing enzymes and hormones, for example lysozymes, secretin and cholecystokinin (CCK), to aid with the absorption of nutrients and form part of the

intestinal defence system. These cells include enterocytes, goblet cells, Paneth cells and enteroendocrine cells such as S cells, CCK cells and K cells. The duodenum also contains duodenal glands which assist with the neutralisation of the gastric acid with the secretion of alkaline mucus. There are also a number of 'finger-like projections' within the small intestine called villi which increase the surface area of the epithelium to also aid absorption.(10)

The submucosal plexus in the enteric nervous system controls the production of intestinal fluid. When food enters the small intestine, there is mechanical stimulation of enterochromaffin cells resulting in the activation of secretomotor neurons due to the stimulation of sensory neurons by 5-hydroxytryptamine from these enterochromaffin cells. These secretomotor neurons release neurotransmitters, such as acetylcholine, which act on enterocytes secreting chloride ions and sodium ions into the lumen of the small intestine. This creates an osmotic gradient leading to the movement of water into the small intestine.(11)

Once the small intestine receives the chyme, it is responsible for a number of functions including mixing the digestive secretions with the chyme, ensuring the chyme and epithelial cells come into contact and to regulate the speed in which the chyme moves through the small intestine. This is done by segmentation and peristalsis. Segmentation is when the circular muscle in the small intestine contracts in short intervals with areas in between these contracted sections relaxed. The contracted areas then relax and the relaxed areas contract helping to mix the intestinal secretions with the chyme. Peristalsis occurs when there is contraction of the circular muscle behind the chyme and relaxation in front of the chyme helping to move it through to the large intestine. This is controlled by the enteric nervous system due to stimulation of mechanoreceptors.(11)

1.2.3.2. Large intestine

The large intestine consists of the caecum, ascending colon, transverse colon, descending colon and sigmoid colon. The junction between the ascending colon and transverse colon lies near the inferior border of the right lobe of the liver and the junction between the transverse colon and descending colon lies just inferior to the spleen. The sigmoid colon is an S-shaped structure which lies at the level of the S3 vertebra and connects the descending colon to the rectum. The blood supply of the large intestine comes from branches of the

abdominal aorta. The superior mesenteric artery supplies the ascending colon and the proximal two-thirds of the transverse colon whereas the distal third of the transverse colon, descending colon and sigmoid colon all receive their arterial blood supply from the inferior mesenteric artery.(8)

The large intestine contains the same four layers as the small intestine: the mucosa, submucosa, muscularis and serosa layers. The mucosa contains muscularis mucosae, lamina propria and simple columnar epithelium, which contains absorptive and goblet cells found in intestinal glands, similar to the small intestine. Goblet cells produce mucus to aid with the movements of the contents of the colon and absorptive cells absorb water in the colon. The muscularis layer contains an inner layer of circular smooth muscle and outer layer of longitudinal smooth muscle, with thickened portions forming three bands called teniae coli. Haustra, pouches of colon, are formed by the contraction of these bands.(10)

The functions of the large intestine include peristalsis to move the contents into the rectum, the breakdown of amino acids into vitamin K and B vitamins by bacteria, the absorption of vitamins and ions and the absorption of water. The movement of contents through the colon and into the colon is achieved by haustral churning and mass peristalsis. Haustral churning is when haustra fill up and then squeeze the contents into the next haustra. Mass peristalsis is a large peristaltic wave around half way along the transverse colon moving the contents into the rectum faster. Mass peristalsis usually occurs after the consumption of a meal due to the gastrocolic reflex.(10) This occurs when food enters the stomach and signals are sent via muscarinic pathways to the colon through neuropeptides and the enteric nervous system producing colonic contractions.(12) The absorption of remaining water, vitamins and ions produces faeces consisting of indigestible food, bacteria, mucosal epithelial cells, inorganic salts and some remaining water.(10)

1.2.3.3. Rectum and anal canal

The rectum is a retroperitoneal structure which lies at the vertebral level S3. The blood supply to the rectum is from the inferior mesenteric artery, internal iliac artery and internal pudendal artery which gives off the superior, middle and inferior rectal arteries, respectively.(8) The anatomy of the anal canal is shown in Figure 1.2. The anal canal consists of the internal anal sphincter (IAS), external anal sphincter (EAS) and the puborectalis muscle with the conjoined longitundinal muscle (CLM) lying in between the two sphincters.

The IAS and CLM are innervated by the autonomic nervous system whereas the EAS and puborectalis muscle are innervated by somatic nerves.(13) The dentate line, which helps to maintain faecal continence, is found in the distal anal canal and divides the superior and inferior parts of the anal canal.(14)

Segmental activity in the upper part of the rectum, along with contraction of the levator ani muscles in the pelvic floor, prevent the movement of faeces into the lower portion of the rectum. Following a large movement of colonic contents, there is distension of the rectum, initiating the defecation reflex.(11) Stretch receptors send sensory signals to the sacral spinal cord (S2-4) and motor signals are sent to the rectum and anus via parasympathetic nerves. This causes contraction of the longitudinal muscles and relaxation of the internal anal sphincter. If there is voluntary relaxation of the external anal sphincter, faeces are released from the anus and defecation occurs. Defecation is able to be postponed due to voluntary contraction of the external anal sphincter.(10)

1.3. Hirschsprung's Disease

1.3.1. Epidemiology

The incidence of Hirschsprung's disease (HSCR) within the UK and Ireland has been estimated to be around 1.8 per 10,000 live births, with around 305 children being born with HSCR every two years.(15) This is similar to the worldwide incidence of HSCR which is estimated to be approximately 1 in 5000 live births.(16, 17) Male children are approximately 3.3 times more likely to have HSCR than female children and around 9% of infants with HSCR having a positive family history.(15, 18) Around 80% of infants with HSCR have short segment HSCR, with only the sigmoid colon and rectum affected, and around 20% of infants have long segment HSCR, where more proximal colon is also affected (19).

1.3.2. Aetiology

1.3.2.1. Neural crest cell migration

HSCR is thought to be a heterogenous disease with a number of aetiologies and genetic causes. By week 12 of gestation, the neural crest cells (NCCs) have normally travelled down the vagus nerves and spread throughout the colon into the enteric nervous system. The rate of infiltration into the distal colon is slower than throughout the rest of the colon due to its

elongation (20). There also has been some research suggesting there is input from sacral neural crest cells forming glia and neurons in the enteric nervous system (21, 22). It is thought that, due to the distance travelled by these NCCs during embryogenesis, factors can interfere with their migration or proliferation resulting in the absence of ganglion cells in the distal gut (20).

Two theories have been suggested as to why this process does not occur in infants with HSCR. One theory is that, once the NCCs reach their required location, they either are unable to differentiate in ganglion cells or are unable to survive due to abnormalities in the microenvironment (23, 24). Proteins within the extracellular matrix (ECM) have been suggested to be important factors in the microenvironment of the NCCs including fibronectin, laminin, collagen type IV and hyaluronic acid. These proteins help with ganglia differentiation within the enteric nervous system and changes to these ECM proteins may result in failure of differentiation (25, 26). The other theory is that the NCCs don't reach the distal end of the intestine due to premature differentiation into ganglion cells which has been shown in studies looking at NCC migration in animal models (23, 27).

1.3.2.2. Genetics

There are a number of characteristics of HSCR indicating a genetic component to the disease. These include an increased prevalence of HSCR in males and in infants with affected siblings, and an association to a number of other diseases, including some chromosomal abnormalities. A non-Mendelian pattern of inheritance is suggested in HSCR due to the presence of incomplete penetrance, differences in aganglionosis lengths between affected siblings and the large percentage of sporadic cases (28).

1.3.2.2.1. RET gene

The RET gene encodes a tyrosine kinase receptor which an important factor in the migration, proliferation, survival and differentiation of NCCs during development alongside acting as a receptor for glial cell line-derived neurotrophic factor (GDNF) to aid enteric nervous system development (29). This gene is the major susceptibility gene for HSCR, however, it has also been found in other diseases such as multiple endocrine neoplasia type

2A (MEN 2A), type 2B (MEN 2B), and medullary thyroid carcinoma (30). Although a RET mutation has high importance in HSCR, it is only responsible for 50% of familial and 15-20% of sporadic HSCR cases suggesting the importance of other gene involvement when assessing its aetiology (30).

1.3.2.2.2. Other gene involvement

A number of other genes have also been identified as HSCR-associated genes. Some patients with HSCR have been found to carry heterozygous mutations in the endothelin receptor type B gene (EDNRB) accounting for around 5% of HD cases (28). It has been indicated that EDNRB is used to help regulate the response of neural cell stem cells to migratory factors such as GDNF (31). This involvement was shown in mice when disruption of the EDNRB gene resulted in aganglionic megacolon with an association to colour spotting of their coats (32). Others genes such as SOX10, the pair mesoderm homeobox 2b gene (PHOX2B) and the HOX gene encode transcription factors, which affect the expression of RET, are thought to have an involvement (33). SOX10 was suggested to be involved in the development of HSCR after a study on mice with HSCR with mutations in the SOX10 gene. These mice indicated the involvement of enteric neurons alongside neural crest-derived melanocytes due to the presence of distal colonic aganglionosis and hypomelanosis of the hair and skin in those with heterozygous mutations (34, 35).

1.3.2.3. Syndromic Hirschsprung's Disease

Chromosomal abnormalities are found in approximately 12% of HSCR cases with trisomy 21 being the most common. Children with trisomy 21 have a 40-fold greater risk of having HSCR than the remainder of the population suggesting the importance of chromosome 21 when assessing the aetiology of HSCR with studies showing associations between the RET gene and chromosome 21 (36). It is thought that either the extra chromosome 21 interferes with the development of the ENS or that the aganglionosis forms part of a wider dysfunction within the ENS in patients with trisomy 21 (37).

In around 18% of cases of HSCR, infants also have an associated congenital anomaly including a cleft palate, a gastrointestinal malformation, polydactyly or cardiac anomalies such as septal defects (16, 38). Mendelian inheritance is suggested in these anomalies with

a 39% rate in familial cases in comparison to a 21% rate in isolated cases (38). SOX10 mutations, found in HSCR cases, have been described in severe cases of Waardenburg syndrome (WS) with central dysmyelinating leukodystrophy and peripheral demyelinating neuropathy (39). WS is due to melanocyte absence in the skin and stria vascularis in the cochlea causing pigmentation disturbances and sensorineural deafness (40). Hypopigmentation and total colonic aganglionosis have also been demonstrated in mice in the absence of SOX10 (41). Mice have been found to show a total absence of vagal neural crest precursors when lacking ZFHX1B and mice lacking PHOX2B show aganglionosis (42, 43). Patients with HSCR along with congenital central hypoventilation syndrome (CCHS) and Mowat-Wilson syndrome have had mutations in transcription factors PHOX2B and zinc finger homeobox 1b (ZFHX1B) identified, respectively (29). PHOX2B has also been found to have an association with neuroblastomas, however these are rare in isolated, sporadic neuroblastomas (40).

1.3.3. Classification

There are different types of HSCR and these are classified according to the length of aganglionosis in the bowel, shown in Figure 1.1. The most common type of HSCR is short segment HSCR which only affects the recto-sigmoid colon and accounts for around 80% of all cases (20). Long segment HSCR is when there is aganglionosis between the sigmoid colon and caecum, however there are still ganglion cells present in the colon making it different to total colonic HSCR where there is aganglionosis of the entire colon and up to 5cm of the terminal ileum (44). Long segment HSCR and total colonic aganglionosis account for around 15% and 5% of cases, respectively (45). A rare and more extreme form of HSCR is total intestinal aganglionosis, when there is the absence of ganglion cells throughout both the small and large intestines (46). The final form of HSCR is ultra-short segment HSCR, which is when only a short area of anal canal above the dentate line has the absence of ganglion cells (47).

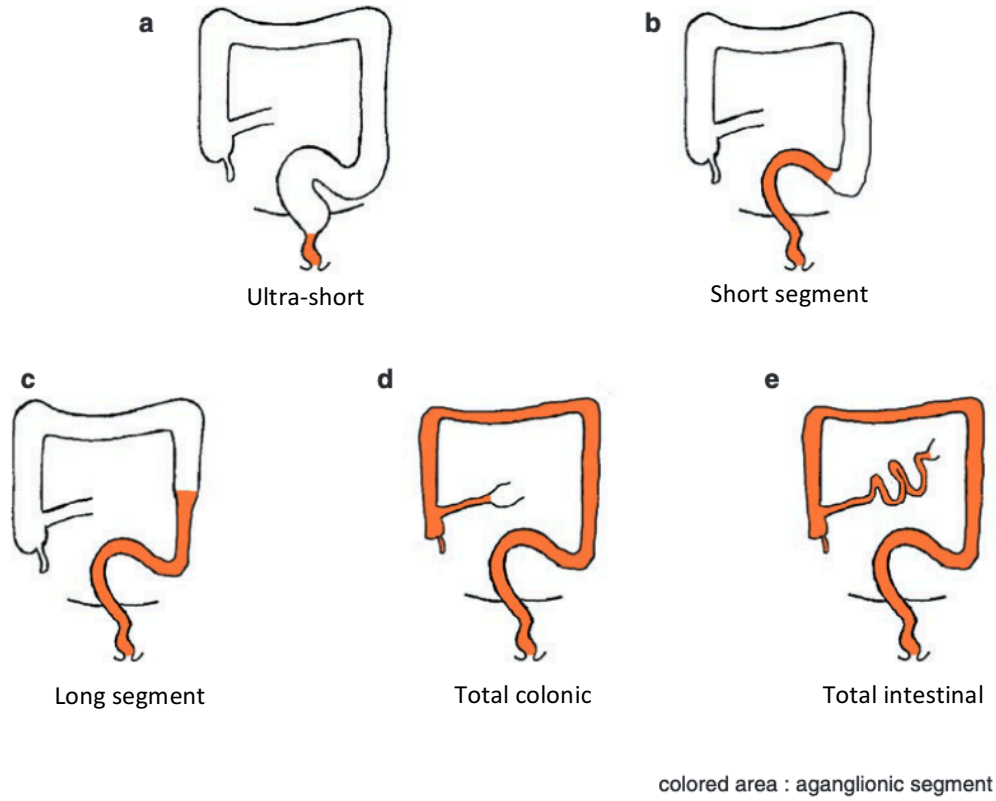

Figure 1.1. The classification of different types of HSCR according to aganglionosis length. Hirschsprung's disease and its allied disorders (28).

1.3.4. Clinical features

The failure to pass meconium within the first few days of life, especially more than 48 hours after birth, is a common presentation of HSCR, with the passage of a meconium plug and sparse bowel movements following this (48). Other symptoms of an intestinal obstruction such as abdominal distension, bilious vomiting and feeding issues also indicate HSCR suggesting the infant should be further investigated (49). Some patients may present with symptoms of Hirschsprung-associated enterocolitis (HAEC) which classically includes abdominal distension, fever and foul-smelling diarrhoea (50, 51). HAEC is a serious complication of undiagnosed HSCR, causing a large portion of morbidity and mortality in this patient cohort (52). Around 80-90% of infants with HSCR present during the neonatal period, with the remaining presenting later in childhood, usually with symptoms such as long-standing refractory constipation followed by failure to thrive and enterocolitis (49). It is therefore important to differentiate between chronic constipation and HSCR in order to

prevent HAEC and its life-threatening complications such as toxic megacolon, presenting with sudden abdominal distension, fever, signs of dehydration and shock (53).
Clinical examination is used to help eliminate any differential diagnoses of HSCR, including an anorectal malformation (ARM) and also to look for any associated abnormalities. Some of these associated abnormalities include trisomy 21, ARMs, structural cardiac defects, inguinal hernias and neural crest-related anomalies such as Waardenburg syndrome (20, 54). Clinical examination should include an inspection of the perianal area, abdominal examination, spinal/gluteal examination and lower limb neuromuscular examination (55). Abdominal examination findings will include abdominal distension in many cases and digital rectal examination can often cause the passage of meconium and therefore alleviate the initial intestinal obstruction (53).

1.3.5. Investigations

After the completion of a history and examination on the patient, a diagnosis of HSCR is confirmed through a combination of imaging and histological analysis of bowel tissue. According to the NICE guidance for Constipation in Children, investigations should include a plain abdominal radiograph, a contrast enema and a rectal biopsy (55). NICE guidance also states that a rectal biopsy should only be performed if there is any of the following:

- A delay in the passage of meconium, >48 hours in a term baby
- Long-term abdominal distension and vomiting
- Constipation starting early after birth
- Family history of HSCR
- Failure to thrive alongside another previously mentioned feature (55)

1.3.5.1. Radiology

The first line investigation to diagnose HSCR is usually a plain abdominal radiograph. In HSCR this may show distended loops of bowel due to gas build-up, with widening of the proximal side. Another characteristic of HSCR which may be found on an abdominal radiograph is the absence of gas in the pelvis due to spasm of the distal aganglionic bowel (28).
Another first line investigation is a water-soluble contrast enema on which the pathognomonic finding of HSCR is a visible transition zone between ganglionic and

aganglionic bowel (23). A study has described the accuracy of these calibre changes and the level of aganglionosis found on rectal biopsy, being correct in 94.4% of cases of recto-sigmoid disease but only correct in 50% of cases with a more proximal transition zone (56). They also allow accurate evaluation of the recto-sigmoid index (RSI), a ratio between the largest part of the rectum and sigmoid colon, with a value of >1.0 excluding a diagnosis of HSCR in some cases (57). Contrast enemas can be used to differentiate other causes of intestinal obstruction, such as meconium ileus or colonic atresia, from HSCR and therefore aid with the decision of which patients should be selected to undergo more invasive investigations, like a rectal suction biopsy (53, 58).

1.3.5.2. Anorectal manometry

Anorectal manometry is described in HSCR to assess the recto-anal inhibitory reflex (RAIR). This is when there is distension of the rectum resulting in the relaxation of the internal anal sphincter, controlled by ganglion cells within the myenteric plexus (28). The absence of RAIR has been proven to have a high-specificity in the diagnosis with HSCR with a diagnostic positive rate of up to 90% (59). A positive RAIR excludes HSCR and a negative RAIR indicates the possibility of HSCR, with these patients then going on to have a rectal suction biopsy to assess the histology of the rectum (60).

1.3.5.3. Histology

The gold standard investigation for the diagnosis of HSCR is a rectal suction biopsy. At least two samples of the rectum should be taken from between 2cm to 4cm proximal to the dentate line (20). Rectal suction biopsies are stained with Haematoxylin and Eosin (H&E), Acetylcholinesterase and Calretinin stains are used to look for the presence of ganglion cells and thickened nerve trunks in the rectum (61). Biopsies indicating HSCR demonstrate total absence of ganglion cells in both the submucosal and myenteric plexus, acetylcholinesterase-positive hypertrophied nerve trunks and the absence of calretinin-positive nerve fibres in the submucosa and lamina propria (62). Due to the invasive nature of the biopsy, patients can have a number of complications including rectal bleeding, bowel perforation or sepsis with a study suggesting a complication rate of 0.65% (63).

Intra-operative biopsies during definitive surgery is also an important investigation to determine the extent of the transition zone estimated by previous contrast enemas and therefore ensure sufficient resection of the aganglionic colon (64). The histological characteristics of the transition zone are partial circumferential aganglionosis, hypoganglionosis within the myenteric plexus and nerve hypertrophy within the submucosal plexus (65). The length of transition zone varies between patients showing the importance of intra-operative biopsies to prevent transition zone pull-through and a higher risk of complications (66).

1.3.5.4. Differential diagnoses

There are a number of other causes of intestinal obstruction which should be excluded when a child presents with HSCR signs and symptoms. These patients can present with failure to pass meconium or abdominal distension but have ganglion cells present on rectal biopsy (67). A list of differential diagnoses is described in Table 1.1 alongside how they are excluded when assessing for HSCR.

Differential diagnosis	Differences to HSCR
Anorectal malformation	Normal histology findings with abnormal anatomical structure
Hypoganglionosis	Sparse and small ganglia in the myenteric plexus (67)
Intestinal neuronal dysplasia (IND)	Giant ganglia and hyperplasia of the submucous plexus (67)
Internal anal sphincter achalasia (IASA)	Normal histology findings and the absence of the rectosphincteric reflex (61)
Megacystis-microcolon intestinal hypoperistalsis syndrome (MMIHS)	Dilated bladder and hydronephrosis present (68)
Meconium ileus	Ganglion cells present within the bowel
Colonic atresia	Absence of the distal bowel, with ganglion cells present throughout the remaining bowel (69)
Volvulus	Intestine loops and mesentery twist causing obstruction, ganglion cells present throughout (70)
Idiopathic constipation	Ganglion cells present within the bowel
Hypothyroidism	Ganglion cells present within the bowel and features of hypothyroidism such as lethargy, hypotonia and prolonged jaundice (71)

Table 1.1. The differential diagnoses and how they differ to Hirschsprung's Disease

1.3.6. Management

1.3.6.1. Initial management

Although the definitive treatment of HSCR is surgical, infants presenting with features of HSCR or enterocolitis need to be managed until they are at an optimal age for an operation, usually >3 months old (72). Patients presenting with sepsis or dehydration need to be stabilised with intravenous fluids and antibiotics and a nasogastric tube is needed for patients with intestinal obstruction (73). These patients should also undergo regular decompression of the bowel using rectal irrigation, which parents can do once the infant is discharged home (73). Rectal irrigations however are unsuccessful in providing bowel

decompression in around 25% of patients with HSCR (50). These patients, those with persistent enterocolitis and those who have had an intestine perforation are all indicated to have a stoma formed with a 'doughnut' biopsy taken to establish ganglionic status (50).

1.3.6.2. Surgical management

The aim of definitive surgery in HSCR is to remove the aganglionic bowel and to pull the ganglionic bowel through to the anus for anastomosis above the dentate line in order to try to preserve normal sensation and sphincter function (23). There are two main steps during a pull-through procedure: intraoperative extramucosal biopsies with frozen section analysis, if the surgeon is unsure on the transition zone location, and then the pull-through of bowel to the dentate line (20). Laparoscopy can be used to obtain intraoperative biopsies, which are used to determine the length of aganglionosis so the surgeon is aware of the length of bowel needed to be resected (20). Resection should continue for about 5cm to 10cm proximal to the ganglionic biopsy to ensure the transition zone is also removed with the aganglionic bowel (49). If intraoperative extramucosal biopsies are not taken, a donut of tissue will be histologically analysed from pulled through bowel to ensure the presence of ganglion cells. The three most common operation techniques used for a pull-through operation are the Swenson, Duhamel and Soave procedures (53, 74).

1.3.6.2.1. Swenson Procedure

The aim of the Swenson procedure is to remove the entire aganglionic portion of the bowel using transanal, full-thickness dissection whilst also preserving the anal canal and the sphincter mechanism to decrease the risk of poor outcomes (75). The long-term outcomes of the Swenson procedure have been shown to be good despite the theoretical risks of deep dissection and therefore the integrity of the surrounding structures and also the increased risk of anastomotic leakage (23, 76).

1.3.6.2.2. Duhamel Procedure

The aim of the Duhamel procedure is to try and prevent injuries from surrounding structures of the pelvis by eliminating the need for anterior rectal dissection (74). During this procedure, the original rectum is left in place and the pulled-through ganglionic bowel is

anastomosed with the native rectum (77). This was previously a multiple-stage procedure, however, the introduction of the one-stage procedure seems to have no significant difference in functional outcomes and avoids the risk of stoma-related complications (78).

1.3.6.2.3. Soave Procedure

The Soave procedure involves colonic dissection of the bowel in the submucosal plane above the dentate line with pull-through of the ganglionic bowel through the rectal muscle sleeve (20). As there is no pelvic dissection, this approach aims to preserve the anatomical structures in the pelvis and sensory receptors in the rectal muscular sleeve (79). The avoidance of the retrorectal plane also means there is less risk of damaging the pelvic nerves responsible for sexual function and urinary continence, with the goal to decrease long-term problems for these patients (80).

1.3.7. Outcomes and prognosis

After having a pull-through procedure, the patient can have some early postoperative complications such as bleeding, infection, anastomotic leak or an abscess (28). Studies have shown that wound infection rates are between 1.7% and 19.2% depending on the surgical approach, and anastomotic leaks have been found in an average of 4.3% of cases (81). Patients may also need have recurrent anal dilatations if there is concern of anastomosis tightness or stricture, which can be done at home or at the same time as IAS botulinum toxin administration if there are concerns of obstructive symptoms (74). Long-term follow-up studies have found that constipation, faecal incontinence, enterocolitis and quality of life were the most common problems in patients after a pull-through procedure (82).

1.3.7.1. Constipation

Constipation is an important long-term complication of HSCR after definitive surgery. Constipation in patients with HSCR can be caused by a number of factors including a mechanical obstruction such as a stricture or aganglionic spur, persistent aganglionosis due to transition zone pull-through or pathologist error, or internal sphincter achalasia (73). A study of 135 patients over 22 years who have had definitive surgery for HSCR reported a

constipation rate of 7.5%, however other studies have shown variable post-operative constipation rates ranging between 8% and 32.4% of patients (83-85).

1.3.7.2. Faecal incontinence

Damage to either the anal sphincter or transitional epithelium controlling anal sensation and anal reflexes during surgery can lead to the inability to distinguish between solid and liquid stools and the urge to defaecate resulting in faecal incontinence (86). In a recent study, assessing the outcomes of laparoscopic-assisted pull-through procedures, faecal incontinence rates were reported at 29% (87). Faecal incontinence has also been shown to affect the mental health and psychosocial functioning of HSCR patients therefore decreasing their quality of life (88).

1.3.7.3. Enterocolitis

Enterocolitis can be a complication of pull-through surgery alongside being a presenting symptom of HSCR. Studies have found that the incidence of HAEC ranges from between 17% to 50% and accounts for half of all HSCR deaths making it the leading cause of mortality in HSCR patients, most frequently in the first 2 years of life (89, 90). It has also been shown that patients with congenital malformations, for example Down's Syndrome, alongside HSCR are more likely to develop HAEC (89). Children presenting with HAEC require urgent broad-spectrum antibiotics, including metronidazole, intravenous fluid resuscitation with haemodynamic monitoring, and frequent rectal washouts (91). Some patients may develop recurrent HAEC which can be managed medically, through the use of antibiotics, washouts and sodium cromoglycate, or surgically using intrasphincteric botulinum toxin therapy or, in the worst case scenarios, with a defunctioning stoma (91).

1.3.7.4. Quality of Life

It has been found that patients diagnosed with HSCR and who have undergone subsequent surgery can have a decreased quality of life due to unfavourable outcomes. Complications such as faecal incontinence have been shown to be an independent predictor of a lower quality of life score and a lower social wellbeing score (92). Females have also reported

worse outcomes in sexual function, fertility and sexual quality of life in adults compared to the remainder of the population (93).

1.4. Anorectal Malformations

1.4.1. Epidemiology

Anorectal malformations (ARM) are a rare cause of intestinal obstruction and occur in around 1 in 4,000-5,000 live births, with 63.6% of these patients having another anomaly present (94). Reports have shown an almost equal male-to-female ratio in patients with an ARM, with a 1.3:1 male:female ratio (95). This study also reported a significantly increased risk of ARM with maternal obesity (95). Male and female patients can have different ARM's, with a rectovestibular fistula being the most common in females and a rectobulbar fistula being the most common in males (96).

1.4.2. Aetiology

The incidence of anorectal malformations caused by genetic disease is around 10% and the risk of recurrence of ARM in a sibling of an infant with an ARM has been reported to be 1 in 92-100 (1%) (97, 98). A deficiency in the dorsal cloacal membrane and dorsal cloaca during development has been suggested by studies on animal models and human fetuses to be a defect resulting in an ARM. This is thought to be due to dysfunction of the tail bud and primitive streak early during development of the caudal aspect of the embryo (99). A smaller defect in the dorsal aspect of the cloacal membranes may result in a distal ARM and a larger defect result in larger malformations such as genitourinary sinus abnormalities (99). There are a number of genetic and environmental factors that are thought to play a role in the development of an ARM.

1.4.2.1. Genetics

Although most ARMs are sporadic and the majority of children don't have an identified genetic anomaly, some ARMs are associated with a number of different genetic conditions suggesting an association with gene mutations or chromosome abnormalities as a cause. Different studies of ARM genetics have suggested different modes of inheritance including X-linked, autosomal dominant and autosomal recessive inheritance, however these have

been difficult to analyse due to the variable types of ARM (100). One study investigated whether specific types of ARM had any effect on heritability of ARMs, suggesting a higher association of perineal or vestibular fistulas with a positive family history. These patients have been shown to have a 2-3 times increased risk of a family member also having an ARM (101).

There are a number of genes found in animal studies thought to be of importance in the genetic aetiology of ARM. These genes include Sonic hedgehog (Shh) gene, Skt, HOX genes, and a number of other genes alongside transcription factors involved in gene signalling pathways including Gli2 and Gli3 (100). Mutations in these genes have been found to result in an ARM. Shh is important for the development of the hindgut with studies of mice with mutations in Shh resulting in the failure of the development of an anus, rectum and lower urinary tract (102). Transcription factors involving in the Shh signalling pathways have also been found to play an important role in the aetiology of ARM. Mice with mutations in Gli2 transcription factor were found to have an imperforate anus with either a rectourethral or rectovaginal fistula, similar to malformations seen in humans (102). In mice with Gli3 mutations, a less severe phenotype is seen with these mice having anal stenosis and sometimes an ectopic anus (102).

Mutations in the Skt gene have been found to increase the incidence of ARMs in mice to 100% due to defects in the dorsal cloacal plate (103). Invalidation of genes such as Fibroblast growth factor 10 (FGF10) and Wnt5a have been shown to result in an ARM phenotype suggesting the critical roles of these genes during the development of the anorectum (104, 105). ARM development may also be linked to chromosome 13 and therefore endothelin receptor type B (EDNRB) including syndromes where ARM is associated with Pallister-Hall or HSCR (106).

1.4.2.2. Environmental factors

Exposure to chemicals such as thalidomide during pregnancy have previously been suggested as potential causes of ARM in infants (107). More recently, a study has shown an increased risk of anal atresia when exposed to benzodiazepine in utero with a significant association between anal atresia and exposure to lorazepam (108). Also, exposure to

ethylenethiourea in utero has been linked to ARM in mice (100). All-transretinoic acid exposure is also thought to be involved in the aetiology of ARM, interfering with caudal migration and possibly inhibiting the Shh signalling pathway (107, 109).

A study assessing the risk factors for ARMs using medical records and questionnaires found higher rates of maternal obesity, an increased age gap between parents, higher rate of infections during pregnancy and the presence of a chronic maternal disease in ARM mothers (110). This study however did not find an increased incidence of ARM in mothers with gestational diabetes mellitus, which was previously suggested in a systematic review on associations between gestational diabetes mellitus and birth defects (111).

1.4.3. Associated conditions

As previously stated, around 63.6% of infants with an ARM also have an associated abnormality (94). There are a number of anomalies associated with ARMs with the most common being urogenital or musculoskeletal anomalies. The most common syndromes associated with ARM are Down's syndrome, HSCR and VACTERL (112).

1.4.3.1. VACTERL

VACTERL includes vertebral anomalies (V), anal atresia (A), cardiac anomalies (C), tracheoesophageal fistula with oesophageal atresia (TE), renal anomalies (R), limb anomalies (L). It has been found in one study that there is a VACTERL association in around 17.8% of patients with an ARM, however around 25.8% have limb anomalies and 61.3% have a cardiac anomaly (113). This shows how some patients may only have one or two anomalies found in VACTERL. This study also suggested a higher risk of poor surgical outcomes and bowel function in patients with VACTERL (113).

1.4.3.2. Urogenital anomalies

Urogenital anomalies found in patients with ARM include vesicoureteric reflux (VUR), renal agenesis, hydronephrosis, undescended testis, hypospadias plus many more (114). These are the most common anomalies found in patients with ARM reportedly occurring in

between 26% to 50% of patients (115, 116). The most common anomaly of the urinary tract in patients with an ARM is VUR with a reported incidence of between 19% to 47.2% (114).

1.4.3.3. Cardiac anomalies

The most common cardiac defects found in patients with ARM are ventricular septal defect (VSD), atrial septal defect (ASD), pulmonary stenosis and tetralogy of Fallot (112). One study found the rate of cardiac anomalies in patients with ARM to be 19.6% however a more recent study reported the incidence at 13.16% (117, 118).

1.4.3.4. Spinal anomalies

The two most common spinal anomalies in patients with ARM are a tethered spinal cord or sacral agenesis. These anomalies are thought to affect between 19% to 26% of patients with an ARM, and therefore is the second most common form of anomaly in this cohort (118, 119). One study suggested a prevalence of a tethered cord in patients to be 24%. Patients with a tethered spinal cord can also have urinary and faecal incontinence alongside lower limb nerve disturbances, suggesting that a tethered cord association may affect the postoperative outcomes of these patients (120). An ARM, sacral defects and a presacral mass form Currarino's triad and has a strong inheritance pattern, familial in 50% of cases, so should be considered in patients with ARM (121, 122).

1.4.4. Classification

1.4.4.1. Males

ARMs are categorised according to their anatomy and therefore some male and female defects are described differently. A rectourethral fistula is the most common ARM in males affecting more than 80% of boys (123). The type of rectourethral fistula depends on the location of the fistula on the urethra and therefore includes recto-bulbar, recto-prostatic and recto-bladder neck fistulas (124). An important sign of recto-urethral fistulas is the passage of meconium through the urethra.(23)

A recto-bulbar fistula connects the bulbar urethra to the rectum, with termination of the rectum above the bulbospongiosus muscle. These patients usually have a normal sacrum

and anal dimple with a voluntary muscle complex superficial to the rectum which shows good contraction (96). The urethra and rectum share a common wall above the fistula, with a patient with a lower fistula therefore having a longer common wall (23).

Recto-prostatic fistulas connect to the higher prostatic part of the urethra and therefore can be associated with an abnormally developed sacrum, poor-quality muscles, a flat perineum and a just visible anal dimple.

Recto-bladder neck and recto-vesical fistulas are more rare than other forms of rectourethral fistula, occurring in around 10% of male patients with ARMs (125). This type of ARM is one of the more severe malformations in male patients, with a fistula between the bladder neck and the rectum, and the termination of the rectum near the bladder neck (126). Due to the poor development of the external anal sphincter, the levator muscles and the striated muscle complex in these patients, the prognosis of bowel function is usually poor (23).

1.4.4.2. Females

There are also some ARMs that can only affect females including a rectovestibular fistula, a rectovaginal fistula and a cloaca. An imperforate anus with a rectovestibular fistula is the most common ARM in females, followed by imperforate anus with rectoperineal fistula and then a cloacal malformation (127). A study on associated malformations in patients with rectovestibular fistulas suggested that around 5% have a vaginal septum (127). The fistula will connect to the posterior vestibule and usually the rectum will terminate above the pubococcygeal line. These patients will have urethral, vaginal and vestibular rectal fistula openings found on physical examination (96).

A cloacal malformation is when the urinary tract, vagina and rectum join to form a common channel. This is the most severe form of ARM and around 10% of females with an ARM have a cloaca (128). The common channel length varies from 1cm to 10cm and opens into a single orifice at the location of the normal urethral opening (129). Around 25% of patients with a cloaca develop a distended vagina filled with fluid (hydrocolpos) which can lead to compression of the trigone of the bladder and therefore the lower ureters causing

hydronephrosis in 30% of female patients with a cloacal malformation (130). Hydrocolpos can also lead to infection and therefore pyocolpos that eventually could perforate (131). The length of the common channel determines the prognosis for faecal continence and difficulty of surgical repair, with those with a shorter channel, <3cm, having a much better prognosis (96). Around 40% of patients with a cloacal malformation have a double Mullerian system, having 2 hemivaginas and 2 hemiuteri which could be symmetric or asymmetric (129).

1.4.4.3. Both males and females

There are also some ARMs that can occur in both male and female patients including rectoperineal fistula, imperforate anus without fistula and rectal atresia. Rectoperineal fistulas are the least severe form of ARM and can sometimes be large enough to be mistaken as a normal anus during a newborn examination meaning they present later on in life (132). Only the lowest portion of the rectum and the anus is anteriorly located outside of the sphincter complex and is usually stenotic, whereas the remainder of the rectum is within the normal sphincter complex (23). In some male infants, there may be a prominent midline skin bridge, also known as a 'bucket handle', or a subepithelial midline raphe fistula with the presence of meconium which helps with the diagnosis of a rectoperineal fistula (133).

Around 5% of patients with an ARM do not have a fistula but do have a blind ending rectum that doesn't reach the perineum (134). This is classified as an imperforate anus without fistula. These patients usually have a good muscle complex and a developed sacrum meaning they have good prognosis for bowel function (23). There is a high frequency of Down's syndrome in patients with an imperforate anus without fistula and over 90% of patients with an imperforate anus without a fistula have Down's syndrome (135, 136).
A rare ARM that also can occur in both male and female infants is rectal atresia or rectal stenosis. These account for around 1% of all ARM cases and have a very good prognosis for faecal incontinence due to the fact they usually have a normal anal canal and intact anal sphincters (137). There is either full interruption of the lumen of the rectum causing rectal atresia or partial interruption, where the lumen is narrowed, causing rectal stenosis. The anal opening is found in the normal position (138). In rectal atresia, termination of the rectal

can occur at any point, however, a fibrous cord is normally connected to the distal bowel or sacrum (96).

1.4.5. Clinical features

All ARMs *should* be diagnosed soon after birth during a routine newborn examination. If missed during newborn examination, ARM commonly presents when the infant is around 4 days old with abdominal distension, bowel obstruction and sometimes sepsis (107). Although prenatal screening ultrasounds are used to detect structural abnormalities, the rate of in utero ARM diagnosis is only 16%, normally due to the presence of other VACTERL anomalies, meaning the majority of patients are diagnosed after birth (139). Patients with an ARM present with rapidly progressing abdominal distension, bilious vomiting after 24 hours and failure to pass meconium within the first 48 hours of life (140).

Many ARMs can be distinguished through newborn examination. For a perineal fistula, a tract to the perineum from the rectum is seen with meconium running along the tract to the midline raphe of the scrotum seen occasionally in males. In females with a perineal fistula, there is a very short perineal body separating the fistula from the urethra and vagina. When there is no perineal opening in males, imperforate anus without fistula may only be excluded when meconium is passed via the urethra (141). Meconium in the urine suggests a rectourethral fistula, although the absence of meconium does not exclude the presence of a fistula and more investigations are needed to determine the specific location of the fistula (107). In rectovestibular fistulas, the fistula opening is seen directly posterior to the vagina with assessment of the vagina also needed to exclude a vaginal septum. A cloacal malformation presents with a single perineal opening. In rectal stenosis, there is a normally located anus however there may be a stricture or complete atresia (141).

1.4.6. Investigations

After the diagnosis of an ARM is made, a thorough physical examination is needed to establish the type of ARM present and the presence of any associated abnormalities. Determining the level of the defect is an important factor in ARM diagnosis as this will determine further management and operative treatment during the neonatal period (142).

In most cases, there should be a delay of 18 to 24 hours before a the decision to form a colostomy is made due to the significant intraluminal pressure needed to expel meconium, with meconium on the perineum suggesting a rectoperineal fistula (143). Alongside clinical examination, diagnosis of ARM can be done through radiology, contrast studies of the fistula and bowel and ultrasound of abdomen, pelvis and spine, although some of these investigations are done when the infant is older (107). These investigations also help to establish whether the patient has any other associated anomalies. If a neonate has a stoma formed as a fistula opening cannot be seen, they normally will have a distal colostogram at around 8 weeks of age.

1.4.6.1. VACTERL Screening

Patients must undergo VACTERL screening to look for associated anomalies. Ultrasound scans of the abdomen and pelvis is important to exclude hydrocolpos and renal anomalies such as hydronephrosis. If the infant needs an NG tube, a chest radiograph should be done to confirm it is in the correct location in the stomach and therefore exclude oesophageal atresia and tracheoesophageal fistula. Cardiac evaluation is also important in these patients to using an echocardiogram (ECHO) to rule out cardiac anomalies (144). A spinal ultrasound scan should be done before the infant is 3 months old to establish whether there is a tethered cord and to assess sacral vertebrae and therefore the sacral ratio (141). Sacral ratio is important as sacral dysplasia is associated with incontinence due to sphincter control from S2 to S5 sacral nerve roots (145). Some patients will then require a spinal MRI, once they are older than 3 months old, if abnormalities are found on ultrasound scans. Limb radiographs can also be done if clinically indicated (141).

1.4.6.2. Preoperative investigations

Contrast studies are performed in infants without an external fistulous opening to locate the fistula and assess of associated anomalies. A distal loopogram can also be performed once the infant has had stoma formation to determine if a fistula is present and aid with operation planning (107). In female patients with a single perineal orifice, a cloacagram is needed to determine the length of the common channel and urethra to decide which operative approach is optimal, either total urogenital mobilisation or urogenital separation

(146). The determination of urethral length preoperatively means the recommended operation can be performed avoiding the need to change approach intraoperatively and therefore minimising the need for additional dissection which increases the risk of ischaemia (147).

Micturating cystourethrography (MCUG) can be done to look for the presence of vesicoureteric reflux which is more common in children with ARM and is always performed in infants with cloaca, often in conjunction with a colostogram to better determine the anatomy of the cloacal defect.

1.4.7. Management

1.4.7.1. Newborn management

When a baby is born with an ARM, the initial management includes the placement of an intravenous line for antibiotics and fluids and insertion of a nasogastric tube to prevent vomiting or aspiration (133). In most cases, there should be a delay of 18 to 24 hours before a decision to form a colostomy is made due to the significant intraluminal pressure needed to expel meconium in patients with a rectoperineal fistula (143). Some patients with an ARM may not need immediate surgical intervention including those with a perineal fistula or rectovestibular fistula if passing meconium easily and those with anal stenosis if the stenosis is dilated easily (148).

In the remainder of patients with an ARM, a colostomy is required to divert the faeces and to able the surgeon to perform a distal loopogram to gain a better understanding of the anatomy of the fistula. Different versions of colostomies are done including loop and divided colostomies, however there are a number of post-operative complications associated with these including prolapse or stenosis (149, 150).

1.4.7.1.1. Males

Figure 1.2 visually explains the decision-making algorithm for the initial management of male patients presenting with an ARM. In males with a perineal fistula, a primary perineal anoplasty without a covering colostomy can be performed (151). If there is no visible fistula

on the perineum but the infant has normal spine, buttock and sacrum, a cross-table lateral x-ray is indicated. If there is rectal gas below the level of the coccyx suggesting the rectal pouch is within 1cm, then a primary repair can also be performed without the need for a colostomy (148). The majority of these are then repaired with a posterior sagittal anorectoplasty (PSARP), with a minority needing an abdominal component either by laparotomy or laparoscopy (133).

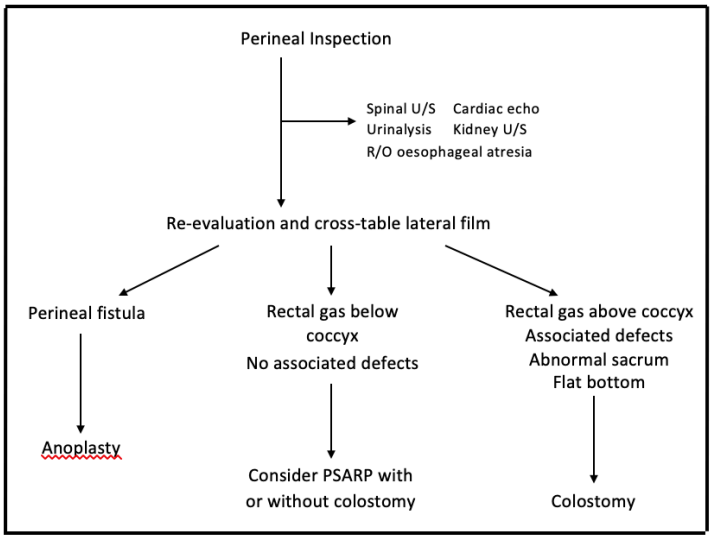

Figure 1.2 Decision-making algorithm for the initial management of male ARM patients (152).

1.4.7.1.2. Females

Figure 1.3 visually explains the decision-making algorithm for the initial management of female patients presenting with an ARM. The management for perineal fistulas and for no visible fistula is the same in females as previously described in males. The decision for either colostomy or primary repair of a rectovestibular fistula should be based on the experience of the surgeon, although primary repair without colostomy has been found to have a higher risk of complications (133). When perineal inspection shows a single perineal orifice and a cloacal malformation is suspected, the presence of hydrocolpos is determined. This hydrocolpos then needs to be drained with a tube vaginostomy and a colostomy is formed in the patient (153). These patients need an urgent urogenital ultrasound to look for persistent hydronephrosis after drainage of hydrocolpos. If there is persistent hydronephrosis, urinary diversion is needed (148).

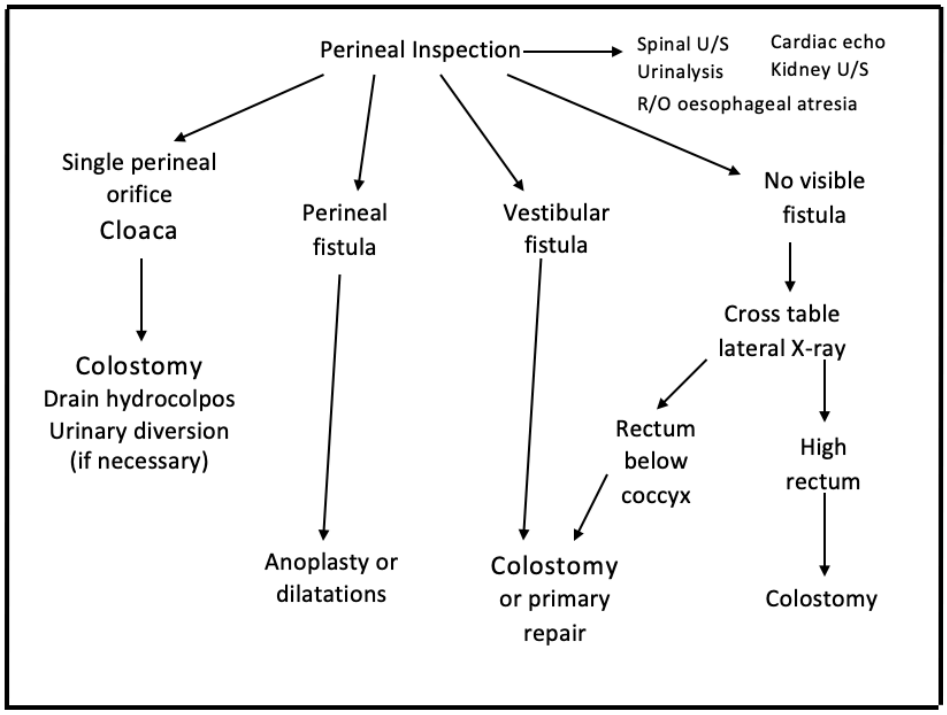

Figure 1.3 Decision-making algorithm for the initial management of female ARM patients (152).

1.4.7.2. Surgical management

1.4.7.2.1. Posterior sagittal anorectoplasty

A posterior sagittal anorectoplasty (PSARP) is a relatively new approach which aims to avoid injury to nerves and other structures within the pelvis (154). It involves a sagittal incision from the sacrum to the perineum and identification of the external sphincter. The muscles are split in the midline and the posterior rectum is identified, dissected and opened just dorsal to the fistula and the fistula is resected (155). In around 10% of males with ARM, the rectum is located higher in the abdomen meaning an additional abdominal approach is needed. Either a laparotomy or laparoscopy can be used to mobilise the rectum (156). The PSARP can also be used for the repair of cloacal malformations with around 30% requiring a laparotomy in addition to the posterior approach due to a longer common channel length and therefore a higher vagina. This is called a posterior-sagittal anorectovaginourethroplasty (157).

1.4.7.2.2. Transanal proctoplasty

This is a relatively new approach used for the management of ARM patients with a low variant of the malformation where there is no fistula to the urethra and the rectum terminates just above the normal anal level. This approach avoids extensive dissection and sphincter muscle division therefore decreasing the risk of complications associated with the PSARP (158). The preservation of the internal anal sphincter, not achieved in previous transperineal approaches, has been shown to improve functional outcomes of patients with an ARM (159, 160).

1.4.7.2.3. Anoplasty (161)

An anoplasty can be used to repair minor ARMs, such as a perineal fistula, in the first few weeks of an infant's life, without the need for a colostomy. The aim of the procedure is to move the anus back to a normal position within the external anal sphincter. It is important to insert a Foley catheter in the urethra in males to avoid damage in all operations. When managing premature, small or very unwell infants, a cutback procedure is another approach that could be used for perineal fistulas.

1.4.8. Outcomes and prognosis

Some short-term complications related to ARM are related to the surgical procedure they have had, including wound infection, anal strictures, femoral nerve injury and anal prolapse, which occurs in around 4% of patients (96, 162). Male patients may have urethral injuries due to rectourethral fistula dissection, and female patients with cloacal malformations, vaginal strictures or fibrosis may occur (96). Long term outcomes for ARMs include the assessment of bowel, urinary and sexual function. Both HSCR and ARM are congenital conditions resulting in problems with the rectum or anus. Both conditions result in obstruction, for which surgical correction requires dissection in a similar tissue plane containing nerves to the distal bowel and bladder (85, 135). Outcomes for both these conditions within literature previously published already include constipation, continence and quality of life, and can be measured in the same way. For example, a study assessing the outcomes reported by previous studies of ARM patients after surgery used similar outcomes, such as voluntary bowel movements and soiling, to those included in the HSCR

COS (163). As the outcomes for these conditions are reported in a similar way, it was therefore decided to use the HSCR COS for ARM patient outcome reporting in later chapters.

1.4.8.1. Bowel function

In a study assessing long term bowel function, around 22% of male patients and 27% of female patients, aged between 20 and 40 years old, reported problems relating to bowel function (164). It has also been reported that around 75% of patients with an ARM have voluntary bowel movements however, around 50% of these patients occasionally have faecal soiling. These patients will undergo a bowel management programme using laxatives or bulking agents and can sometimes need daily enemas if affecting the social activity of these patients (156). There are a limited number of studies assessing the long-term bowel function of ARM patients, highlighting the importance of this study.

1.4.8.2. Urinary function

A study looking at urinary function in patients with an ARM reported urinary incontinence in around 33% of patients with a high ARM, with a lower incidence of urinary incontinence in patients undergoing a PSARP by up to 8% (165). Neurogenic bladder has also been reported in around 10% of patients who underwent definitive ARM surgery causing a decrease in urinary function (123). A positive correlation between partial or severe sacral agenesis and abnormal lower urinary tract function has been reported (123). It has also been found that urinary tract anomalies are more common in patients with a higher ARM which could potentially lead to worse outcomes for these patients (114).

1.4.8.3. Sexual function

A study looking at sexual function in patients with an ARM found that most females had normal reproductive function and most avoid difficulties in pregnancy if not complicated by severe genital or sacral anomalies (165). Another study assessing sexual function in males found abnormal ejaculatory function in 41.2%, with 71.4% of these patients with sexual problems also having sacral anomalies suggesting a need for long-term follow-up in patients with ARM complicated by a sacral anomaly (166).

1.5. Core Outcome Set

A core outcome set (COS) is a group of outcomes chosen by key stakeholder groups to be the most important factors when assessing the success of management of the specific condition being looked at (167). This is important as, theoretically, it would mean there would be less selective reporting of outcomes and outcomes would be easier to compare and contrast in systematic reviews in order to find gold standard treatments (168). Once a COS has been produced for a specific condition, the intention is for it to be used in all future studies on that condition and these studies should include data for every outcome within that disease-specific COS. The reason for implementing this across different studies is to reduce outcome reporting heterogeneity and therefore provide the ability to identify management options producing optimal outcomes for patients with this specific condition.(169) A core outcome set for HSCR has been developed, however due to the similarities in outcome reporting, this core outcome set is also able to be applied to ARM.

1.5.1. Development (169)

The aim of the development of the HSCR COS was to produce a COS which could be used in future studies comparing interventions for the management of children with HSCR in high-income countries. Participants for the development of the COS were recruited into key stakeholder groups with either experience of living with HSCR, patient or parent, or those with experience of management HSCR. These stakeholder groups were paediatric surgeons, neonatologisits, paediatric gastroenterologists, specialist nurses or people with HSCR and parents of children with HSCR. Each member in the groups had an equal input into the selection of outcomes.

First a systematic review on surgical interventions for HSCR was done to identify outcomes to be involved in the three-phase Delphi process being used to identify the COS. This was then followed by a face-to-face consensus meeting

1.5.1.1. Three-phase Delphi process

In phase one, outcomes were scored from 1 to 9 based on importance of deciding whether the management of HSCR was working. In phase two, participants were shown their groups

scores for the outcomes and asked if they wanted to change their score. Outcomes scored 1 to 3 by more than 50% of participants and those scored 7-9 by less than 50% of participants were removed. In phase three, participants were shown all groups scores and asked again if they wanted to change their score. Following phase three, outcomes with scores of less than 15% 1 to 3 and more than 70% 7 to 9 were included.

1.5.1.2. Consensus meeting

A consensus meeting was held to identify the final 10 outcomes for the HSCR COS and to identify the measures to be used for these outcomes included. A total of 17 participants were selected to attend the consensus meeting from all three panels (neonatal, non-neonatal and personal experience panels) to ensure a range of expertise were represented. 45 outcomes met the threshold for discussion at the consensus meeting after the three-phase Delphi process. Participants in the consensus meeting were shown the results of the Delphi process and graphical representation of the scores for each outcome, and after discussion of each outcome, re-scoring occurred. When these 45 outcomes were scored at the consensus meeting, those outcomes with more than 70% of participants scoring the outcome between 7 and 9, and less than 15% scoring the outcome between 1 and 3 were included in the next stage. 15 of the 45 outcomes met the criteria for inclusion.

Prior to this process, it was decided that only up to 10 outcomes would be included in the COS. If there were more than 10 outcomes included, 10 would be picked using the following method:

- The highest scoring outcomes in each of the four OMERACT 2.0 core areas (death, life impact, pathophysiological manifestation or resource use/economical impact)
- Highest scoring adverse event outcomes if not already included
- The next five highest scoring outcomes

Therefore, only 10 of these 15 outcomes could be included in the HSCR COS according to the protocol. As the highest scoring adverse event outcome was already included, a sixth highest scoring outcome was included in the final HSCR COS.

1.5.2. Outcomes (169)

Outcomes in the COS can be split into clinician reported outcomes and patient reported outcomes. Clinician reported outcomes include death with cause specified, unplanned reoperation with indication specified, need for a permanent stoma with indication specified and Hirschsprung-associated enterocolitis. Patient reported outcomes include long-term faecal incontinence, objective score of bowel function, long-term voluntary bowel movements without need for enemas or colonic irrigation, long-term psychological stress for the patient with HSCR, long-term urinary incontinence, and objective score of quality of life. The outcomes included in the Hirschsprung's Disease COS are shown in Table 1.2 alongside the definitions for each outcome.

	Core Outcome	Definition
Clinician reported outcomes	Death with cause specified	Death with a cause due to: 1. A complication of treatment 2. Hirschsprung-associated enterocolitis 3. An associated anomaly 4. Other
	Unplanned reoperation with indication specified	Unplanned to any procedure not part of routine practice. This should include procedures performed as a direct result of diagnosis or treatment and any episode of general anaesthesia required as a direct result of the diagnosis or treatment, regardless of whether an operative intervention is undertaken (e.g. examination under anaesthesia or manual evacuation).

	Core Outcome	Definition
Clinician reported outcomes	Need for a permanent stoma with indication specified	Need for a permanent stoma as a direct result of the diagnosis or treatment, including where decision was made out of patient or parental preference, or for continence management. Permanent stoma is defined as one created without the intention for later reversal.
	Hirschsprung-associated enterocolitis	A score of 10 or more on the Hirschsprung-associated enterocolitis Delphi score by Pastor et al. Where this is not possible, it should be defined as 'Clinician decision to admit and instigate treatment for HAEC. Information should be reported on whether a participant has had any episodes of HAEC up to a standard time-point, but also the number of episodes.
Patient reported outcomes	Long-term faecal incontinence	Involuntary passage of faecal matter in an inappropriate place by a child aged 5 years or over. Severity should be graded as: 1. Occasionally (once or twice a week), with or without social problems 2. Every day, but without social problems 3. Constant, with social problems

	Core outcome	Definition
Patient reported outcomes	Objective score of bowel function	Objective score of bowel function, as measured by the Paediatric Incontinence and Constipation Score (PICS) in children under 18 years of age, and the Gastrointestinal Quality of Life Index (GIQLI) in adults over 18 years of age.
	Long-term voluntary bowel movements	Long-term voluntary bowel movements without need for enema or rectal or colonic irrigation.
	Long-term psychological stress for the individual with HSCR	Long-term psychological stress for the individual with HSCR as measured by the Pediatric Quality of Life score (PedsQL) in children under 18 years of age, and the GIQLI in adults over 18 years of age.
	Long-term urinary incontinence	Involuntary voiding of urine that is constant, associated with social problems or requiring catheterisation.
	Objective score of quality of life using appropriate age-specific measures	Quality of life measured by the age-appropriate PedsQL questionnaire.

Table 1.2. The Hirschsprung's Disease Core Outcome Set and each of their definitions (169)

1.6. Summary

In summary, HSCR and ARMs are rare diseases, with a small number of babies born with these each year. Due to these small numbers, there is very limited data on the outcomes following surgery for children with either HSCR or an ARM, with significant outcome reporting heterogeneity in studies reporting these outcomes. Also, studies reporting information on these conditions and their outcomes are usually of low quality, highlighting

the need for a higher quality study assessing the outcomes of patients with either HSCR or ARM. Therefore, it is important to use to HSCR COS to determine the current outcomes of children with either HSCR or an ARM to potentially help with future counselling of patients with these conditions.

2. A systematic review of the differences in outcome reporting in Hirschsprung's disease

2.1. Chapter introduction

Systematic reviews are an effective method of collecting all relevant studies on a certain topic in order to analyse information currently being reported and to assess missing areas of research. Although there are a large number of studies reporting outcomes of patients with Hirschsprung's Disease (HSCR), variability of the outcomes reported and the age at which outcomes are reported has created limitations when assessing treatment effectiveness. The HSCR Core Outcome Set (COS) was created in order to reduce variability in outcome reporting aiming to reduce reporting bias and improve meta-analyses in studies reporting outcomes of patients with HSCR. The use of a COS in other conditions, such as Ankylosing Spondylitis, has greatly improved outcome reporting in research, demonstrating the power that a COS in HSCR studies may have on the quality of reproducibility of research into this rare condition (170).

This systematic review identifies studies reporting outcomes of patients with HSCR in the five years before and after the publication of the HSCR COS. The outcomes reported and their measures or tools used in each study were qualitatively analysed for changes in COS reporting. Before this piece of research, no study has evaluated the variability in outcome reporting before and after the publication of the HSCR COS.

2.2. Research question and objectives

2.2.1. Research question

How do the timings and methods of measuring outcomes in publications about patients with Hirschsprung's disease in the five years prior to the publication of the Hirschsprung's disease core outcome set differ to the publications after the publication of the core outcome set?

2.2.2. Objectives

- To identify published studies reporting outcomes of patients with Hirschsprung's disease
- To identify the outcomes being reported and the methods being used to measure these outcomes at different time points
- To qualitatively analyse the published literature reporting outcomes of patients with Hirschsprung's disease
- To highlight areas where future research is needed

2.3. Methods

2.3.1. Protocol

The systematic review protocol was registered on PROSPERO (CRD42022298594) prior to starting any database searches. The study was reported in accordance with the guidelines set out by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (171).

2.3.2. Search Strategy

A systematic review was performed to identify studies reporting outcomes in patients with Hirschsprung's disease and to assess which outcomes were being reported, including the outcome measures being used and timings of these outcomes.

An initial scoping search was carried out to identify and examine previous studies analysing differences in outcome reporting in patients with Hirschsprung's disease before and after the publication of the core outcome set. No studies assessing this were found, therefore justifying the need for a systematic review of outcome reporting in Hirschsprung's disease.

The electronic databases used to identify relevant articles for this systematic review were PubMed, Scopus and Medline (OVID), with the final search of these databases being conducted on the 10th of January 2022. The search strategy was designed based on terms identified from a previous systematic review on outcomes in Hirschsprung's disease (172) and through the use of a thesaurus using terms, identified in free-text, related to

Hirschsprung's disease and outcome reporting. The search strategy was adapted for the requirements of each database used and contained a mixture of free text and MeSH (medical sub-headings) terms which were combined using Boolean operators. The search strategy was limited to publications after 2012 (five years prior to the COS publication), publications in the English language, and publications with their full text available.

The final search strategy contained terms related to Hirschsprung's disease and outcomes:

- Hirschsprung's disease:
    - "Hirschsprung's disease"
    - "Hirschsprung disease"
    - Hirschsprung*
    - recto-sigmoid
    - aganglionosis
    - colon* aganglionosis
- Outcomes:
    - outcome
    - "quality of life"
    - "bowel function"

The full search strategy can be found in Appendix 1.

2.3.3. Inclusion and exclusion criteria

Table 2.1 shows the inclusion and exclusion criteria for this systematic review. The comparator aspect of the inclusion and exclusion criteria was not deemed relevant for this question. The aim of this systematic review is to identify outcomes being reported in patients with Hirschsprung's disease. This therefore means that patients without histologically diagnosed Hirschsprung's disease and patients with mixed diagnoses were excluded as this would make it difficult to determine which outcomes were being reported for Hirschsprung's disease specifically. Also, animal studies were excluded for the same reason. Outcomes included were any outcome, either included or not included in the HSCR core outcome set, reported for patients with Hirschsprung's disease. Both the measure used for the outcome and the timing of the measurement were also included in this. Study types

including review articles and systematic reviews with meta-analyses were excluded to ensure data from the same study was not extracted more than once. Finally, case reports were excluded as they only include very small numbers of children and are therefore unlikely to represent the majority of the children with HSCR whose outcomes are within the published literature. Case reports are also more likely to describe unusual cases and therefore described outcomes are less likely to be typical.

	Include	Exclude
Population	• Any human patient	• Animal studies
Intervention	• Any management of Hirschsprung's disease	
Condition	• Histologically diagnosed Hirschsprung's disease	• Not histologically diagnosed Hirschsprung's disease • Mixed diagnosis
Comparator		
Outcome	• Any outcome reported in the Hirschsprung's disease core outcome set • Any outcome not reported in the Hirschsprung's disease core outcome set	
Study design	• Primary research • Randomised control trial • Cohort study • Case control study • English language • Full text available • Published after 1st January 2012	• Case reports • Review articles • Systematic review and meta-analysis

Table 2.1. A PICOS table of inclusion and exclusion criteria

2.3.4. Article Screening

Articles found from the electronic database searches were imported into the systematic review online platform Rayyan (https://www.rayyan.ai/) on which the duplicate articles were able to be found and removed (173). All remaining non-duplicated articles were then independently screened by two reviewers (EO and RH) using titles and abstracts, assessing them against the inclusion criteria. Both reviewers were required to agree on the exclusion of any article. Any disagreements in the decision to exclude an article was first discussed between the two reviewers. If a consensus was not reached after this stage, the article was screened independently by a third member of the team (SK – a consultant paediatric surgeon) to decide whether it met the inclusion criteria.

For 695 of the articles, the two reviewers were already in agreement. 49 out of the remaining 57 articles were then agreed upon after a discussion leaving 8 articles to be screened by the third reviewer.

2.3.5. Full Text Review

The full texts for each of the articles were reviewed at the end of the screening process and when there was a disagreement in whether to exclude the article. The full text was assessed according to the inclusion and exclusion criteria which was then discussed between the two reviewers.

2.3.6. Additional methods of study identification

One additional study was identified through another source which was the reference lists of included articles. The initial study that helped form the search strategy could not be included as it was a systematic review (172).

2.3.7. Data Extraction

Each included article was read, and the data was extracted and entered into a Microsoft Excel spreadsheet. This data extraction tool was constructed by the two reviewers (EO and RH). The extracted data included study details, number of patients, outcomes reported,

measures used for outcome reporting and timings of outcome reporting. Table 2.2 shows the full list of data that was extracted.

Area	Description
Study details	Author, title, year of publication, study location, study type
Population	Number of Hirschsprung's disease patients, number of controls, age of patients at follow up, type of Hirschsprung's disease
Intervention	Type of intervention
Outcome	Name of outcome, method used to measure outcome, time point of measurement of outcome

Table 2.2. A PICOS table of extracted data from included studies

2.3.8. Qualitative Synthesis

The main aim of this systematic review was to produce a list of all outcomes being reported by studies at different time points. If two outcomes being reported were similar, for example post-operative complications and post-operative wound infection, these outcomes were discussed with other members of the research team to discuss whether they should be classed under the same outcome term to prevent excessive numbers of outcomes being extracted under different categories, allowing for more accurate data extraction and less risk of missing outcomes being reported in studies when extracted as a group.

Outcomes were classified as either being a part of the Hirschsprung's disease core outcome set or not part of the core outcome set. Those outcomes in the COS were further classified as either patient-reported outcomes or clinician-reported outcomes. The OMERACT filter 2.0 acts as a framework for consistent outcome reporting in research and is used in the COS as five important areas of outcome reporting (174). These five areas are death, pathophysiological manifestations, resource use, life impact and adverse events.

2.3.9. Quality Assessment

A quality assessment of each study was not performed in this systematic review as only the outcomes being reported by each of the studies were collected. No data from the outcomes being reported was analysed in this systematic review and therefore meaning a quality assessment of the studies was not necessary.

2.3.10. Statistical analysis

Statistical analyses were performed using Prism 9.0 (Graphpad). Outcomes are presented as counts and percentages, medians (IQR) or means (SD). Categorical data were compared using Fisher's Exact Test and an Odds Ratio (OR [95% CI]) was also calculated.

2.4. Results

2.4.1. Study identification

A total of 1008 studies were identified from the three electronic databases through use of the previously mentioned search strategy, with one additional article identified from searching through the included articles. 258 duplicates were found and removed, leaving 751 articles left to be screened according to their title or abstract. Of these studies, 532 were excluded, leaving 219 to be screened for eligibility using the full text. 26 of these only had their abstracts accessible, 3 did not have an available full text and 2 did not report outcomes in their study. A total of 188 studies were deemed eligible according to the inclusion criteria for this systematic review. Figure 2.1 shows a flowchart explaining the study identification process.

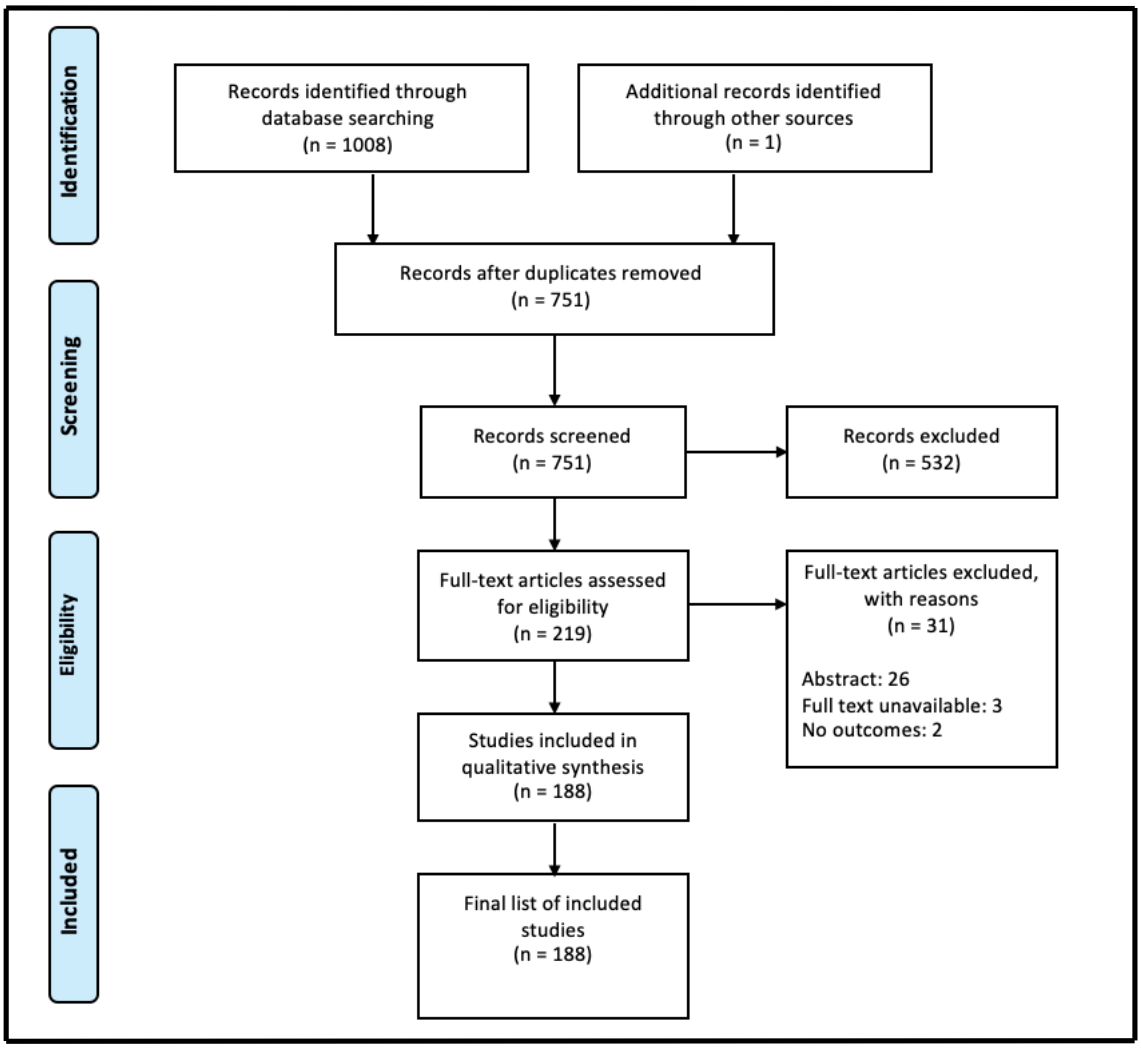

Figure 2.1. PRISMA flow diagram

2.4.2. Study and patient characteristics

The 188 studies were completed in 35 different countries. The most common countries for the location of the studies were China (n=41), USA (n=24), Sweden (n=15) and Japan (n=14). India, The Netherlands and UK each completed 9 studies, and Indonesia, France, Iran and Egypt each completed 6 studies. There were also 5 studies from each of Finland and Norway, and 4 studies from each of Italy, Australia and Korea. The remaining number of studies from each country were as follows: 2 from each from Turkey and Canada, and 1 each from Brazil, Belgium, South Africa, Uzbekistan, Pakistan, Niger, Seoul, Serbia, Morocco, Austria, Nepal, Germany, Saudi Arabia, Ireland, Romania, Tanzania and Tunisia.

The total number of HSCR patients included in all studies was 25,525 with a median of 49 patients in each study, ranging from 2 to 3635 (IQR 71) HSCR patients per study. 37 studies had a control group as part of their study, with the remaining studies either comparing outcome results to the general population or not comparing their results at all. The average age of HSCR patients ranged from 1 month (0.1 years) to 38 years of age however, 15 studies did not specify any ages of the patients at data collection. Also, the majority of studies had a low proportion of female patients (median percentage= 23.55, range= 0.0 – 88.3), with 16 studies no reporting the proportion of female HSCR patients in their study. Table 2.3 shows the study and patient characteristics in more detail.

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Delgado-Miguel C (2022) (175)	USA	HSCR: 15	Median: 6.6	66.6	SS: 12 LS: 3	Surgery: pull-through
Onishi S (2021)(176)	Japan	HSCR: 65	At 5, 7 and 9	20	SS: 50 LS: 13 TCA: 2	Surgery: pull-through
Davidson JR (2021)(177)	UK	HSCR: 32 Controls: 186	With learning difficulties: 20 Without learning difficulties: 28	28.4	SS: 241 LS: 50 TCA: 41	Surgery: pull-through and stoma
Bapaye A (2021)(178)	India	HSCR: 9	Median: 5.4	22.2	SS: 9	Surgery: pull-through
Pecoraro AR (2021)(179)	USA	HSCR: 3345	Median: 0.3	24.1	Unspecified	Surgery: pull-through
Shankar G (2021)(180)	India	HSCR: 11	Mean: 5.2	18.2	Unspecified	Surgery: pull-through
Svetanoff WJ (2021)(181)	USA	HSCR: 21 Controls: 19	Median: 0.9	25	SS: 26 LS: 14	Surgery: pull-through
Pini Prato A (2021)(182)	Italy	HSCR: 280	Unspecified	23.6	SS: 203 LS: 21 TCA: 44 TIA: 7	Surgery: pull-through or stoma
Nasr A (2021)(183)	USA	HSCR: 673	Mean: 13.7	24.7	Unspecified	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Arafa A (2021)(184)	Egypt	HSCR: 15	Between 3-7	33.3	SS: 10 LS: 5	Surgery: pull-through
Li Q (2021)(185)	China	HSCR: 36	Median: 5.1	19.4	SS: 15 LS: 11 TCA: 10	Surgery: pull-through
Davidson JR (2021)(92)	UK	HSCR: 186	Median: 28	27.4	SS: 141 LS: 45	Surgery: pull-through or stoma
Kastenberg ZJ (2021)(186)	USA	HSCR: 82	Unspecified	17	SS: 56 LS: 11 TCA: 4 Unknown: 11	Surgery: pull-through
Rentea RM (2021)(187)	USA	HSCR: 67 Controls: 1372	Mean: 3.9	21.6	Unspecified	Surgery: pull-through
Peng C (2021)(188)	China	HSCR: 7	Median: 11.1	0	Unspecified	Unspecified
Zbaida R (2021)(189)	South Africa	HSCR: 76	Mean: 6	25	SS: 55 LS: 14 Unknown: 7	Surgery: pull-through
Yuan Y (2021)(190)	China	HSCR: 46	Mean: 8.1	17.4	SS: 14 LS: 27 TCA: 5	Surgery: pull-through
Telborn L (2021)(191)	Sweden	HSCR: 10	Median: 4.3	20	SS: 7 LS: 1 TCA: 2	Surgery: pull-through or stoma

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Loganathan AK (2021)(192)	India	HSCR: 86	Mean: 7	17.4	SS: 58 LS: 21 TCA: 7	Surgery: pull-through
Apfeld JC (2021)(193)	USA	HSCR: 1268	All younger than 2	20.6	Unspecified	Surgery: pull-through
Kim S-H (2021)(194)	Korea	HSCR: 82	Mean: 6.3	34.1	SS: 82	Surgery: pull-through
Allin BSR (2020)(195)	UK	HSCR: 239	Median 6.8	Unspecified	Unspecified	Unspecified
Verkuijl SJ (2022)(196)	The Netherlands	HSCR: 334	Median: 17	20.9	SS: 280 LS: 29 TCA: 25	Surgery: pull-through
Askarpour S (2021)(197)	Iran	HSCR: 70	Unspecified	Unspecified	Unspecified	Surgery: pull-through
Youn JK (2021)(198)	Korea	HSCR: 33	Median: 18.6	27.3	TCA: 33	Surgery: pull-through
Yan J-Y (2020)(199)	China	HSCR: 9 Controls: 21	Mean: 8.4	22.2	TCA: 9	Surgery: re-do pull-through
Gunadi IG (2021)(200)	Indonesia	HSCR: 50	Median: 2.6	32	Unspecified	Surgery: pull-through
Lin Z (2021)(201)	China	HSCR: 47	Mean: 0.4	14.9	SS: 47	Surgery: pull-through
Lin Z (2021)(202)	China	HSCR: 95	Mean: 0.5	17.9	SS: 78 LS: 17	Surgery: pull-through
Kabbash MM (2021)(203)	Egypt	HSCR: 32	Mean: 5.5	25	Unspecified	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Chen F (2021)(204)	China	HSCR: 30	Mean: 7.5	6.7	Unspecified	Surgery: pull-through
Hoel AT (2021)(205)	Norway	HSCR: 17	Median: 29	47.1	SS and LS: 16 TCA: 1	Surgery: pull-through
Liu Q (2021)(206)	China	HSCR: 40 Controls: 40	Mean: 1.6	20	SS: 39 TCA: 1	Home nursing
Roorda D (2021)(207)	The Netherlands	HSCR: 131	Median: 8	22.1	SS: 89 LS:23 TCA: 16 Unknown: 7	Intrasphincteric botox injection
Davidson JR (2021)(93)	UK	HSCR: 137	Median: 29	29.9	Unspecified	Unspecified
Mohamed W (2021)(208)	Egypt	HSCR: 23	Median: 0.9	26.1	SS: 23	Surgery: pull-through
Gabriela GC (2020)(209)	Indonesia	HSCR: 21	Median: 6.4	28.6	Unspecified	Surgery: pull-through
Fosby MV (2020)(210)	Norway	HSCR: 50	Median: 8.1 then 15.4	20	Unspecified	Surgery: pull-through
Khamroev UA (2020)(211)	Uzbekistan	HSCR: 61	Mean: 0.5	13.1	SS: 40 LS: 21	Surgery: pull-through
Watanabe T (2020)(212)	Japan	HSCR: 5	Median: 2.5	20	LS: 3 TCA: 2	Surgery: pull-through
Saysoo MR (2020)(213)	Indonesia	HSCR: 11	Aged over 6	18.2	Unspecified	Surgery: pull-through
Brooks LA (2020)(214)	USA	HSCR: 45 Controls: 22	At 1 and 2	13.3	SS: 45	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Granstrom AL (2020)(215)	Sweden	HSCR: 739 Controls: 7390	Median: 19	23.5	Unspecified	Unspecified
Pruitt LCC (2020)(216)	USA	HSCR: 138 Controls: 1892	Unspecified	23.2	Unspecified	Surgery: pull-through
Espeso L (2020)(217)	France	HSCR: 63	Mean: 11	30.2	SS: 50 LS: 11 Unknown: 2	Surgery: pull-through
Ali S (2020)(218)	Pakistan	HSCR: 31	Mean: 1.1	12.9	SS: 31	Surgery: pull-through
Peters NJ (2020)(219)	India	HSCR: 69	Mean: 7.7	13	SS: 69	Surgery: pull-through
Svetanoff WJ (2020)(220)	USA	HSCR: 27	Unspecified	14.8	SS: 14 LS: 10 TCA: 1 Unknown: 2	Surgery: pull-through
Stenstrom P (2020)(221)	Sweden	HSCR: 93	Median: 12	32.8	TCA: 93	Surgery: pull-through
Gunadi (2020)(222)	Indonesia	HSCR: 64	Unspecified	29.7	SS: 62 LS: 2	Surgery: pull-through
Dai Y (2020)(223)	China	HSCR: 84	Median: 3.8	13.1	SS: 65 LS: 13 TCA: 1 Other: 5	Surgery: pull-through
Meng X (2020)(224)	China	HSCR: 109 Controls: 95	Mean: 4.5	21.6	Unspecified	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Oh C (2020)(225)	Korea	HSCR: 396	Median: 6.23	24.7	SS: 348 LS 37 TCA: 11	Surgery: pull-through
Mille E (2020)(226)	France	HSCR: 15	Mean: 10.3	40	SS: 13 LS: 2	Surgery: pull-through
Quiroz HJ (2020)(227)	USA	HSCR: 3635	Groups of <1, 1-6, 7-12 and 13-18	25.2	Unspecified	Surgery: pull-through
Townley OG (2020)(228)	UK	HSCR: 71	Mean: 5.4	19.7	SS and LS: 71	Surgery: pull-through
Schlund D (2020)(229)	USA	HSCR: 32	Mean: 36	25	Unspecified	Surgery: pull-through
Tang J (2020)(230)	China	HSCR: 75 Controls: 73	Mean: 0.4	18.2	SS: 101 LS: 43 TCA: 4	Surgery: pull-through
Pini Prato A (2020)(231)	Italy	HSCR: 11	Median: 3.4	18.2	SS: 6 LS: 3 TCA: 2	Surgery: pull-through
Zhuansun D (2020)(232)	China	HSCR: 97 Controls: 101	Mean: 11.9	24.2	SS: 55 LS: 143	Surgery: pull-through
Zhu J (2020)(233)	China	HSCR: 109	Between 3 and 6	Unspecified	SS: 82 LS: 27	Surgery: pull-through
Halleran DR (2020)(234)	USA	HSCR: 12 Controls: 74	Median: 2.8	41.7	SS: 11 LS: 1	Surgery: pull-through
Yan J (2020)(235)	China	HSCR: 35	Mean: 4.9	31.4	TCA: 35	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Zhang X (2020)(236)	China	HSCR: 190 Controls: 193	Mean: 2	37.1	SS: 391 LS: 69 TCA: 19	Surgery: pull-through
Xu P-P (2019)(237)	China	HSCR: 53	Mean: 0.5	24.5	SS: 11 LS: 26 TCA:16	Surgery: pull-through
Elsherbeny M (2019)(238)	Egypt	HSCR: 21	Mean: 2	38.1	Unspecified	Surgery: pull-through
Adamou H (2019)(239)	Niger	HSCR: 2	21 and 22	50	SS: 2	Surgery: pull-through
Youn JK (2019)(240)	Seoul	HSCR: 15	Median: 4.8	20	SS:14 TCA: 1	Surgery: pull-through
Roorda D (2019)(241)	The Netherlands	HSCR: 3	Mean: 3.2	0	SS: 2 LS: 1	Surgery: pull-through
Hoff N (2019)(242)	Sweden	HSCR: 69	Median: 0.2	26.1	SS: 61 LS: 8	Surgery: pull-through
Amin L (2019)(243)	Sweden	HSCR: 739 Controls: 7390	Mean: 19	23.5	Unspecified	Unspecified
Berrios CD (2019)(244)	USA	HSCR: 368	Mean: 38	88.3	Unspecified	Unspecified
Fusaro F (2019)(245)	Italy	HSCR: 14	Median: 6.7	28.6	TIA: 14	Surgery: intestinal reconstruction
Louis-Borrione C (2019)(246)	France	HSCR: 15	Mean: 7.1	Unspecified	SS: 11 LS: 2 TCA: 2	Intrasphincteric Botox injection

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Ashjaei B (2019)(247)	Iran	HSCR: 15 Controls: 18	Mean: 8.1	26.7	Unspecified	Surgery: pull-through
Meinds RJ (2019)(248)	The Netherlands	HSCR: 346	Median: 18	20.8	US: 10 SS: 282 LS: 29 TCA: 25	Surgery: pull-through
Gustafson E (2019)(249)	Sweden	HSCR: 69 Controls: 138	Mean: 37.8	18.8	Unspecified	Unspecified
Ghorbanpour M (2019)(250)	Iran	HSCR: 55	Mean: 0.3	56.4	Unspecified	Surgery: pull-through
Askarpour S (2019)(251)	Iran	HSCR: 160	Unspecified	32.5	Unspecified	Surgery: pull-through
Gupta DK (2019)(252)	India	HSCR: 32	Mean: 3.6	18.8	SS: 28 LS: 2 TCA: 2	Surgery: pull-through
Obata S (2019)(253)	Japan	HSCR: 327	Unspecified	Unspecified	SS: 286 LS: 36 TCA: 4 TIA: 1	Surgery: pull-through
Hedbys J (2019)(254)	Sweden	HSCR: 53	Median: 7	Unspecified	SS and LS: 53	Surgery: pull-through
Sekioka A (2019)(255)	Japan	HSCR: 6 Controls: 7	Mean: 0.1	0	TIA: 6	Surgery: stoma
Freedman-Weiss MR (2019)(256)	USA	HSCR: 282	Mean: 0.1	18.1	Unspecified	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Jiao C (2019)(257)	China	HSCR: 36 Controls: 44	Mean: 1	27.8	Unspecified	Surgery: pull-through
Obata S (2019)(258)	Japan	HSCR: 11	Unspecified	27.8	Unspecified	Surgery: stoma
Drissi F (2019)(259)	France	HSCR: 34	Mean: 32	23.5	SS: 20 LS: 3 TCA: 3 Unknown: 8	Surgery: pull-through
Sola R Jr (2019)(260)	USA	HSCR: 100	Unspecified	18	Unspecified	Unspecified
Zhu T (2019)(72)	China	HSCR: 198	Less than 1	20.2	SS: 198	Surgery: stoma
Peng CH (2018)(261)	China	HSCR: 5	Median: 6.8	Unspecified	SS: 4 LS: 1	Surgery: pull-through
Zheng Z (2018)(262)	China	HSCR: 172	Mean: 1.1	19.8	SS: 111 LS: 61	Surgery: pull-through
Gunadi (2018)(263)	Indonesia	HSCR: 67	Unspecified	26.9	SS: 66 LS: 1	Surgery: pull-through
Xi Z (2018)(264)	China	HSCR: 50	Mean: 1.6	24	Unspecified	Surgery: pull-through
Widyasari A (2018)(265)	Indonesia	HSCR: 53	Mean: 2.5	15.1	SS: 47 LS: 6	Surgery: pull-through
Chung PHY (2018)(266)	China	HSCR: 45	Median: 4.3	24.4	SS: 45	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Sood S (2018)(267)	Australia	HSCR: 58	Median: 14.5	15.5	SS: 49 LS: 5 TCA: 2 Unknown: 2	Surgery: pull-through
Yokota K (2018)(268)	Japan	HSCR: 16 Controls: 27	Median: 3.8	12.5	SS: 13 LS: 3	Surgery: pull-through
Neuvonen MI (2018)(269)	The Netherlands	HSCR: 34 Controls: 141	Median: 12	17.6	SS: 30 LS: 3 TCA: 1	Surgery: pull-through
Roorda D (2018)(270)	The Netherlands	HSCR: 53	Median: 16.5	22.6	TCA: 53	Surgery: pull-through
Miyano G (2018)(271)	Japan	HSCR: 106	At 1, 3, 5, 7 and 10	35.8	SS: 106	Surgery: pull-through
Huang WK (2018)(272)	China	HSCR: 181	Mean: 6.3	21.5	SS: 153 LS: 21 TCA: 7	Surgery: pull-through
Tran VQ (2018)(273)	Belgium	HSCR: 53	Mean: 16.1	32.1	SS: 38 LS: 11 TCA: 4	Surgery: pull-through
Zhang X (2018)(274)	China	HSCR: 23	Median: 5.2	56.5	TCA: 23	Surgery: pull-through
Zhang J (2017)(275)	China	HSCR: 29	At 0.25, 0.5, 2 and 5	27.6	SS: 22 LS: 7	Surgery: pull-through
Lof Granstrom A (2017)(90)	Sweden	HSCR: 739 Controls: 7390	Median: 19	23.5	Unspecified	Unspecified

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Bjornland K (2017)(276)	Norway	HSCR: 200	Median: 9.5	Unspecified	SS: 200	Surgery: pull-through
Bradnock TJ (2017)(15)	UK	HSCR: 305	Under 0.5	22.9	SS: 198 LS: 60 TCA: 8 Unknown: 4	Unspecified
Neuvonen M (2017)(277)	Finland	HSCR: 59 Controls: 177	Median: 18	27.1	SS: 51 LS: 6 TCA: 2	Surgery: pull-through
Onishi S (2017)(278)	Japan	HSCR: 16	Median: 25	50	SS: 12 LS: 4	Surgery: pull-through
De la Torre L (2017)(279)	USA	HSCR: 39	Mean: 7	20.5	SS: 39	Surgery: pull-through
Collins L (2017)(280)	Australia	HSCR: 60	Mean: 6.4	18.3	SS: 47 LS: 7 TCA: 5 TIA: 1	Surgery: pull-through
Cheng S (2017)(281)	China	HSCR: 80	Median: 2.7	18.8	SS: 61 LS: 19	Surgery: pull-through
Hasserius J (2017)(282)	Sweden	HSCR: 13 Controls: 40	Median: 7	23.1	SS and LS: 13	Surgery: pull-through
Graneli C (2017)(283)	Sweden	HSCR: 51	Median: 5	23.5	SS and LS: 51	Surgery: pull-through
Bing X (2017)(284)	China	HSCR: 148	Mean: 3.5	Unspecified	SS: 130 LS: 18	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Yasui Y (2017)(285)	Japan	HSCR: 7	Mean: 10.6	14.3	SS: 4 LS: 3	Surgery: pull-through
Lu C (2017)(286)	China	HSCR: 650	Mean: 0.3	23.5	SS: 650	Surgery: pull-through
Neuvonen MI (2017)(287)	Finland	HSCR: 79	Median: 15	25.3	SS: 66 LS: 7 TCA: 3 Extended: 3	Surgery: pull-through or stoma
Church JT (2017)(288)	USA	HSCR: 12	Mean: 4.8	25	Unspecified	Intrasphincteric botox injection
Thakkar HS (2017)(289)	UK	HSCR: 72	Median: 6	27.8	SS: 50 LS: 17 TCA: 5	Surgery: pull-through
Stenstrom P (2017)(290)	Sweden	HSCR: 27	Median: 9.5	37	TCA: 27	Surgery: pull-through
Tannuri AC (2017)(291)	Brazil	HSCR: 41 Controls: 59	Mean: 10.4	26.8	SS: 41	Surgery: pull-through
Dingemans A (2017)(292)	The Netherlands	HSCR: 16	Median: 6.7	37.5	Unspecified	Surgery: re-do pull-through
Bischoff A (2017)(293)	USA	HSCR: 54 Controls: 49	Mean: 6.1	24.1	SS: 44 LS: 6 TCA: 4	Surgery: pull-through
Ghosh DN (2017)(294)	Australia	HSCR: 8 Controls: 42	Median: 1.3	12.5	SS: 3 LS: 5	Surgery: pull-through
Ladi-Seyedian SS (2017)(295)	Iran	HSCR: 15 Controls: 15	Mean: 7.2	33.3	Unspecified	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Adiguzel U (2017)(296)	Turkey	HSCR: 50	Median: 0.3	14	SS: 48 LS: 2	Surgery: pull-through
Taguchi T (2017)(297)	Japan	HSCR: 287	Unspecified	Unspecified	Unspecified	Unspecified
Lukac M (2016)(298)	Serbia	HSCR: 84	Unspecified	20.2	SS: 84	Surgery: pull-through
Onishi S (2016)(299)	Japan	HSCR: 110	Median: 8.5	20.9	SS: 87 LS: 19 TCA: 3 Unknown: 1	Surgery: pull-through
Kwendakwema N (2016)(300)	USA	HSCR: 26 Controls: 181	Median: 2.4	19.2	SS: 17 LS: 9	Unspecified
Granstrom AL (2016)(301)	Sweden	HSCR: 389 Controls: 3847	Median: 25	23.9	Unspecified	Unspecified
Ouladsaiad M (2016)(302)	Morocco	HSCR: 15	Mean: 6	26.7	SS: 13 LS: 1 Unknown: 1	Surgery: pull-through
Guerra J (2016)(303)	Canada	HSCR: 36	Mean: 0.3	36.1	SS: 36	Surgery: pull-through
Li Q (2016)(304)	China	HSCR: 12 Controls: 7	Median: 3.5	41.7	TCA: 12	Surgery: pull-through
Xia X (2016)(305)	China	HSCR: 18	Mean: 19.7	11.1	Unspecified	Surgery: pull-through
Xia X (2016)(306)	China	HSCR: 75	Mean: 4.8	20	SS: 51 LS: 24	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Nam SH (2015)(307)	Korea	HSCR: 8	Median: 9.9	37.5	SS: 8	Surgery: pull-through
Xiong X (2015)(308)	China	HSCR: 92 Controls: 90	Mean: 26.8	26.1	SS: 41 LS: 51	Surgery: pull-through
Miyano G (2015)(309)	Japan	HSCR: 74	Median: 7	Unspecified	SS and LS: 74	Surgery: pull-through
Aubdoollah TH (2015)(310)	China	HSCR: 90	Mean: 1	30	SS: 80 LS: 10	Surgery: pull-through
Khazdouz M (2015)(311)	Iran	HSCR: 136	Median: 5.5	40.4	Unspecified	Surgery: pull-through
Granstrom AL (2015)(312)	Sweden	HSCR: 39 Controls: 39	Median: 28	43.6	SS: 37 TCA: 2	Surgery: pull-through or stoma
Amerstorfer EE (2015)(313)	Austria	HSCR: 8	Median: 13.5	25	TCA: 8	Surgery: pull-through
Hukkinen M (2015)(314)	Finland	HSCR: 21	Mean: 6.8	28.6	TCA: 21	Surgery: pull-through or stoma
Khalil M (2015)(315)	Egypt	HSCR: 53	Mean: 5.9	30.2	SS and LS: 53	Surgery: pull-through
Stensrud KJ (2015)(316)	Norway	HSCR: 52	Median: 8.8	19.2	Unspecified	Surgery: pull-through
Neuvonen MI (2015)(317)	Finland	HSCR: 146	Mean: 15	23.3	SS: 121 LS: 10 TCA: 6 TIA: 9	Surgery: pull-through
Wester T (2015)(318)	Sweden	HSCR: 18	Mean: 6.8	16.7	SS: 14 TCA: 4	Intrasphincteric botox injections

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Shrestha MK (2014)(319)	Nepal	HSCR: 20	Mean: 3	15	SS: 20	Surgery: pull-through
YK S (2014)(320)	India	HSCR: 12	Mean: 0.03	16.7	TCA: 12	Surgery: pull-through or stoma
Sulkowski JP (2014)(321)	USA	HSCR: 1555	Mean: 2	21.7	Unspecified	Surgery: pull-through
Yeh YT (2014)(322)	China	HSCR: 9	Median: 9	55.6	TCA: 9	Surgery: pull-through
Ralls MW (2014)(323)	USA	HSCR: 32 Controls: 89	Mean: 18.7	46.9	SS: 18 LS: 6 Unknown: 8	Surgery: pull-through
Han-Geurts IJ (2014)(324)	The Netherlands	HSCR: 33	Median: 7.3	21.2	SS: 30 LS: 3	Intrasphincteric botox injection
Basson S (2014)(325)	UK	HSCR: 43	Median: 10.8	32.6	Unspecified	Intrasphincteric botox injection
Mabula JB (2014)(326)	Tanzania	HSCR: 110	Median: 0.7	21.8	SS: 75 LS: 18 TCA: 1 Unknown: 16	Surgery: pull-through or stoma
Zhang JS (2014)(327)	China	HSCR: 127	Median: 12.2	29.9	SS: 113 LS: 14	Surgery: pull-through
Nasr A (2014)(328)	Canada	HSCR: 54	Mean: 3	Unspecified	SS: 50 LS: 4	Surgery: pull-through
Spataru R (2014)(329)	Romania	HSCR: 17	Mean: 3.1	23.5	SS: 15 LS: 2	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Mathur MK (2014)(330)	India	HSCR: 20	At 0.1 and 0.3	5	SS: 15 LS: 5	Surgery: pull-through
Hukkinen M (2014)(331)	Finland	HSCR: 8	Median: 3.2	0	TCA: 8	Surgery: pull-through
More K (2014)(332)	Australia	HSCR: 54	Mean: 1	38.9	SS: 40 LS: 11 TCA: 3	Surgery: pull-through
Wang L (2014)(333)	China	HSCR: 59	Mean: 22	47.5	SS: 48 LS: 9 TCA: 2	Surgery: pull-through
Ksia A (2013)(334)	Tunisia	HSCR: 20	Unspecified	30	Unspecified	Surgery: pull-through
Granstrom AL (2013)(335)	Sweden	HSCR: 27	Mean: 7.4	14.8	SS: 25 LS: 2	Surgery: pull-through
Levitt MA (2013)(75)	USA	HSCR: 67	Unspecified	23.9	SS: 47 LS: 5 Unknown: 15	Surgery: pull-through
Tang ST (2013)(336)	China	HSCR: 28 Controls: 30	Mean: 0.25	35.7	Unspecified	Surgery: pull-through
Van de Ven TJ (2013)(337)	The Netherlands	HSCR: 43	Median: 4.2	20.9	SS: 43	Surgery: pull-through
Demirbag S (2013)(338)	Turkey	HSCR: 18	Mean: 3.5	22.2	SS: 14 LS: 3 TCA: 1	Surgery: pull-through
El-Sawaf M (2013)(339)	USA	HSCR: 28 Controls: 32	At 0.1, 0.25, 0.5 and 1	10.7	SS: 21 LS: 7	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Miyano G (2013)(340)	Japan	HSCR: 14	Mean: 11.6	Unspecified	TCA: 14	Surgery: pull-through
Zhu T (2013)(341)	China	HSCR: 22	Mean: 2.6	36.7	LS: 22	Surgery: pull-through
Stensrud KJ (2012)(342)	Norway	HSCR: 11	Mean: 8.5	Unspecified	SS: 10 TCA: 1	Surgery: pull-through
Aworanti OM (2012)(343)	Ireland	HSCR: 51	Mean: 4.6	21.6	SS: 48 LS: 3	Surgery: pull-through
Al-Jazaeri A (2012)(344)	Saudi Arabia	HSCR: 99	Mean: 0.6	24.2	Unspecified	Surgery: pull-through
Yang L (2012)(345)	China	HSCR: 137	Mean: 4.7	32.8	SS: 137	Surgery: pull-through
Li N (2012)(346)	China	HSCR: 19 Controls: 30	Mean: 2.8	Unspecified	Unspecified	Unspecified
Zakaria OM (2012)(347)	Egypt	HSCR: 40	Mean: 1.9	30	SS: 40	Surgery: pull-through
Kothari PR (2012)(348)	India	HSCR: 48	Mean: 3.8	Unspecified	SS: 38 LS: 10	Surgery: pull-through
Sheng Q (2012)(349)	China	HSCR: 24	Mean: 2.5	37.5	Unspecified	Surgery: pull-through
Nah SA (2012)(350)	UK	HSCR: 76	Median: 6.8	19.7	SS: 76	Surgery: pull-through
Urushihara N (2012)(351)	Japan	HSCR: 26	Mean: 5.6	11.5	SS: 26	Surgery: pull-through
Sharma S (2012)(352)	India	HSCR: 112	Mean: 4.6	21.4	SS: 112	Surgery: pull-through

Lead Author (year)	Location	Number of patients and controls	Age of patient at time of assessment (years)	Sex (% female)	Classification of HSCR	Intervention
Dagorno C (2020)(353)	France	HSCR: 10	Mean: 8.5	50	SS: 2 LS: 5 TCA: 3	Surgery: pull-through
Urla C (2018)(354)	Germany	HSCR: 11	Median: 7	27.3	TCA: 11	Surgery: pull-through
Broch A (2019)(355)	France	HSCR: 33	Median: 15	54.5	SS: 7 LS: 21 TCA: 5	Surgery: pull-through or stoma
Pini Prato A (2019)(356)	Italy	HSCR: 23 Controls: 362	Median: 7	34.8	SS: 16 LS: 1 TCA: 6	Surgery: pull-through

Table 2.3. Study and patient characteristics

SS – short-segment, LS – long-segment, TCA – total colonic aganglionosis, TIA – total intestinal aganglionosis

2.4.3. Outcome characteristics of studies

Appendix 2 describes every outcome and the outcome measure in each of the 188 studies included in this review. Outcomes have been separated into clinician and patient-reported outcomes, with further classification into outcomes in the COS and outcomes not included in the COS. A total of four studies reported the full HSCR core outcome set after the publication of the COS. Only one out of these four studies also reported the outcomes using the correct outcome measures outlined by the HSCR core outcome set. No studies reported the full list of outcomes in the HSCR COS before it was published. Also, two studies failed to report any of the HSCR COS outcomes before the publication of the COS and three studies failed to report any COS outcomes after the publication of the COS.

2.4.4. HSCR core outcome set reporting

2.4.4.1. Clinician-reported outcomes

The clinician-reported outcomes in the COS include death with cause specified, unplanned re-operation, permanent stoma and HAEC. The number of studies reporting each of these outcomes per year is shown in Table 2.4.

Publication year	Number of studies reporting COS clinician reported outcomes, n (%)			
	Death with cause specified	Unplanned reoperation	Permanent stoma	HAEC
2012 (n=11)	4 (36.6)	6 (54.5)	4 (36.6)	7 (63.6)
2013 (n=9)	3 (33.3)	3 (33.3)	1 (11.1)	9 (100.0)
2014 (n=15)	5 (33.3)	8 (53.3)	6 (40.0)	10 (66.7)
2015 (n=12)	3 (25.0)	5 (41.7)	4 (33.3)	7 (58.3)
2016 (n=9)	2 (22.2)	2 (22.2)	0 (0.0)	8 (88.9)
2017 (n=25)	6 (24.0)	11 (44.0)	11 (44.0)	13 (52.0)
2018 (n=15)	5 (33.3)	4 (26.7)	5 (33.3)	11 (73.3)
2019 (n=27)	13 (48.1)	13 (48.1)	11 (40.7)	15 (55.6)
2020 (n=31)	20 (64.5)	13 (41.9)	8 (25.8)	20 (64.5)
2021 (n=32)	22 (68.8)	13 (40.6)	5 (15.6)	20 (62.5)
2022 (n=2)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)

Table 2.4. Core outcome set clinician reported outcomes per year

2.4.4.1.1. Death

Out of the 188 studies included in this study, 85 (45.2%) reported mortality rates of HSCR when assessing the outcomes of these patients. All 85 studies reported this outcome in accordance to the HSCR core outcome set, specifying the cause of death including: a complication of treatment, HAEC, an associated anomaly or another cause of death. Table 2.5 shows the outcome measures used to measure the COS outcomes. Death with cause specified was not included in Table 2.5 as no specified measure of data collection was outlined in the HSCR COS.

Before the publication of the HSCR COS, a total of 23 out of 81 papers (28.4%) reported death with cause specified as an outcome. After the publication of the COS, 62 out of the 107 papers (57.9%) reported death with cause specified as an outcome. This is a statistically significant increase in the reporting of death with cause specified before and after the

publications of the HSCR COS (OR 3.47 [1.87-6.44], p<0.05). The number of studies reporting each COS clinician-reported outcome per year is shown in Table 2.4.

Outcomes reported in the COS	Outcome measure tool	Number of studies using this outcome measure tool (% of studies reporting the outcome)
Hirschsprung-associated enterocolitis (n=122)	Clinician diagnosis of HAEC	111 (91.0)
	2009 HAEC scoring system	1 (0.8)
	Delphi score system by Pastor et al.	3 (2.4)
	El Halabi criteria	2 (1.6)
	HAEC grading system	2 (1.6)
	HD-associated EC score	1 (0.8)
	Severity scoring system	1 (0.8)
	Teitelbaum and Coran criteria	1 (0.8)
Long-term faecal incontinence (n=136)	Subjective measure	55 (40.4)
	Rintala bowel function score	25 (18.4)
	Krickenbeck classification	12 (8.8)
	Holschneider incontinence score	6 (4.4)
	Wingspread score	7 (5.1)
	Stooling survey from El-Sawaf et al.	4 (2.9)
	Pediatric incontinence/constipation scoring system (PICSS)	4 (2.9)
	Evacuation score defined by Japan Society of Ano-Rectal Malformation Study Group	3 (2.2)
	HSCR/Anorectal malformation quality of life questionnaire	3 (2.2)
	Validated bowel function questionnaire	2 (1.5)
	Rome IV criteria	2 (1.5)
	Miller's incontinence score	2 (1.5)
	Baylor continence scale	2 (1.5)
	Clinical bowel function scoring system	1 (0.7)
	Evacuation score	1 (0.7)
	HD anal function criteria	1 (0.7)
	Heikkinen defecation function score	1 (0.7)
	Jorge-Wexner fecal incontinence score	2 (1.5)
	Postoperative bowel function evaluation score	1 (0.7)
	Postoperative fecal continence (POFC)	1 (0.7)
	Wildhaber score	1 (0.7)

Outcomes reported in the COS	Outcome measure tool	Number of studies using this outcome measure tool (% of studies reporting the outcome)
Objective score of bowel function (n=84)	Rintala bowel function score	24 (28.6)
	Krickenbeck classification	13 (15.5)
	Pediatric incontinence/constipation scoring system (PICSS)	5 (6.0)
	Stooling survey from El-Sawaf et al.	4 (4.8)
	Holschneider incontinence score	5 (6.0)
	Evacuation score defined by Japan Society of Ano-Rectal Malformation Study Group	4 (4.8)
	HSCR/Anorectal malformation quality of life questionnaire	3 (3.6)
	Rome IV criteria	2 (2.4)
	Rome III criteria	2 (2.4)
	Baylor continence scale	2 (2.4)
	Miller's incontinence score	4 (4.8)
	Gastrointestinal quality of life index	1 (1.2)
	Clinical bowel function scoring system	1 (1.2)
	Defaecation and faecal incontinence questionnaire	1 (1.2)
	HD anal function criteria	1 (1.2)
	Heikkinen defecation function score	1 (1.2)
	Jorge-Wexner fecal incontinence score	3 (3.6)
	Kohno's rating scale	1 (1.2)
	Long term prognosis survey following pull-through	2 (2.4)
	Postoperative bowel function evaluation score	1 (1.2)
	Postoperative fecal continence (POFC)	1 (1.2)
	Rome II criteria	1 (1.2)
	Wildhaber score	1 (1.2)
	Wingspread score	1 (1.2)
Long-term voluntary bowel movements (n=142)	Subjective measure	64 (45.1)
	Rintala bowel function	24 (16.9)
	Krickenbeck classification	14 (9.9)
	Stooling survey from El-Sawaf et al.	4 (2.8)
	Pediatric incontinence/constipation scoring system (PICSS)	4 (2.8)

Outcomes reported in the COS	Outcome measure tool	Number of studies using this outcome measure tool (% of studies reporting the outcome)
Long-term voluntary bowel movements (n=142)	Evacuation score defined by Japan Society of Ano-Rectal Malformation Study Group	4 (2.8)
	Holschneider incontinence score	4 (2.8)
	HSCR/Anorectal malformation quality of life questionnaire	3 (2.1)
	Miller's incontinence score	4 (2.8)
	Wexner constipation score	3 (2.1)
	Rome IV criteria	2 (1.4)
	Rome III criteria	2 (1.4)
	Cleveland clinic constipation scoring system	2 (1.4)
	Clinical bowel function scoring system	1 (0.7)
	HD anal function criteria	1 (0.7)
	Heikkinen defecation function score	1 (0.7)
	Postoperative bowel function evaluation score	1 (0.7)
	Postoperative fecal continence (POFC)	1 (0.7)
	Rome II criteria	1 (0.7)
	Wildhaber score	1 (0.7)
	Wingspread score	1 (0.7)
Long-term psychological stress (n=34)	Subjective measure	3 (8.8)
	PedsQL	11 (32.3)
	GIQLI	4 (11.8)
	CHQ-CF87 and WHOQOL-100	3 (8.8)
	HSCR/Anorectal malformation quality of life questionnaire	3 (8.8)
	Quality of life scoring for children with fecal incontinence	3 (8.8)
	SF-36 questionnaire	5 (14.7)
	GI quality of life index	1 (2.9)
	Assessment of quality of life in children and adolescents with fecal incontinence	1 (2.9)
	Barrena scoring system	1 (2.9)
	Psychological adaptation scale	1 (2.9)
	Quality of life score for defecation	1 (2.9)
	Rintala bowel function score	1 (2.9)
	Spielberg State-Trait Anxiety Inventory questionnaire	1 (2.9)
	TACQOL scale	1 (2.9)
	WHO QOL-BREF	1 (2.9)

Outcomes reported in the COS	Outcome measure tool	Number of studies using this outcome measure tool (% of studies reporting the outcome)
Long-term urinary incontinence (n=16)	Subjective measure	8 (50.0)
	HSCR/Anorectal malformation quality of life questionnaire	3 (18.8)
	Vancouver symptom score	2 (12.5)
	Modified DanPSS	3 (18.8)
Objective score of quality of life (n=32)	PedsQL	11 (34.4)
	GIQLI	5 (15.6)
	Quality of life scoring criteria for children with fecal incontinence	3 (9.4)
	CHQ-CF87 and WHOQOL-100	3 (9.4)
	HSCR/Anorectal malformation quality of life questionnaire	3 (9.4)
	Subjective measure	1 (3.1)
	Adolescents' Health and Perceived Health and Kidscreen 10	1 (3.1)
	Assessment of quality of life in children and adolescents with fecal incontinence	1 (3.1)
	Barrena scoring system	1 (3.1)
	Quality of life score for defecation	1 (3.1)
	Rintala bowel function score	1 (3.1)
	SF-36 questionnaire	2 (6.3)
	TACQOL scale	1 (3.1)
	WHO QOL-BREF	1 (3.1)

Table 2.5. Outcome measures used to measure COS outcomes

2.4.4.1.2. Unplanned re-operation

A total of 80 studies (42.6%) reported whether patients had undergone an unplanned reoperation during their follow-up period. There is no specific data collection measure outlined in the HSCR core outcome set for unplanned re-operation, therefore this outcome was also not included in Table 2.5.

35 studies out of the 81 (43.2%) published before the publication of the COS reported unplanned re-operation as an outcome and 45 studies out of the 107 (42.1%) published

after reported unplanned re-operation as an outcome, which is not a statistically significant difference (OR 0.95 [0.53-1.71], p=0.8827).

2.4.4.1.3. Permanent stoma

57 studies (30.3%) assessed and reported whether their patients were given a permanent stoma. All 57 studies provided indications for stoma formation and therefore, reported this outcome in accordance with the HSCR core outcome set. Permanent stoma was also excluded from Table 2.5 due to the absence of an outcome measure for reporting this outcome.

Out of the 81 studies published before the COS, 26 studies (32.1%) reported the proportion of patients having a permanent stoma as an outcome. This changed to 31 out of the 107 studies (29.0%) published after the COS. This difference however was not statistically significant (OR 0.86 [0.46-1.61], p=0.7488).

2.4.4.1.4. Hirschsprung-associated enterocolitis (HAEC)

122 out of the 188 studies (64.9%) reported the outcomes of HAEC in their study. According to the HSCR core outcome set, HAEC is defined as "a clinician decision to admit and treat for HAEC and be correlated to the HAEC Delphi score from Pastor et al where possible"(169). All 122 studies reported HAEC according to the definition from the HSCR core outcome set, however only 3 studies out of the 122 (2.4%) used the HAEC Delphi score developed by Pastor et al. In total, there were 7 different scoring systems used to evaluate the severity of HAEC in 11 different studies, with the HAEC grading system and El Halabi criteria being the next most commonly used after the HAEC Delphi score, each used in 2 studies (1.6%). 111 out of the 122 studies (91.0%) did not use a scoring system to assess HAEC with data on HAEC rates being collected from a clinician review of previous medical records.

54 studies (66.7%) reported HAEC as an outcome before the publication of the COS and 68 studies out of the 107 (63.6%) published after the publication of the COS (OR 0.87 [0.48-1.60], p=0.7579).

2.4.4.2. Patient-reported outcomes

The patient-reported outcomes in the HSCR COS include long-term faecal incontinence, an objective score of bowel function, voluntary bowel movements, psychological stress, long-term urinary incontinence and an objective score of quality of life. The number of studies reporting each of these patient-reported outcomes per year is shown in Table 2.6.

Publication year	Number of studies reporting COS patient reported outcomes and COS outcome measures, n (%)								
	Long-term faecal incontinence	Long-term urinary incontinence	Long-term voluntary bowel movements	Objective score of bowel function	Bowel function measure	Long-term psychological stress	Psychological stress measure	Objective score of quality of life	Quality of life measure
2012 (n=11)	8 (72.7)	2 (18.2)	8 (72.7)	6 (54.5)	1 (9.1)	1 (9.1)	1 (9.1)	0 (0.0)	0 (0.0)
2013 (n=9)	5 (55.6)	0 (0.0)	7 (77.8)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2014 (n=15)	11 (73.3)	1 (6.7)	9 (60.0)	3 (20.0)	0 (0.0)	1 (6.7)	1 (6.7)	1 (6.7)	1 (6.7)
2015 (n=12)	12 (100.0)	1 (8.3)	12 (100.0)	7 (58.3)	0 (0.0)	4 (33.3)	2 (16.7)	4 (33.3)	2 (16.7)
2016 (n=9)	6 (66.7)	0 (0.0)	7 (77.8)	3 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2017 (n=25)	18 (72.0)	3 (12.0)	21 (84.0)	15 (60.0)	1 (4.0)	3 (12.0)	2 (8.0)	4 (16.0)	2 (8.0)
2018 (n=15)	14 (93.3)	2 (13.3)	15 (100.0)	11 (73.3)	0 (0.0)	4 (26.7)	1 (6.7)	4 (26.7)	1 (6.7)
2019 (n=27)	16 (59.3)	2 (7.4)	19 (70.4)	8 (29.6)	0 (0.0)	6 (22.2)	0 (0.0)	5 (18.5)	0 (0.0)
2020 (n=31)	22 (71.0)	2 (6.5)	21 (67.7)	17 (54.8)	2 (6.5)	9 (29.0)	3 (9.7)	9 (29.0)	3 (9.7)
2021 (n=32)	22 (68.8)	3 (9.4)	22 (68.8)	11 (34.4)	0 (0.0)	5 (15.6)	4 (12.5)	4 (12.5)	4 (12.5)
2022 (n=2)	2 (100.0)	0 (0.0)	1 (50.0)	2 (100.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)

Table 2.6. Core outcome set patient reported outcomes and outcome measures per year

2.4.4.2.1. Long-term faecal incontinence

136 different studies (72.3%) assessed long-term faecal incontinence in HSCR patients involved in their studies. The HSCR core outcome set suggests that the severity of faecal incontinence should be graded when reporting this outcome, which all 136 studies did. The COS also does not suggest an outcome measure tool to be used when assessing long-term faecal incontinence so there was a total of 21 different methods used to collect this outcome data. A subjective measure of faecal incontinence was the most common data collection method used in these studies, with 55 studies (40.4%) using this method and not calculating an objective score. The two most common scores used to assess long-term faecal incontinence in these 136 studies were the Rintala bowel function score and the Krickenbeck classification, used in 25 (18.4%) and 12 (8.8%) studies, respectively. The other outcome measures and scores used to measure long-term faecal incontinence in the remaining 50 studies are shown in Table 2.5.

A total of 60 out of 81 studies (74.1%) reported faecal incontinence as an outcome in their study before the publication of the HSCR COS and 76 out of 107 studies (71.0%) reported faecal incontinence after the publication of the COS. This difference was not statistically significant (OR 0.86 [0.45-1.64], p=0.7424).

2.4.4.2.2. Objective score of bowel function

An objective score of bowel function was reported as an outcome in 84 of the 188 studies (44.7%). The HSCR core outcome set outlines that this objective score should be measured by the Pediatric Incontinence and Constipation Score (PICS) in patients under the age of 18, and by the Gastrointestinal Quality of Life Index (GIQLI) in patients over the age of 18. Only 5 out of the 84 studies (6.0%) reporting an objective score of bowel function used the PICS system, and only 1 study (1.2%) used the GIQLI. This suggested that only 6 studies (7.2%) reported an objective score of bowel function in accordance to the HSCR core outcome set. A total of 24 different outcome measures were used to calculate an objective score of bowel function across the 84 papers. The two most common outcome measures used were the same as for long-term faecal incontinence, which were the Rintala bowel function score and

the Krickenbeck classification, used in 24 (28.6%) and 13 (15.5%) studies, respectively. The remaining outcome measures for objective scores for bowel function are shown in Table 2.5.

In total, before the publication of the HSCR COS, 35 out of the 81 studies (43.2%) reported an objective score of bowel function as an outcome. 49 out of 107 studies (45.8%) reported an objective score of bowel function after the publication of the COS. This was not statistically significant difference (OR 1.11 [0.62-1.99], p=0.7681). When assessing studies reporting an objective score of bowel function using the correct outcome measure outlined by the COS, 3 studies (3.7%) used the correct measure before and 2 studies (1.9%) used the correct measure after the publication of the COS. Therefore, there was no increase in the number of studies correctly reporting an objective score of bowel function. The percentage of studies using the outcome measures outlined by the COS for outcome reporting in patients with HSCR is shown in Figure 2.2.

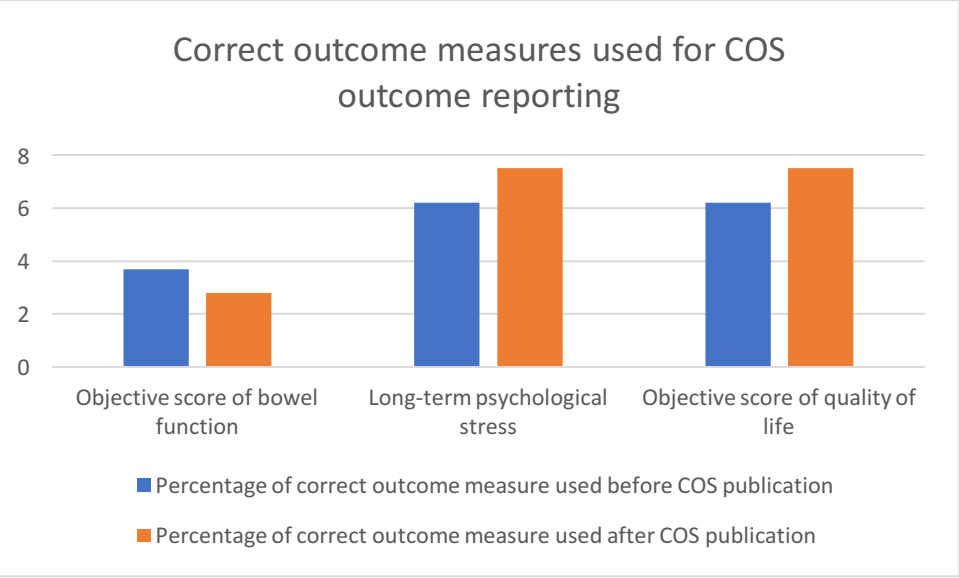

Figure 2.2. Correct outcome measures used for outcome reporting as outlined by the COS

2.4.4.2.3. Long-term voluntary bowel movements

142 studies (75.7%) assessed long-term voluntary bowel movements as part of their outcome reporting. The HSCR core outcome set defines long-term voluntary bowel movements as there being no need for enemas or rectal irrigation, but no scoring system is

suggested to measure this outcome. This means that all 142 studies, reporting voluntary bowel movements, reported this outcome in accordance to the HSCR core outcome set. A total of 21 different methods of measuring this outcome were used, with 20 different scoring systems being used. 64 studies (45.1%) used a subjective measure to report voluntary bowel movements without using an objective score. The most common two objective scores used to measure long-term voluntary bowel movements were the Rintala bowel function score and the Krickenbeck classification, used in 24 (16.9%) and 14 studies (9.9%), respectively. A number of other scores were used to measure this outcome, including the PICS system, and are shown in Table 2.5.

Before the publication of the HSCR COS, 64 out of the 81 studies (79.0%) reported long-term voluntary bowel movements as an outcome in HSCR patients. 78 out of 107 studies (72.9%) reported long-term voluntary bowel movements after the publication of the COS. This difference was not statistically significant (OR 0.71 [0.36-1.42], p=0.3931).

2.4.4.2.4. Long-term psychological stress

A total of 34 studies (18.1%) reported long-term psychological stress in individuals with HSCR as part of their research. The HSCR core outcome set states that long-term psychological stress should be measured by the PedsQL questionnaire in patients under the age of 18, and by the Gastrointestinal Quality of Life Index (GIQLI) in patients over the age of 18. Within these 34 studies, 16 different outcome measures were used, including 1 study using a subjective measure and 33 studies using 15 different scoring systems to calculate an objective score for psychological stress for the patient. Only 11 studies (32.3%) out of the 34 studies used the PedsQL questionnaire and only 4 (11.8%) used the GIQLI to measure psychological stress. Therefore, only 15 studies (44.1%) reported long-term psychological stress as an outcome in accordance to the HSCR core outcome set. A number of other scoring systems were used to calculate this outcome, with the two most common being the SF-36 questionnaire, in 5 studies (14.7%), and the HSCR/Anorectal malformation quality of life questionnaire, in 3 studies (8.8%). All other outcome measures for long-term psychological stress are shown in Table 2.5. In table 2.5, the number of outcome measures being reported adds up to 41 which is more than the total number of studies reporting long-term psychological stress, 34 studies. This is because 3 studies used the SF-36 questionnaire,

PedsQL questionnaire and GIQLI in the same study and 1 study used both the SF-36 questionnaire and GIQLI in the same study.

A total of 9 studies out of the 81 (11.1%) published prior to the publication of the COS reported psychological stress as an outcome. 25 out of 107 studies (23.4%) reported psychological stress after the publication of the COS. This increase was statistically significant (OR 2.44 [1.07-5.57], p<0.05]. However, when looking at studies reporting psychological stress using the correct measures outlined by the COS, 5 studies (6.2%) used the correct measure before the publication of the COS and 8 studies (7.5%) after. This difference was not statistically significant (OR 1.23 [0.39-3.91], p=0.7802).

2.4.4.2.5. Long-term urinary incontinence

Out of the 188 studies included in the systematic review, 16 studies (8.5%) reported long-term urinary incontinence as an aspect of their research. The HSCR core outcome set does not specify a specific outcome measure for the reporting of urinary incontinence meaning all 16 studies reported this outcome in accordance to the HSCR core outcome set. A total of 4 outcome measures were used to measure long-term urinary incontinence, with 8 studies using a subjective measure and 8 studies using scoring system to calculate an objective score. These scoring systems were the HSCR/Anorectal malformation quality of life questionnaire, the Vancouver symptom score and the Modified DanPSS, which were used in 3 (18.8%), 2 (12.5%) and 3 studies (18.8%), respectively.

Before the publication of the HSCR COS, only 7 studies out of 81 (8.6%) reported long-term urinary incontinence as an outcome in HSCR patients. 9 out of 107 studies (8.4%) reported long-term urinary incontinence after the COS publication. This difference was not statistically significant (OR 0.97 [0.35-2.73], p>0.9999).

2.4.4.2.6. Objective score of quality of life

32 studies (17.0%) reported an objective score of quality of life as an outcome in patients with HSCR. The HSCR core outcome set states that an objective score of quality of life should be measured by the age-appropriate PedsQL questionnaire. In the 32 studies

reporting quality of life, there are 14 different outcome measures used, with 1 study using a subjective measure and the remaining 31 studies using 13 different scoring systems to calculate an objective score of quality of life. Only 11 studies (34.4%) used the PedsQL questionnaire as the outcome measure meaning that only 11 studies, out of the 32 studies reporting quality of life, reported this outcome in accordance with the HSCR core outcome set. The next most common scoring system used for an objective score of quality of life was the GIQLI, used in 5 studies (15.6%). The remaining outcome measures for quality of life reporting are shown in Table 2.5. In table 2.5, the number of outcome measures being reported adds up to 35 which is more than the total number of studies reporting long-term psychological stress, 32 studies. This is because 2 studies used the both the PedsQL questionnaire and the GIQLI in the same study and 1 study used both the PedsQL questionnaire and the SF-36 questionnaire in the same study.

In total, 9 studies out of the 81 (11.1%) published before the publication of the HSCR COS reported an objective score of quality of life in HSCR patients. 23 out of 107 studies (21.5%) reported an objective score of quality of life after the COS publication, which was a statistically significant increase (OR 2.19 [0.95-5.04], $p<0.05$]. When assessing the studies using the correct measure for quality of life outlined by the COS, only 5 studies (6.2%) used this measure before the COS publication and 8 studies (7.5%) used it after the COS publication. This was not a statistically significant difference (OR 1.23 [0.39-3.91], $p=0.7802$]. The percentage of studies reporting outcomes from the Core Outcome Set before and after the publication of the HSCR COS is shown in Figure 2.3.

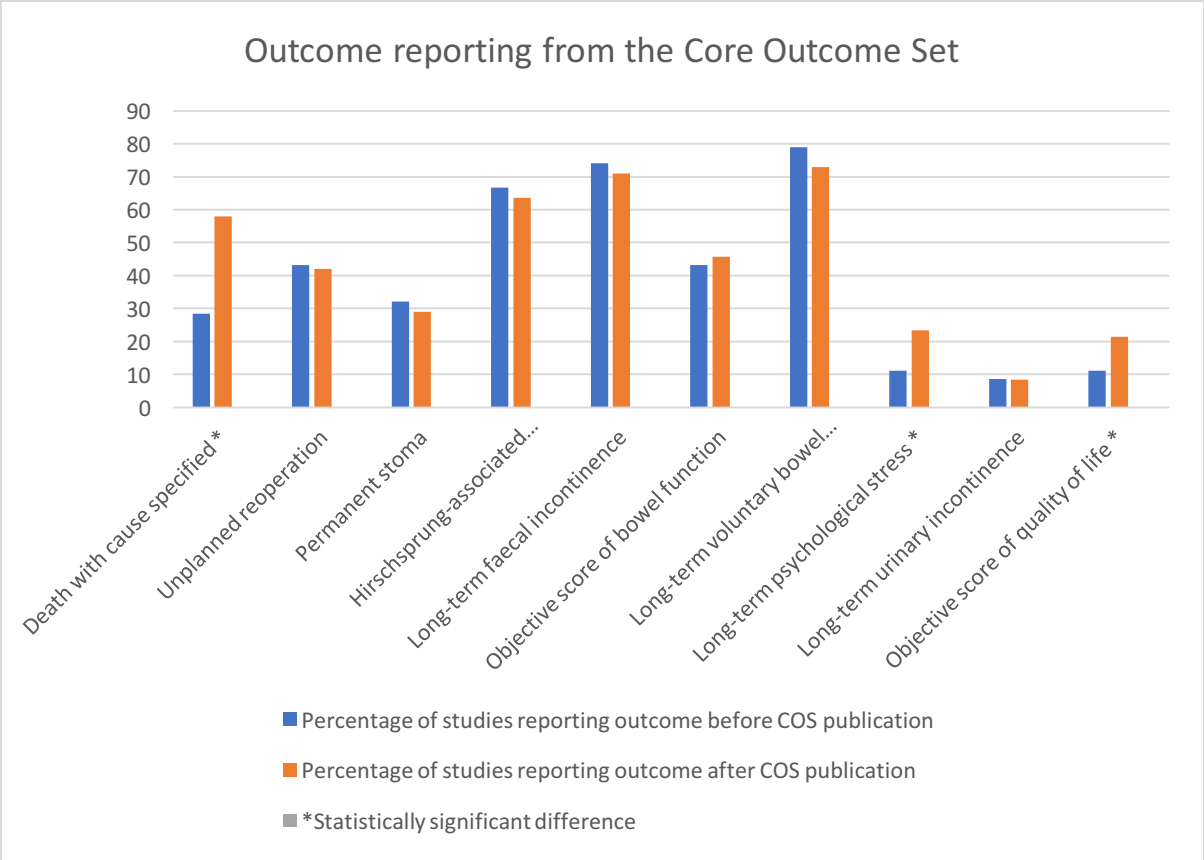

Figure 2.3. Outcome reporting before and after the publication of the COS

2.4.5. Non-COS outcome reporting

154 studies (81.9%) included in this systematic review reported outcomes that are not included in the HSCR COS, with the most common being perioperative complications, postoperative stay and, growth and nutritional status. 120 studies (63.8%) reported perioperative complications in HSCR patients, with a minority, 2 studies (1.7%), being graded by the Clavien-Dindo classification. Postoperative stay was also assessed in 66 studies (35.1%), all using a review of patient's medical records. Growth and nutritional status was assessed in 32 studies (17.0%), with 24 of these (75.0%) using height and weight to evaluate this outcome. A number of studies also assessed sexual function and sexual quality of life in an older cohort of patients, using the erectile hardness score and the sexual quality of life questionnaire as outcome measures. The Manchester scar scale was also used in 2 studies to assess visibility of HSCR patients' scars. The full list of non-COS outcomes reported in the 188 studies and their outcome measures are shown in Table 2.7

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Outcomes reported not in the COS	Outcome measures	Number of studies using this outcome measure tool (% of studies reporting the outcome)
Perineal rash (n=45)	Review of medical records	45 (100.0)
Postoperative stay (n=66)	Review of medical records	66 (100.0)
Readmission (n=20)	Review of medical records	20 (100.0)
Patients' and families' perspectives of symptoms (n=8)	Fecal incontinence and constipation quality of life questionnaire	2 (25.0)
	Adolescent's Health and Perceived Health Questionnaire	1 (12.5)
	Family impact module	1 (12.5)
	Illness perceptions questionnaire	1 (12.5)
	Modified Visick scoring system	1 (12.5)
	Parental self-efficacy in the management of home care of children with HD or ARM	1 (12.5)
	Self-rating Anxiety Scale	1 (12.5)
Urinary tract infection (n=1)	Review of medical records	1 (100.0)
Perioperative complications (n=120)	Review of medical records	118 (98.3)
	Clavien-Dindo classification	2 (1.7)
Sexual function (n=6)	Subjective measure	4 (66.7)
	Erectile hardness score	2 (33.3)
Fertility (n=3)	Subjective measure	3 (100.0)
Sexual quality of life (n=5)	Subjective measure	4 (80.0)
	Sexual quality of life questionnaire	1 (20.0)
Growth and nutritional status (n=32)	Height and weight	24 (75.0)
	Weight	5 (15.6)
	Subjective measure	3 (9.4)
Intelligence (n=2)	Griffiths Mental Development Scale	1 (50.0)
	Wechsler Children's Intelligence Scale	1 (50.0)
Behaviour (n=2)	Ages and stages questionnaire	1 (50.0)
	Child behaviour checklist	1 (50.0)
Cancer diagnosis (n=1)	Review of medical records	1 (100.0)
Feeding issues (n=11)	Subjective measure	11 (100.0)

Outcomes reported not in the COS	Outcome measures	Number of studies using this outcome measure tool (% of studies reporting the outcome)
Anorectal manometry (n=13)	Anorectal manometry readings	13 (100.0)
Visibility of scar (n=7)	Subjective measure	5 (71.4)
	Manchester Scar Scale	2 (28.6)
Educational level and income (n=2)	Subjective measure	2 (100.0)

Table 2.7. Outcome measures used to measure outcomes not in the COS

2.4.6. Total COS reporting

As previously mention, only 4 studies out of the 188 studies (2.1%) included in the review reported the full HSCR COS, with only one of these studies using the correct outcome measures to report these outcomes. The study reporting the full COS using the outcome measures outlined by the COS (Allin BSR et al.) mention that they were reporting their outcomes in accordance to the COS. The author of this paper was also involved in the production of the COS indicating why the correct outcome measures may have been used. Of the remaining three papers, two were written by the same primary author, with one of these papers stating the outcomes were being reported in accordance with the HSCR COS. The two papers written by the same primary author (Davidson JR) were conducted in the UK and the other paper (Roorda D et al.) was conducted in The Netherlands. The number of outcomes from the COS reported in each study per year are shown in Table 2.8.

Year	Number of COS outcomes reported										
	0 (n=5)	1 (n=13)	2 (n=22)	3 (n=34)	4 (n=32)	5 (n=35)	6 (n=24)	7 (n=12)	8 (n=6)	9 (n=1)	10 (n=4)
2012 (n=11)	1	1	0	1	2	2	4	0	0	0	0
2013 (n=9)	0	0	2	4	2	1	0	0	0	0	0
2014 (n=15)	0	2	2	3	3	2	3	0	0	0	0
2015 (n=12)	0	0	0	3	3	2	1	2	1	0	0
2016 (n=9)	1	0	2	2	2	2	0	0	0	0	0
2017 (n=25)	0	3	1	6	5	2	5	3	0	0	0
2018 (n=15)	0	0	1	2	5	3	1	0	2	0	1
2019 (n=27)	0	3	3	5	4	9	0	1	2	0	0
2020 (n=31)	1	3	4	2	4	5	5	5	1	0	1
2021 (n=32)	2	1	7	6	2	7	4	1	0	0	2
2022 (n=2)	0	0	0	0	0	0	1	0	0	1	0

Table 2.8. Number of COS outcomes reported by each study per year

2.4.7. Timing of outcome reporting

Not all of the 188 studies included in this systematic review reported the timings of when their outcomes were collected. 15 studies (8.0%) did not report timings of outcome reporting, with the remaining 169 studies (89.9%) either reporting a specific timepoint, a mean or a median age at outcome collection. This therefore meant that timing of outcome reporting could not be included in this systematic review due to the different methods of outcome reporting used by the studies.

2.5. Discussion

The aim of this systematic review was to identify all studies reporting outcomes of patients with HSCR. In total, 188 studies were identified to have reported at least one outcome for this patient cohort. These studies showed a large variability in outcome reporting with 27 different outcomes being reported across the 188 studies.

Since the publication of the HSCR Core Outcome Set, only 4 papers out of the 188 included in this review (2.1%) reported the full COS, with only one of these reporting the full COS using the outcome measures outlined by the COS. This shows a lack of engagement with the HSCR COS as the only study using the correct measures was conducted by one of the members of the research team who developed the HSCR COS.

There were also 15 studies (8.0%) that failed to report the timings and ages of patients reporting outcomes, meaning there was an inability to determine whether these outcomes were reporting in accordance to the COS, due to time points specified by the COS for specific outcomes, such as long-term faecal incontinence in children over the age of 5.
The search strategy and inclusion criteria were selected to identify all relevant studies reporting outcomes of HSCR patients. The decision to exclude studies published before 2012 was to create an equal timeframe before and after the publication of the COS. This exclusion criteria however, may result in important studies reporting a full range of outcomes in HSCR patients being missed. This could therefore have affected the data when comparing outcome reporting before the COS. However, it was important to have an equal timeframe for papers before and after the COS to get a similar number of studies in each group.

This HSCR COS is the only current COS for patients with HSCR, meaning that all recent studies reporting outcomes in these patients should be including as many of these outcomes in the HSCR COS that are relevant to their paper to help reduce reporting bias and allow improved meta-analysis across different studies. This however, was found to not be the case with the remaining 184 studies, who did not report all 10 COS outcomes, with only a few outcomes from the COS, including death with cause specified and psychological stress, being increasingly reported in studies after the publication of the HSCR COS. There were also 3 studies published after the publication of the COS that failed to report any of the outcomes in the COS making it difficult for comparisons to be made with other studies reporting outcomes in HSCR patients.

When looking at the outcome measures used to report outcomes from the COS, only 5 studies used the correct measure for bowel function. Other measures were used more

commonly including the Rintala bowel function score, in 24 studies, and the Krickenbeck classification, in 13 studies. This raises the question as to whether the objective measures chosen by the COS to report specific outcomes were the correct measures to use, with more studies, even after the publication of the COS, using these more common measures to report their outcomes, meaning if one of these other measures were chosen, more studies would be reporting in accordance to the COS.

There were also a large number of studies reporting outcomes not present in the HSCR COS. 120 studies reported perioperative complications, being one of the most frequently reported outcomes, and 45 studies reporting perineal rash as an outcome suggesting its importance when assessing HSCR patients. Many patients need to have a stoma created due to having a severe perineal rash meaning that this outcome may be of high importance to patients and their families, which could provide an explanation for why so many studies reported this as an outcome.

A previous systematic review comparing the reporting of outcomes from the COS for ankylosing spondylitis 14 years after the publication of this disease specific COS showed utilisation of this COS, including in specific instruments outlined by the COS.(169) This systematic review assessing HSCR outcome reporting has only been completed 5 years after the publication of the HSCR COS and therefore sufficient time may not have been provided for studies including those underway at the time of COS publication to utilise the HSCR COS for new research. However, this systematic review also demonstrates that there is a long way to go in consistent publishing of outcomes specified by the COS using the specified tools.

The utilisation of the HSCR COS could be widened by lobbying for medical journals publishing research on HSCR to promote the use of the COS specified outcome measures and to reduce the scoring of articles not reporting according to the COS. Lobbying of grant providers, for example the NIHR to increase the scoring of grant applications including the COS outcomes will also promote their uptake.

It is important to highlight that although there were 107 studies published after the publication of the HSCR COS, some of these studies may have already collected outcome data or written up their article before the HSCR COS was published and therefore wouldn't have influenced the outcome reporting of these studies. This may provide an explanation for why there were little changes in HSCR outcome reporting after the publication of the HSCR COS.

2.5.1. Comparison to previous reviews

There has only been one previous systematic review assessing the variability in outcome reporting in studies on HSCR patients. This, however, was completed before the publication of the HSCR COS to assess the need for a COS and therefore has not compared outcome reporting in studies before and after the publication of the HSCR COS.

2.5.2. Strengths and limitations

One of the strengths of this study was the search strategy used to identify 751 unique studies from multiple sources. This search strategy was based off previous systematic reviews assessing HSCR patients and was altered to select the more relevant studies for this specific systematic review. However, due to this large number of studies, it was not feasible to assess the full articles of all of these studies and therefore only the abstracts were initially screening for outcomes of patients with HSCR. It is therefore possible that a small number of studies assessing outcomes in HSCR patients may not have been identified and included in the systematic review, although this would most probably mean that HSCR outcome reporting was a minor aspect of these studies and therefore may not have been relevant.

Another strength of this study was that the screening of the studies initially identified from the searches was completed by two reviewers blindly and any differences were discussed. If a definitive answer was no able to be reached, a third reviewer also helped decide whether to include these studies. A limitation however was that the data extraction was completed by only one reviewer, which increases the chance of error and potential for bias. However, this reviewer completed the data extraction twice to decrease the chance of errors occurring when assessing which outcomes were being reported.

One limitation of this systematic review was that the search strategy contained some terms for specific outcomes, for example ‘quality of life’. This could have resulted in more studies reporting these specific outcomes being found in the database searches and therefore could have biased the results of the systematic review. However, it was deemed necessary to include these specific terms due to the risk of certain studies not stating the term ‘outcome’ and instead reporting the specific outcome such as ‘quality of life’ or ‘bowel function’, and therefore would have been excluded if these outcome specific search terms were not included. If this systematic review was completed again, it would be suggested to include specific outcome terms for all of the COS to prevent biased results.

Another limitation of this study was that only studies written in the English language were included due to difficulties in data extraction if written in another language. There is therefore potential that a number of important studies reporting outcomes in HSCR patients may have been excluded and therefore the data may have been different if studies in all languages were included. Also, there may be current HSCR research ongoing which may be taking time to set up using the COS outcomes and therefore, it may be potentially useful to repeat this study in 5 years time to look at any changes in the trends of COS outcome reporting.

The systematic review firstly aims to describe which outcomes are published on within the literature, whether or not the specified COS measure is used, to highlight whether the outcomes which families and clinicians deemed to be the most important are represented within the literature. As a secondary analysis the frequency of reporting of outcome measures specified within the COS are described. A decision to use this two-tier strategy was made as some studies did not report how certain outcomes were collected or did not specify the definition e.g. of long-term faecal incontinence. Exclusion of studies not using the COS definition would have significantly reduced the number of studies that could be included. It was therefore decided to include all of these studies to ensure studies were not unnecessarily excluded. This however, may have had an impact on the result of this systematic review suggesting more studies were reporting COS outcomes than actually were.

Finally, we did not assess the quality of the studies included in this systematic review. This was due to the fact that only the types of outcomes being reported were collected from the studies and not the actual results of these outcome studies. We therefore deemed it not necessary to undergo this assessment.

2.6. Conclusion

This systematic review highlights the lack of use of the HSCR COS across different studies with little changes in outcome reporting after the publication of the COS. Only a very small number of studies were identified to be using the COS after its publication, with multiple important outcomes for these patients being excluded. It shows the need for the COS to be put into use across all centres in order to reduce the risk of reporting bias and improve meta-analyses of outcomes of HSCR patients across multiple centres in the future.

3. The qualitative and quantitative outcomes of children with Hirschsprung's disease and anorectal malformations

3.1. Introduction

The outcomes of infants with Hirschsprung's disease (HSCR) and anorectal malformations (ARM) are hugely variable and can be influenced by a large number of factors including type of defect, operative approach and additional medical problems (89, 114, 166). The HSCR core outcome set (COS), outlined in Chapter 2, has not been widely used to report outcomes for patients with HSCR or ARM, with the majority of studies reporting only a small number of these outcomes and using different outcome measures. This has produced a significant gap in the knowledge of outcomes for patients with these pathologies leaving these children and their families unclear on their future.

This chapter describes the initial findings of a cohort study on children with HSCR or ARM, reporting both clinician and patient reported outcomes according to the HSCR core outcome set.

3.2. Research question and objectives

3.2.1. Research question

What are the short and long-term outcomes for children with HSCR and ARM including surgical complications, functional outcomes and quality of life outcomes?

3.2.2. Objectives

The primary aim of this study is to use the standardised core outcome measures outlined for the Hirschsprung's disease COS to determine the current outcomes for children with HSCR or ARM. This information may enable identification of factors influencing outcomes in these children and may help with counselling of parents and patients with these conditions with regards to continence and quality of life outcomes in the future.

The secondary aims of this study are:

- To compare the outcomes of children with recto-sigmoid and extended-segment HSCR.
- To compare the outcomes of children with low, intermediate and high ARM.
- To determine how the outcomes of children with HSCR and ARM change with age.

3.3. Methods

3.3.1. Ethical approval

Ethical approval for this study was granted by the North West – Liverpool East Research Ethics Committee and the Confidentiality Advisory Group (REC Reference: 18/NW/0608, IRAS ID: 219338).

3.3.2. Research team

Ms Sarah Almond is the chief investigator for this study. Co-investigators for the study included Professor Simon Kenny, Miss Rachel Harwood, Mr Colin Baillie, Mr Graham Lamont and Miss Sumita Chhabra.

3.3.3. Study design

3.3.3.1. Design and location

The study is a retrospective observational cohort study completed at Alder Hey Children's Hospital (Alder Hey) in Liverpool between January and July 2022.

Prior to my starting the project, the protocol was written, ethical and confidential advisory group permission given and Health Research Authority permission given. It took approximately 3 months for the sponsor to give the green light for the study to start at Alder Hey after which I took on the day-to-day research activity. This included screening potential participants and establishing whether they met the inclusion and exclusion criteria. All of these screened patients were entered into the screening log. I then undertook collection of the clinician reported outcomes from the notes whilst in parallel contacting families. Contact with families was undertaken in clinic, on the ward and through the post, initially sending out a 'pre-survey card', patient and parent information forms and consent

and assent forms. When consent and assent forms were returned I entered the patient's details and study number into the recruitment log and checked the consent forms were correctly completed. I then sent the relevant age-group questionnaires to the families in order and when these were returned I entered the data into the study red-cap database along with the clinician reported outcomes.

Children were identified from two hospital databases of patients who have been given an ICD-10 code based on their diagnosis (Table 3.1), two databases from previous studies on HSCR and ARM, and from clinic visits. These children were screened for eligibility based on the inclusion and exclusion criteria (Table 3.2). Deceased children were identified and no contacted for patient or parent reported outcome measures. Patient contact details were identified from patient records on Alder Hey's electronic patient record (EPR), Meditech, (Medical Information Technology Incorporated, Massachusetts, United States).

ICD-10 code	Diagnosis
Q43.1	Hirschsprung's Disease
Q42.0	Congenital absence, atresia and stenosis of rectum with fistula
Q42.1	Congenital absence, atresia and stenosis of rectum without fistula
Q42.2	Congenital absence, atresia and stenosis of anus with fistula
Q42.3	Congenital absence, atresia and stenosis of anus without fistula
Q43.6	Congenital fistula of rectum and anus
Q43.7	Persistent cloaca

Table 3.1. ICD-10 classification key (357)

3.3.3.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria for this study are shown in Table 3.2. The aim of this study is to determine the outcomes of children with Hirschsprung's disease and anorectal

malformations. Children who were labelled as having HSCR but had no histological evidence in their records were excluded from the study. Children diagnosed with anorectal malformations who did not require any surgical management were excluded as it would make it difficult to determine whether management options had any effect on the outcomes of these infants. Children whose initial treatment or majority of follow-up were not undertaken by Alder Hey were also excluded as relevant information such as clinic letters or operative reports would not be accessible and therefore these children would not have a full set of notes in order for their outcomes to be compared. Only children born between July 2011 and July 2021 were included in this study, partially due to time constraints for submission, and in order for data to be collected at specific time points.

	Inclusion Criteria	Exclusion Criteria
Hirschsprung's Disease cohort	• All children treated at Alder Hey Children's Hospital with histologically confirmed Hirschsprung's disease born between July 2011-July 2021	• Children with no documented evidence of histologically diagnosed Hirschsprung's disease
Anorectal Malformation cohort	• All children diagnosed with an anorectal malformation on the basis of position relative to external sphincter born between July 2011-July 2021	• Children with a funnel anus • Children diagnosed with an anorectal malformation which did not require any surgical procedure
General	• Children born between July 2011 and July 2021	• Children whose initial primary treatment or majority of follow-up for either condition has been external to Alder Hey Children's Hospital • Children with insufficient hospital notes for outcome measures • Children born before July 2011 and after July 2021

Table 3.2. Study inclusion and exclusion criteria

3.3.3.3. Patient recruitment

Families of eligible children were approached either by post or through their routine clinic appointments. Eligible children attending routine appointments between February 2022 and July 2022 were approached and invited to participate in the study verbally with written information. Written information was posted to families of children not attending routine clinic appointments in this time, as per the study protocol. As all children were under 16 years of age, consent was obtained through the parents of children with these conditions. Parents were given an information leaflet and consent form based on their age (Appendix 3) and given the chance to ask any questions regarding the study. Parents who had previously signed a consent form, either in a previous clinic or via post, were given the study questionnaires to either fill out in clinic or at home depending on their preference.
All eligible children who had not been contacted in regards to the study through a clinic appointment by May 2022 were contacted by post. Parents of eligible children were sent a pre-survey card with a telephone number on for any questions, an age appropriate information leaflet and a parent consent form. This pack also contained a pre-paid return envelope for parents to return the consent form. Those parents who returned the signed consent form were posted age appropriate study questionnaires with another pre-paid return envelope.

3.3.4. Data collection

3.3.4.1. Clinician reported outcomes

Eligible children were given a unique study number on a locally formulated REDCap database, which was used for all patient information and outcomes identified in this study. Data were collected from the hospital records on the EPR of these eligible children including patient characteristics and clinician reported outcomes, such as unplanned reoperation and the need for a permanent stoma. Clinician reported outcomes were also collected from specific time points during follow-up, in which a defined range of time was allowed for these outcomes to be collected:

- 1 year old – between 6 and 18 months of age
- 5 years old – between 4 and 6 years of age
- 10 years old – between 9 and 11 years of age

Clinical data were collected from the EPR and input into the REDCap database for children with HSCR or ARM meeting the eligibility criteria. Information including patient demographics, HSCR/ARM phenotype and interventions were extracted from clinical notes. COS clinician reported outcomes including faecal incontinence and voluntary bowel movements were collected from eligible clinical notes. When reporting clinician reported outcomes with less than 4 patients in, '<4' was put in the outcome table to ensure confidentiality of those patients. Table 3.3 shows data extracted from the clinical notes on the EPR.

Variables	Description	
	Hirschsprung's disease	Anorectal malformation
Patient	• Gender • Date of Birth • Phenotype	• Gender • Date of Birth • Phenotype
Additional medical problems	• Trisomy 21 • Other syndromes • Family History	• VACTERL association
Investigations	• Imaging • Histopathology	• Imaging
Interventions	• Pre-operative management • Surgical management	• Surgical management
Complications	• Early post-operative complications	
Outcomes collected at 1, 5 and 10 years of age	• Faecal incontinence • Voluntary bowel movements • HAEC • Urinary continence • Unplanned re-operation • Permanent stoma	• Faecal incontinence • Voluntary bowel movements • Urinary continence • Unplanned re-operation • Permanent stoma

Table 3.3. Study data extracted from online patient hospital notes

The following definitions were used and are defined within the HSCR COS:

3.3.4.1.1. Unplanned reoperation

Any procedure which is not considered part of routine post-operative management. This outcome included any additional procedure performed as a direct result of the diagnosis of HSCR or ARM or as a result of the standard management of these children, either surgical or non-surgical. For example, planned stoma closures completed after the pull-through procedure would not be considered to be an unplanned reoperation.

3.3.4.1.2. Permanent stoma

A stoma that is created without the intention of later reversal. The need for a permanent stoma should be either due to the diagnosis of HSCR or ARM, or due to the treatment of these conditions. This includes when the decision for a permanent stoma has been made out of child or parent preference or for continence management. The indication for permanent stoma formation should also be reported.

3.3.4.1.3. Hirschsprung-associated enterocolitis

Clinician decision to admit and instigate treatment for Hirschsprung's Associated Enterocolitis due to factors such as admission with clinical presentation of HACE, bloods and/or x-ray findings in keeping with enterocolitis (169). This outcome was only reported for children with HSCR, with the number of episodes also being reported for these patients.

3.3.4.1.4. Voluntary bowel movements

Children using no assistance, including stoma, laxatives, enemas or rectal washouts, as outlined by the HSCR core outcome set. When assessing bowel outcomes, bowel sensation, soiling and constipation were also assessed for both cohorts. Children who have a stoma were included in this outcome, however bowel outcomes excluding children with a stoma at specific time-points have also been stated in accordance with the COS. Bowel sensation was defined as the ability to feel when they needed to open their bowels and hold until they reached the toilet. Soiling was defined as the involuntary passage of faecal matter in an inappropriate place. Both bowel sensation and soiling were not reported in the 1 year follow-up cohort as their age meant these were not possible. Constipation was defined as the need for diet changes, laxatives or other bowel management strategies in order for the infant to have a bowel movement.

3.3.4.1.5. Urinary continence

The involuntary voiding of urine that is constant, associated with social problems, or requires catheterisation. Both daytime and night time urinary continence were reported, however these were not reported in the 1 year age group.

3.3.4.2. Patient reported outcomes

On admission to the study, after signing the consent form, the most age appropriate questionnaires were administered. Different questionnaires were posted out to patients in different age groups with patients' families providing information on current treatments such as dilatations, laxatives and suppositories. Table 3.4 outlines the different questionnaires completed by children and their families at the different time points depending on the age of the child.

Age group	Questionnaires
1 year	• PedsQL Family Information Form
5 years	• PedsQL Family Information Form • PedsQL 5-7 Young Child Report • PedsQL 5-7 Parent Report • Bowel Function Questionnaire – Age 5 and 10 years
10 years	• PedsQL Family Information Form • PedsQL 8-12 Child Report • PedsQL 8-12 Parent Report • Bowel Function Questionnaire – Age 5 and 10 years

Table 3.4. Questionnaires completed by children and parents at different time points

3.3.4.2.1. Objective score of bowel function

The Paediatric Incontinence and Constipation Score (PICS) was chosen to measure bowel function as this was the scoring system outlined in the HSCR core outcome set. The PICS questionnaire is made up of 13 questions and it calculates an incontinence and constipation score, using 8 and 10 questions, respectively, with 5 questions being used for both scores. The patient scores calculated from the questionnaires were compared with the age-specific mean scores and 95% confidence intervals (CI) for both incontinence and constipation. Scores that fell within the age-specific 95% confidence intervals were interpreted as an absence of incontinence or constipation and scores falling below the age-specific 95% confidence interval were interpreted as impaired continence or the presence of constipation.

For the HSCR cohort, all 14 children returning the bowel function score questionnaire had sufficient PICS data to calculate the incontinence and constipation scores for each child. Children are said to have impaired continence or constipation when their scores fall below the age-specific lower 95% confidence interval (358). The lower 95% confidence interval for impaired continence was 23.2 for all children in this HSCR cohort, as all children were over 35 months of age. The lower 95% confidence interval for constipation was 17.8 for 2 children, 17.9 for 1 child, 20.1 for 4 children and 20.0 for the remaining 7 children.

For the ARM cohort, all 16 children who returned the bowel function score questionnaire had sufficient PICS data to calculate the incontinence and constipation scores for each child. Using the same method as was used earlier for children with HSCR, children with an ARM are said to have impaired continence or constipation when their scores fall below the age-specific lower 95% confidence interval (358). The lower 95% confidence interval for impaired continence was 23.2 for 15 children in this ARM cohort, as these 15 children were over 35 months of age, with the remaining 1 child having lower 95% confidence interval of 15.1. The lower 95% confidence interval for constipation was 18.0 for 1 child, 17.8 for 2 children, 16.2 for 2 children, 17.9 for 2 children, 20.1 for 1 child and 20.0 for the remaining 8 children.

3.3.4.2.2. Objective score of quality of life and psychological stress

The Paediatric Quality of Life (PedsQL) score was used to measure quality of life and psychological stress, as outlined by the HSCR core outcome set. Both the child self-reported and parent proxy-reported PedsQL questionnaires were used to calculate these scores for both cohorts. The PedsQL questionnaires contains 23 items and assess 4 quality of life domains: physical functioning, emotional functioning, social functioning, school functioning. To calculate a quality of life score, all 4 domains were included and to calculate a psychosocial score, the physical functioning questions were excluded. The mean scores calculated for each cohort were compared with a healthy reference population (358). The PedsQL scoring guide states that scores are still able to be calculated if more than 50% of the questions in each section have been answered, and a mean score can be calculated by dividing the total score by the number of questions that have been answered (359).

3.3.5. Statistical analysis

Statistical analyses were performed using Prism 9.0 (GraphPad). Outcomes are presented as counts and percentages, medians (IQR) or means (SD). Outcomes were presented for the whole cohort, and into groups of infants according to HSCR or ARM phenotype. The HSCR cohort were also split into two groups according to pull-through operative approach, however this was not done in the ARM cohort due to the large number of different operative approaches used for anal reconstruction in this cohort. Outcomes were compared using appropriate categorical and continuous statistical tests, with a P value of <0.05 being considered statistically significant. Categorical data were compared using Fisher's Exact Test or Chi-squared, and an Odds Ratio (OR [95% CI]) was also calculated. For continuous variables, a Student's T test was performed for 2 variables and a one-way ANOVA test was performed when there were 3 variables.

3.4. Results – HSCR Cohort

3.4.1. Patient inclusion in study

A total of 141 children with HSCR were identified from the four databases and from clinic visits. 15 (10.6%) children were excluded due to having either their initial primary treatment or majority of their follow-up at another centre, 12 (8.5%) children were excluded due to insufficient hospital notes with important data for this study missing. The total HSCR study population was 114 children, of whom 8 (7.0%) had died. The cause of death of these children is described later in this chapter. A flow chart of HSCR children included in this study is shown in Figure 3.1.

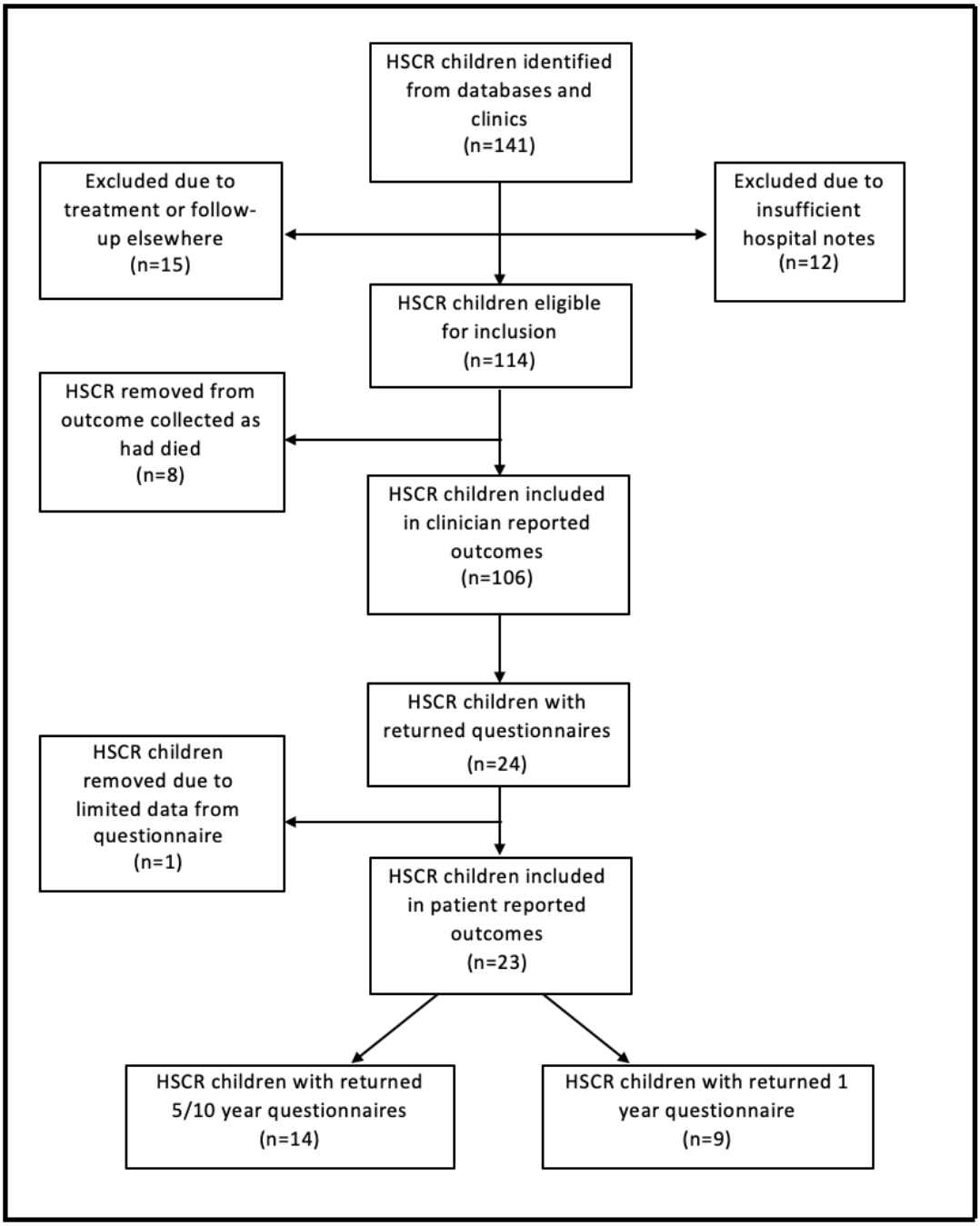


Figure 3.1. Flow chart of HSCR children included in this study

3.4.2. Clinician reported outcomes – Overall HSCR cohort

3.4.2.1. Patient characteristics

The total HSCR study population was 114 children, of whom 8 had died. The cause of death of these children is described later in this chapter. Core outcome set outcomes are described for the remaining 106 children below.

The median age of eligible children included in this cohort study was 67 months (IQR 38.25-95, range 6-124). 82 (77.4%) of the cohort were male and 24 (22.6%) were female. Children had a range of HSCR phenotypes with 76 (71.7%) having short-segment HSCR, 16 (15.1%) having long-segment HSCR, 10 (9.4%) having ultra-short HSCR, 2 (1.9%) having total colonic HSCR, and 2 (1.9%) having total intestinal HSCR (Table 3.5).

Characteristic	Value n=106 (%)
Sample size	106 (100)
Median age in months at beginning of data collection (IQR)	67 (38.25-95)
Sex	
Male	82 (77.4)
Female	24 (22.6)
Phenotype	
Short-segment HSCR	76 (71.7)
Long-segment HSCR	16 (15.1)
Ultra-short HSCR	10 (9.4)
Total Colonic HSCR	2 (1.9)
Total Intestinal HSCR	2 (1.9)

Table 3.5. HSCR cohort characteristics

All results in Table 3.5 are reported as number of children and percentages unless stated otherwise, n (%).

In this cohort, 10 (9.4%) had Trisomy 21 and 7 (6.6%) had other syndromes, including Di George syndrome, West syndrome, Shah Waardenburg syndrome and Mowat-Wilson syndrome. Table 3.6 shows the number of children with additional syndromes and family history of HSCR.

Additional syndromes	Value n=106 (%)
Trisomy 21	10 (9.4)
Other chromosomal abnormalities	7 (6.6)
Family History	9 (8.5)

Table 3.6. Additional syndromes in the HSCR cohort

All results in Table 3.6 are reported as number of patients and percentages unless stated otherwise, n (%).

All children (n=106) had a histological diagnosis confirming Hirschsprung's Disease, either a rectal suction biopsy or intra-operative frozen sections. 93 (87.7%) of children had a rectal suction biopsy and 99 (93.4%) of children had intra-operative frozen sections, with 87 (82.1%) of children undergoing both a rectal suction biopsy and intra-operative frozen sections. When assessing preoperative imaging in HSCR children had, 87 (82.1%) children had an abdominal x-ray and 85 (80.2%) had a contrast enema, with 66 of these 85 (77.6%) children having a visible transition zone on their contrast enema correlating with intraoperative findings. 71 (67.5%) children with HSCR underwent both an abdominal x-ray and a contrast enema and 5 (4.7%) had neither investigation done (Table 3.7).

Pre-operative management	Value n=106 (%)
Histology	
Rectal suction biopsy	93 (87.7)
Intra-operative frozen sections	99 (93.4)
Imaging	
Abdominal X-ray	87 (82.1)
Contrast enema	85 (80.2)
Pre-operative management	
Rectal washouts	83 (78.3)
Anal dilatations	62 (58.5)
Both	62 (58.5)

Table 3.7. Pre-operative management in the HSCR cohort

All results in Table 3.7 are reported as number of patients and percentages unless stated otherwise, n (%).

3.4.2.1.1. Surgical management

94 (88.7%) children underwent a pull-through procedure, with 67 (71.3%) children undergoing a Soave pull-through and 27 (28.7%) children undergoing a Swenson pull-through. 3 (2.8%) children underwent a subtotal colectomy and 4 (3.8%) children had a permanent stoma formation as definitive surgical management, with 3 (75.0%) of these patients having additional syndromes, which would make future continence difficult. Table 3.8 shows a full list of the HSCR patient cohorts characteristics including surgical management.

Surgical management	Value n=106 (%)
Pre-pull-through stoma formation	51 (48.1)
Level of stoma formation	
Descending colon	21 (41.2)
Ileum	29 (56.9)
Jejunum	1 (2.0)
Definitive surgery	
Pull-through procedure • Soave • Swenson	94 (88.7) • 67 (71.3) • 27 (28.7)
Subtotal colectomy	3 (2.8)
Permanent stoma formation as initial management	4 (3.8)
No surgical management due to ultra-short segment	5 (4.7)
Pull-through operative approach	
Laparoscopic-assisted	45 (47.9)
Open	49 (52.1)

Table 3.8. HSCR cohort surgical management

All results in Table 3.8 are reported as number of patients and percentages unless stated otherwise, n (%).

3.4.2.1.2. Patient characteristics according to age group

Clinician reported outcomes were collected at 1 year, 5 years and 10 years of age. For the 1 year outcome form, outcomes for all children (n=106) could be collected as the whole cohort had hospital patient notes available from when they were within the age range for this outcome form. For the 5 year outcome form, outcome data was able to be completed for 70 (66.0%) children as they were older than 4 years. For 10 year follow up, 14 (13.2%) children were older than 9 years old and were therefore able to be included in the outcome collection for this age group. The majority of children in both the 5 year and 10 year cohort underwent a pull-through procedure, with 63 (90%) children having undergone a pull-through in the 5 year cohort and 13 (92.9%) children in the 10 year cohort. Table 3.9 shows the full list of HSCR characteristics at 5 and 10 years of age.

Characteristic	5 years (n=70)	10 years (n=14)
Sex		
Male	55 (78.6)	12 (85.7)
Female	15 (21.4)	2 (14.3)
Phenotype		
Recto-sigmoid HSCR	58 (82.9)	13 (92.9)
Extended segment HSCR	12 (17.1)	1 (7.1)
Additional syndromes		
Trisomy 21	6 (8.6)	2 (14.3)
Additional chromosomal abnormalities	5 (7.1)	0 (0)
Pre-pull-through stoma formation	33 (47.1)	3 (21.4)
Level of stoma formation		
Descending colon	15 (45.5)	2 (66.6)
Ileum	17 (51.5)	1 (33.3)
Jejunum	1 (3.0)	0 (0)
Definitive surgery		
Pull-through procedure • Soave • Swenson	63 (90.0) • 50 (79.4) • 13 (20.6)	13 (92.9) • 13 (100) • 0 (0)
Subtotal colectomy	3 (4.3)	0 (0)
No surgical management	2 (2.9)	0 (0)
Pull-through operative approach		
Laparoscopic-assisted	27 (42.9)	7 (53.8)
Open	36 (57.1)	6 (46.2)

Table 3.9. 5 and 10 year HSCR patient cohort characteristics

All results in Table 3.9 are reported as number of patients and percentages unless stated otherwise, n (%).

3.4.2.2. Death

The overall mortality rate for HSCR children within this cohort was 7.0% (n=8) with all children having histologically diagnosed HSCR. The median age of these children was 7 months (IQR 2.5-15.5, range 1-72). 6 (75%) children had undergone a colostomy formation and 3 (37.5%) had undergone a pull-through procedure. 4 (50%) children had Trisomy 21 and 4 (50%) children had cardiac anomalies, with 2 (25%) children having both. The hospital patient notes for 3 (37.5%) children did not report a cause of death as these children attended an external centre but had their HSCR management at Alder Hey. All of the remaining 5 (62.5%) children had significant co-morbidities, including Smith-Lemli-Opitz syndrome and chronic liver failure, and 3 out of these 5 (60.0%) deaths were related to sepsis, prior to having a pull-through procedure. The cause of death in the remaining 2 (25%) children were due to post-operative complications, with one child developing problems after cardiac surgery for congenital heart disease and the other having a hypoxic brain injury after developing an anastomotic leak and sepsis post pull-through. Therefore the operative mortality as a direct consequence of HSCR was 0.9%.

3.4.2.3. Unplanned reoperation

In total, 22 children out of the 106 (20.8%) in this HSCR patient cohort required further unplanned surgical management, either after initial stoma formation or after a pull-through procedure. Of the 94 (88.7%) children who had undergone a pull-through procedure, 20 (21.3%) of these required an additional surgical procedure with 18 (19.1%) children requiring unplanned surgery following pull-through. These 18 children had 28 surgical procedures between them; with 2 (1.9%) children requiring 3 operations, 6 (5.7%) children requiring 2 operations and the remaining 10 (9.4%) children requiring a single operation each. 5 (4.7%) children underwent permanent stoma formation following pull-through procedure, 2 (50.0%) of whom required further revision of stoma. 2 (1.9%) children had a stoma formed due to enterocolitis which was subsequently closed. 1 (0.9%) child required a post pull-through stoma which was later closed but who then required a permanent stoma.

4 (4.3%) children had an appendicocaecostomy (ACE) to permit antegrade colonic enemas after their pull-through surgery. 1 (1.1%) child subsequently required a caecostomy due to appendix perforation. 1 (1.1%) child underwent stoma formation and then an ACE

procedure and 1 child underwent primary caecostomy formation. The remaining 2 (2.1%) children underwent emergency exploratory laparotomies either due to obstruction caused by adhesions or due to sepsis.

4 (3.8%) children had a permanent stoma formed (colostomy n=2; ileostomy n=2) as primary treatment because their underlying condition precluded attainment of faecal continence. The 2 children who underwent additional surgery prior to a pull-through procedure both needed refashioning of their stoma either due to wound reopening or herniation of omentum.

3.4.1.4. Permanent stoma

In total 16 (15.1%) children required the formation of a permanent stoma, with 3 (18.8%) children having undergone a subtotal colectomy and 4 (25.0%) children having had a permanent stoma formed as their initial management. This gives a permanent stoma rate of 15.1% in this HSCR cohort.

9 (9.6%) children required permanent stoma formation after their pull-through procedure, due to faecal incontinence in 6 (66.6%) children, recurrent HAEC in 2 (22.2%) children and development of an anal stricture in 1 (11.1%) children. 3 of these children (33.3%) required refashioning of their stoma, either due to perforation or prolapse of the stoma.

3.4.1.5. Hirschsprung-associated enterocolitis

Based on patient hospital records from prior to their pull-through procedure, 20.8% of all children with HSCR had at least one episode of HAEC (n=22), with 1/22 (4.5%) of these children having 3 episodes of HAEC prior to their pull-through and the remaining 21 (95.5%) children having 1 episode each. Figure 3.2 shows the percentages of children who had at least one episode of HAEC at each time point.

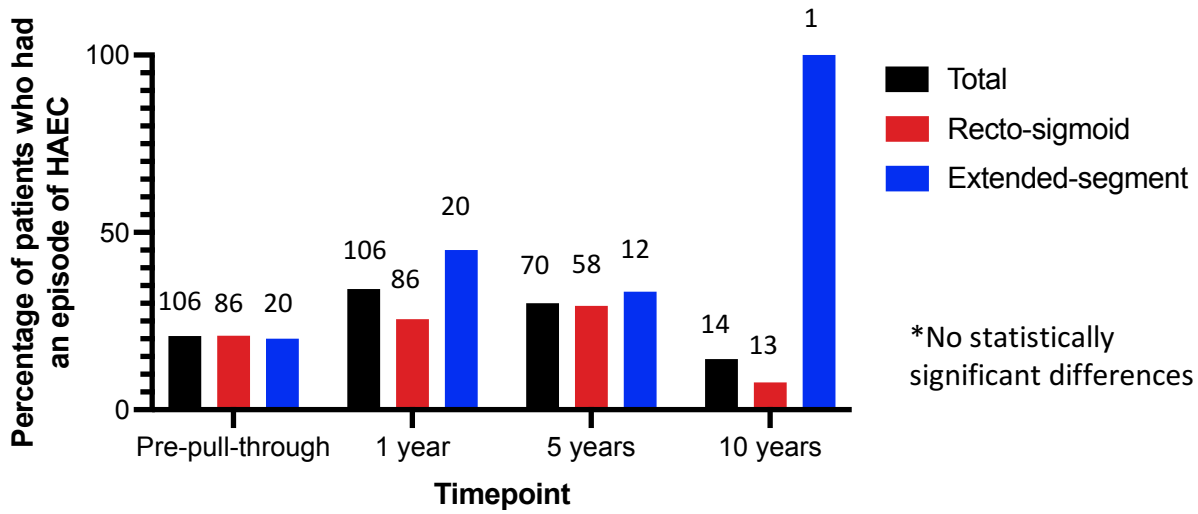


Figure 3.2. The percentages of each age group who have had at least one episode of HAEC since previous data-collection point.

The numbers above each bar represent the total number of patients in each category.

Clinician reported incidences of HAEC at follow-up at 1 year of age were reported as 34.0% of all children with HSCR (n=36) after having surgical management, either pull-through procedure or stoma formation. 25/36 (69.4%) of these children had one episode of HAEC, 9/36 (25.0%) had two episodes, and 2/36 (5.6%) had three episodes of HAEC since surgery. At 5 years of age, 21/70 (30.0%) children had developed HAEC at least once since follow up at 1 year of age. 14/21 (66.7%) of these children had one episode of HAEC, 5/21 (23.8%) had two episodes, 1/21 (4.8%) had three episodes and 1/21 (4.8%) had four episodes of HAEC over the previous four years. At follow up at 10 years of age, 2/14 (14.3%) children had developed one episode of HAEC since follow-up at 5 years of age, with both children having just one episode of HAEC in this time frame. When comparing the HAEC rates across the different age groups, the differences were not statistically significant (p=0.31).

3.4.1.6. Voluntary bowel movements

3.4.1.6.1. Bowel management

In the cohort assessing outcomes at 1 year of age, 69 out of all 106 (65.1%) children in this cohort were able to have voluntary bowel movements with no assistance with 67 of these 69 (97.1%) children having undergone a pull-through procedure. As 13 of the 106 (12.3%)

children had a stoma at 1 year of age, 69 out of the 93 (74.2%) children without a stoma were able to have voluntary bowel movements with no assistance. Figure 3.3 describes the full list of bowel management strategies used.

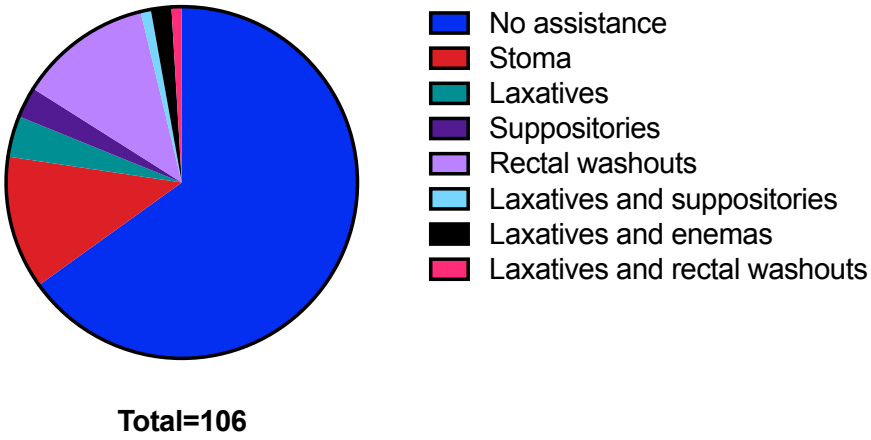


Figure 3.3. A pie chart showing the proportions of children using different bowel management strategies at 1 year

At 5 years of age, 41 out of 70 (58.6%) children required no assistance for bowel movements, with all children who required no assistance having undergone a pull-through procedure. As 12 (17.1%) children in this cohort had a stoma at 5 years of age, 41 out of the 58 (70.7%) children without a stoma were able to have voluntary bowel movements with no assistance. A full list of the bowel management strategies used at 5 years of age is shown in Figure 3.4.

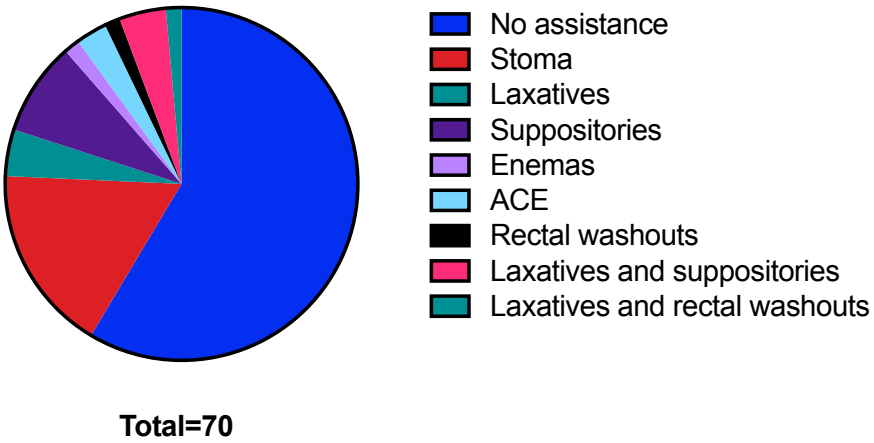


Figure 3.4. A pie chart showing the proportions of children using different bowel management strategies at 5 years

At 10 years old, 4 out of the 14 (28.6%) children in the 10 year HSCR patient cohort required no assistance for bowel management, with all 4 of these children having undergone a pull-through procedure. When comparing the number of children that were able to have voluntary bowel movements in the different age groups, a statistically significant difference was found ($p<0.05$). As 2 (14.3%) of the children at age 10 years had a stoma, 4 out of the 12 (33.3%) children without a stoma were able to have voluntary bowel movements with no assistance. The full list of bowel management strategies used by children at 10 years of age is shown in Figure 3.5.

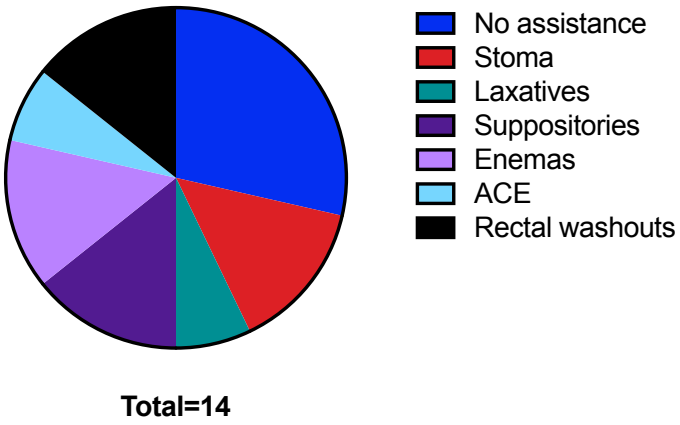


Figure 3.5. A pie chart showing the proportions of children using different bowel management strategies at 10 years

3.4.2.3.1. Continence

In the 5 year cohort, 37/70 (52.9%) children reported soiling, with 36 (97.3%) of these having undergone a pull-through procedure prior to this time point. As 12 (17.1%) children had a stoma at 5 years of age, 37 out of the 58 (63.8%) children who do not have a stoma reported soiling.

5 (35.7%) children reported soiling at 10 years of age, with all of these children having previously undergone a pull-through procedure. As 2 (14.3%) children had a stoma at 10 years of age, 5 out of the 12 (41.7%) children without a stoma reported soiling. Table 3.10

shows a comparison of bowel function clinician reported outcomes across different age groups.

	1 year	5 years	10 years	P value
Proportion of patients requiring no assistance, n (%)	69 (65.1)	41 (58.6)	4 (28.6)	<0.05*
Proportion of patients soiling, n (%)	N/A	37 (52.9)	5 (35.7)	0.38

Table 3.10. Comparison of clinician reported bowel outcomes in each age group.
*Statistically significant value

3.4.2.4. Urinary continence

At 5 years of age, 52 (74.3%) children reported daytime urinary continence out of the 70 in the 5 year patient cohort, in comparison to the 10 year cohort, in which only 9 (64.3%) children reported daytime urinary continence (OR 1.61 [0.52-4.98], p=0.52). For night time urinary continence, 47 (67.1%) children in the 5 year age group reported this, which was similar to the night time urinary continence rate (64.3%) in the 10 year cohort (OR 1.14 [0.38-3.98], p>0.99).

3.4.2.5. Non-COS outcomes

3.4.2.5.1. Early post-operative complications

In the cohort of children with HSCR who had undergone a pull-through procedure (n=94), no anastomotic leaks were reported in patient's clinical records and 3 (3.2%) children developed a pelvic abscess early after their pull-through procedures. 2/3 (66.7%) of these children had short-segment HSCR and the other had long-segment HSCR, with all 3 children undergoing a Soave pull-through procedure.

14 (14.9%) children developed other forms of early post-operative complications, with 3 (3.2%) children developing HAEC in the early post-operative period and 2 (2.1%) children developing a post-operative ileus. 2 (2.1%) children were admitted to the high dependency

unit as they required oxygen and 2 (2.1%) children developed surgical wound dehiscence due to wound infection. The remaining early post-operative complications developed by children included bleeding from the mucous fistula, low haemoglobin requiring a blood transfusion, vomiting requiring a nasogastric tube, reduced feeds leading to admission to hospital and perineal breakdown requiring ileostomy formation.

3.4.2.5.2. Bowel sensation

Due to the age of children at 1 year follow-up, bowel sensation was only collected from the 5 and 10 year follow-up notes. At 5 year of age, 42/70 (60.0%) children in the 5 year HSCR cohort reported an ability to feel when they need to open their bowels, with 39/63 (61.9%) children who had previously undergone a pull-through procedure being able to feel bowel movements.

At 10 year follow-up, 8/14 (57.1%) children in the 10 year cohort were able to feel when they needed to open their bowels, with 7/13 (53.8%) children who had previously undergone a pull-through procedure being able to feel bowel movements. Table 3.11 shows the number of HSCR children with bowel sensation in each age group.

3.4.2.5.3. Constipation

At follow up at 1 year, 15 out of 106 (14.2%) children had some form of constipation and as 13 (12.3%) of these children had a stoma at 1 year of age, 15 out of 93 (16.1%) children without a stoma had constipation.

In the 5 year HSCR cohort was 15 out of 70 (21.4%) of children reported constipation and, as 12 of these children had a stoma at 5 years of age, 15 out of the 58 (25.9%) children without a stoma reported constipation.

5 out of 14 (35.7%) children reported constipation at 10 years of age and, as 2 (14.3%) children had a stoma at 10 years of age, 5 out of the 12 (41.7%) children without a stoma reported constipation. Table 3.11 shows the number of HSCR children with constipation in each age group

	1 year	5 years	10 years	P value
Proportion of patients able to feel bowel movements n (%)	N/A	42 (60.0)	8 (57.1)	>0.99
Proportion of patients with constipation, n (%)	15 (14.2)	15 (21.4)	5 (35.7)	0.11

Table 3.11. Comparison of bowel sensation and constipation rates in each age group.

3.4.3. Clinician reported outcomes – HSCR phenotype

3.4.3.1. Patient characteristics according to HSCR phenotype

Out of the 106 HSCR children in this cohort, 86 (81.1%) had recto-sigmoid HSCR, which includes short-segment and ultra-short segment HSCR, and 20 (18.9%) had extended-segment HSCR, which includes long-segment, total colonic and total intestinal HSCR. Table 3.12 shows the characteristics of this cohort according to HSCR phenotype.

Characteristic	Recto-sigmoid (n=86)	Extended-segment (n=20)
Age in months, median (IQR)	67 (37.5-94.75)	63 (40-99)
Sex		
Male	68 (79.1)	14 (70.0)
Female	18 (20.9)	6 (30.0)
Primary stoma formation	34 (39.5)	17 (85.0)
Definitive procedure		
Pull-through procedure • Soave • Swenson	79 (91.9) • 56 (65.1) • 23 (26.7)	15 (75.0) • 11 (55.0) • 4 (20.0)
Subtotal colectomy	0 (0)	3 (15.0)
Permanent stoma formation as initial management	2 (2.3)	2 (10.0)
No surgical management	5 (5.8)	0 (0)

Table 3.12. Patient characteristics according to HSCR phenotype

All results in Table 3.12 are reported as number of children and percentages unless stated otherwise, n (%).

3.4.3.2. Unplanned reoperation

When comparing the number of children requiring additional surgical management between different HSCR phenotypes, 17 out of the 86 (19.8%) children with recto-sigmoid HSCR, and 5 out of the 20 (25%) children with extended-segment HSCR needed additional surgical management (OR 0.74 [0.26-2.06], p=0.56).

3.4.3.3. Permanent stoma

When comparing HSCR phenotypes, 10 out of the 86 (11.6%) children with recto-sigmoid HSCR and 6 out of the 20 (30.0%) children with extended-segment disease required permanent stoma formation (OR 0.31 [0.09-1.06], p=0.08).

3.4.3.4. Hirschsprung-associated enterocolitis

A comparison between the different HSCR phenotypes according to the HAEC rates is shown in Table 3.13.

	Recto-sigmoid (n=86)	Extended-segment (n=20)	Odds Ratio [95% CI]	P value
Pre-surgery, n (%)	18 (20.9)	4 (20.0)	1.06 [0.34-3.20]	>0.99
1 year, n (%)	27 (25.5)	9 (45.0)	0.56 [0.20-1.46]	0.30
5 years, n (%)	17 (29.3)*	4 (33.3)*	0.83 [0.23-2.75]	0.74
10 years, n (%)	<4	<4	0.00 [0.00-1.39]	0.13

Table 3.13. Number of children who have had at least one episode of HAEC at different time points.

*As the number of children changed in the 5 and 10 year cohort, percentages are out of the number of children in these time points and not the overall number.

3.4.3.5. Voluntary bowel movements

3.4.3.5.1. Bowel management

When comparing the different phenotypes of HSCR at 1 year of age, 56 out of the 86 (65.1%) children with recto-sigmoid disease were not using any assistance with bowel movements in comparison with 11 out of the 20 (55.0%) children with extended-segment disease (OR 1.53 [0.59-4.27], p=0.45). When comparing the different phenotypes of these children with HSCR at 5 years, 34 out of the 58 (58.6%) children with recto-sigmoid disease required no assistance for bowel movements in comparison to 7 out of the 12 (58.3%) children with extended-segment HSCR (OR 1.01 [0.31-3.51], p>0.99). At 10 years, 4 out of the 13 (30.8%) children with recto-sigmoid disease and 0 (0%) children with extended-segment disease required no assistance for bowel movements.

3.4.3.5.2. Continence

When comparing the HSCR phenotypes and their soiling rates at 5 years of age, 32 out of 58 (55.2%) children with recto-sigmoid disease and 5 out of 12 (41.7%) children with extended-segment HSCR reported some form of soiling, varying between occasional and constant

soiling (OR 1.72 [0.50-5.55], p=0.53). When looking at the HSCR phenotypes at 10 years, 4 out of the 13 (30.8%) children with recto-sigmoid disease reported soiling and the only (100%) child with extended-segment disease also reported soiling (OR 0.00 [0.00-5.00], p=0.36).

3.4.3.6. Urinary continence

Table 3.14 shows the proportion of children in each cohort that are continent for urine separated into HSCR phenotypes.

	5 years			10 years		
	Recto-sigmoid disease (n=58)	Extended-segment HSCR (n=12)	Odds ratio [95% CI] and P value	Recto-sigmoid disease (n=13)	Extended-segment HSCR (n=1)	Odds ratio [95% CI] and P value
Daytime urinary continence, n (%)	41 (70.7)	11 (91.6)	OR 2.63 [0.93-6.66], p=0.07	8 (61.5)	<4	OR 1.60 [0.07-33.75], p>0.99
Night time urinary continence n (%)	39 (67.2)	8 (66.7)	OR 1.02 [0.31-3.62], p>0.99	8 (61.5)	<4	OR 1.60 [0.07-33.75], p>0.99

Table 3.14. Proportion of children in each cohort with urinary continence

3.4.3.7. Non-COS outcomes

3.4.3.7.1. Early post-operative complications

In total, 12/86 (14.0%) children with recto-sigmoid HSCR and 5/20 (25.0%) children with extended-segment disease had early post-operative complications (OR 0.49 [0.15-1.43], p=0.31).

3.4.3.7.2. Bowel sensation

When comparing those with different HSCR phenotypes at 5 years of age, 35/58 (60.3%) children with recto-sigmoid disease and 7/12 (58.3%) children with extended-segment HSCR were able to feel bowel movements (OR 1.09 [0.33-3.79], p>0.99). All 8 children who could feel when they needed a bowel movements at 10 years of age had recto-sigmoid disease (61.5%), with the only child with extended-segment disease in the 10 year cohort not being able to feel when they needed to have a bowel movement (p=0.43).

3.4.3.7.3. Constipation

When comparing HSCR phenotypes at 1 year of age, 14 (16.3%) children with recto-sigmoid disease had constipation, in comparison to 1 (5.0%) child with extended-sigmoid disease (OR 3.69 [0.60-41.10], p=0.29). When comparing the different phenotypes of HSCR at 5 years, 12 out of the 58 (20.7%) children with recto-sigmoid disease and 3 out of the 12 (25.0%) children with extended-segment disease reported constipation (OR 0.78 [0.19-3.03], p=0.71). Of the 5 (35.7%) children who reported constipation at 10 years of age, all 5 (100%) children had recto-sigmoid disease.

3.4.4. Clinician reported outcomes – HSCR operative approach

3.4.4.1. Patient characteristics according to intervention

Table 3.15 shows the patients characteristics of the HSCR cohort according to the pull-through operative approach they underwent.

	Soave (n=67)	Swenson (n=27)
Age in months, median (IQR)	80 (51-102)	51 (35-62)
Sex		
Male	55 (82.1)	21 (77.8)
Female	12 (17.9)	6 (22.2)
Phenotype		
Short segment HSCR	53 (79.1)	21 (77.8)
Long segment HSCR	11 (16.4)	4 (14.8)
Ultra-short HSCR	3 (4.5)	2 (7.4)
Total colonic HSCR	0 (0)	0 (0)
Total intestinal HSCR	0 (0)	0 (0)
Additional syndromes		
Trisomy 21	6 (9.0)	2 (7.4)
Additional chromosomal abnormalities	1 (1.5)	2 (7.4)
Primary stoma formation	30 (44.8)	12 (44.4)

Table 3.15. Patient characteristics according to operative approach

All results in Table 3.15 are reported as number of children and percentages unless stated otherwise, n (%).

3.4.4.2. Unplanned reoperation

When comparing operative approaches, 7 out of the 27 (25.9%) children who underwent a Swenson pull-through required further surgical management in comparison to 11 out of the 67 (16.4%) children who underwent a Soave pull-through, shown in Table 3.16.

3.4.4.3. Permanent stoma

No significant difference was seen in the number of children requiring unplanned surgery, a permanent stoma or ACE between children undergoing a Soave or Swenson procedure (Table 3.16).

	Soave (n=67)	Swenson (n=27)	Odds Ratio	P value
Children requiring additional surgical procedures after pull-through, n (%)	11 (16.4)	7 (25.9)	0.5612 [0.20-1.52]	0.38
Children requiring a permanent stoma after pull-through, n (%)	5 (7.5)	4 (14.8)	0.4637 [0.12-1.63]	0.27
Children requiring an ACE procedure, n (%)	5 (7.5)	<4	2.097 [0.26-25.56]	0.67

Table 3.16. Comparison of pull-through operative approaches for additional operations and permanent stoma formation.

3.4.4.4. Voluntary bowel movements

3.4.4.4.1. Bowel management

At 1 year of age, 14/64 (21.9%) children who had undergone a Soave procedure and 7/24 (29.2%) children who had undergone a Swenson pull-through before this time point required no assistance for bowel movements. Of the 50 children, in the 5 year HSCR cohort, who had undergone a Soave pull-through procedure, 15 (30.0%) of these required bowel management, in comparison with 7 out of the 13 (53.8%) children who had undergone a Swenson pull-through. Of the 14 children in the 10 year cohort, 13 (100%) had undergone a pull-through procedure, with all of these being the Soave technique. Therefore 4 out of 13 (30.8%) children having the Soave pull-through required no assistance with bowel movements. This comparison of operative techniques is shown in Table 3.17.

	Soave	Swenson	Odds Ratio [95% CI]	P value
Requiring bowel management at 1 year, n (%)	14 (21.9)	7 (29.2)	0.68 [0.25-1.81]	0.58
Requiring bowel management at 5 years, n (%)	15 (30.0)	7 (53.8)	0.37 [0.11-1.28]	0.19
Requiring bowel management at 10 years, n (%)	4 (30.8)	0 (0)	N/A	N/A

Table 3.17. The number of children requiring no bowel management according to operative technique and age.

3.4.4.4.2. Continence

In the 5 year cohort, of those who had undergone a Soave pull-through procedure, 30 (60.0%) children reported soiling, in comparison is 6 out of the 13 (46.2%) children who had undergone a Swenson pull-through (OR 1.75 [0.52-5.86], p=0.53). All 5 of children who reported soiling in the 10 year cohort had undergone a Soave pull-through procedure, giving a 38.5% rate of soiling at 10 years after a Soave pull-through.

3.4.4.5. Urinary continence

At 5 years of age, 37/50 (74.0%) children who had previously undergone a Soave pull-through procedure and 9/13 (69.2%) children who had previously undergone a Swenson pull-through procedure reported daytime urinary continence (OR 1.27 [0.38-4.55], p=0.74). 34/50 (68.0%) children who had undergone a Soave pull-through and 7/13 (53.8%) children who had undergone a Swenson pull-through reported night time urinary continence (OR 1.82 [0.52-6.31], p=0.35).

3.4.4.6. Non-COS outcomes

3.4.4.6.1. Early post-operative complications

When comparing the early post-operative complications in the Soave and Swenson approaches, 13 out of the 67 (19.4%) children who underwent a Soave pull-through and 4 out of the 27 (14.8%) children who underwent a Swenson pull-through in this cohort had early post-operative complications reported in clinical notes (OR 1.38 [0.43-4.21], p=0.77).

3.4.4.6.2. Bowel sensation

33/50 (66.0%) children who had undergone a Soave pull-through by 5 years of age were able to feel when they needed a bowel movement, in comparison to 6/13 (46.2%) children who had undergone a Swenson pull-through (OR 2.27 [0.66-7.43], p=0.21). At 10 years, out of all 13 the children who had undergone a Soave pull-through, 7 (53.8%) were able to feel when to open their bowels.

3.4.4.6.3. Constipation

Of the 15 children reporting constipation at 1 year, 7 (46.7%) had not undergone a pull-through procedure, 5 (33.3%) had undergone a Soave pull-through and the remaining 3 (20.0%) had undergone a Swenson pull-through. Therefore, the constipation rate after a Soave pull-through at 1 year was 7.8%, and 12.5% after a Swenson pull-through (OR 0.59 [0.14-2.41], p=0.68). Of the 63 patients who had undergone a pull-through procedure, 12 (19.0%) reported constipation at 5 years of age, with 11 (22%) children who had undergone a Soave procedure and 1 (7.7%) child who had undergone a Swenson procedure reporting constipation (OR 3.39 [0.44-39.27], p=0.43). Of the 5 (35.7%) children reporting constipation at 10 years of age, all 5 (100%) had previously undergone a Soave pull-through procedure.

3.4.5. Patient reported outcomes – Overall HSCR cohort

106 children were deemed eligible for inclusion in this study and were contacted via post with a consent form for the study. Of these consent forms sent out, 44 (41.5%) consent forms were returned signed by parents and out of these 44 children, 24 returned the questionnaires. The postal response rate for the HSCR cohort was therefore 22.6%. 1 child

returned some of the questionnaires with very limited data on and therefore was excluded from this study, leaving 23 (21.7%) children.

3.4.5.1. Patient characteristics

As children in the 1 year cohort did not complete a bowel function or quality of life questionnaires, these children have been separated into a different group from the 5 and 10 year old cohorts. For the 1 year cohort, the median age was 7 months (IQR 7-21, range 6-35), with 7 male children (77.8%) and 2 female children (22.2%). 7 (77.8%) children had recto-sigmoid disease and the remaining 2 (22.2%) children had extended-segment HSCR. 1 (11.1%) child had Trisomy 21, and another 2 (22.2%) children had additional syndromes alongside HSCR. 1 (11.1%) child had a family history of HSCR, with an affected brother, and 7 (77.8%) children had undergone a pull-through procedure. Table 3.18 shows the full list of characteristics for the 1 year HSCR cohort for patient reported outcomes.

All patients in the 5 and 10 year cohorts completed a bowel function and quality of life questionnaires and therefore these cohorts were grouped together to look at patient characteristics. The median age of these patients was 72 months (IQR 65-96, range 38-118), and out of the 14 patients, 11 were male (78.6%) and 3 were female (21.4%). 12 patients had recto-sigmoid disease (85.7%), and 2 patients had extended-segment HSCR (14.3%). 1 patient had Trisomy 21 (7.1%) and no patients had other neurological problems. 2 patients had a family history of HSCR (14.3%), one having immediate family with HSCR, and the other with more distant relatives. 13 out of the 14 (92.9%) children had undergone a pull-through procedure, with the remaining patient having undergone a subtotal colectomy (7.1%) due to total intestinal aganglionosis. Table 3.18 shows the patient characteristics of the 5 and 10 year cohort for patient reported outcomes.

	1 year (n=9)	5 and 10 years (n=14)
Median age in months (IQR)	7 (7-21)	72 (65-96)
Male (%)	7 (77.8)	11 (78.6)
Phenotype		
Short-segment HSCR	7 (77.8)	12 (85.7)
Long-segment HSCR	1 (11.1)	1 (7.1)
Total colonic HSCR	1 (11.1)	0 (0)
Total intestinal HSCR	0 (0)	1 (7.1)
Additional syndromes		
Trisomy 21	1 (11.1)	1 (7.1)
Shah Waardenburg syndrome	1 (11.1)	0 (0)
Chromosome 22 abnormality (non Di George syndrome)	1 (11.1)	0 (0)
Family History	1 (11.1)	2 (14.3)
Ethnicity		
White: British, Irish, European	7 (77.8)	13 (92.8)
Asian: British, Indian, Pakistani	1 (11.1)	1 (7.1)
Mixed race: White/Afro Caribbean	1 (11.1)	0 (0)
Definitive surgery		
Pull-through procedure • Soave • Swenson	7 (77.8) • 4 (57.1) • 3 (42.9)	13 (92.9) • 10 (76.9) • 3 (23.1)
Subtotal colectomy	0 (0)	1 (7.1)
Permanent stoma formation as initial management	1 (11.1)	0 (0)

	1 year (n=9)	5 and 10 years (n=14)
Not surgery yet as awaiting pull-through	1 (11.1)	0 (0)
Pull-through operative approach		
Laparoscopic-assisted	4 (57.1)	6 (46.2)
Open	3 (42.9)	7 (53.8)

Table 3.18. HSCR patient characteristics according to age

All results in Table 3.18 are reported as number of children and percentages unless stated otherwise, n (%).

3.4.5.2. Bowel function score

The mean (SD) incontinence score in the HSCR cohort was 16.14 (5.92) and the mean (SD) constipation score was 19.18 (4.60). 13 children's scores met the criteria for impaired continence (92.9%) and 8 children's scores met the criteria for constipation (57.1%), with 7 children meeting the criteria for both impaired continence and constipation (50.0%).

3.4.5.3. Quality of life

Of the 14 children who returned the questionnaires, all 14 (100%) children returned the PedsQL child form and 11 (78.6%) children returned the PedsQL parent report. Therefore, child reported PedsQL total scale scores and psychosocial health scores were calculable for all 14 (100%) children and parent reported scores were calculable in 11 (78.6%) children. The mean (SD) parent reported total score was 75.40 (17.50) which was not statistically significantly lower (p=0.77) than the mean (SD) parent reported total score of 80.87 (16.73) from the reference population (359), and the mean (SD) parent reported psychosocial score was 74.32 (18.17) which was also not significantly lower (p=0.75) than the mean (SD) parent reported psychosocial health score of 80.58 (16.52) from the same reference population. The mean (SD) child reported total score was 78.01 (16.61) which was not significantly lower (p=0.93) than the mean (SD) child reported total score of 79.62 (15.26) from the reference population, and the mean (SD) child reported psychosocial score was 74.41 (17.98) which was not significantly lower (p=0.79) than the mean (SD) child reported psychosocial score of

79.37 (15.70) from the reference population (359). Figure 3.6 shows the PedsQL scores for the overall cohort.

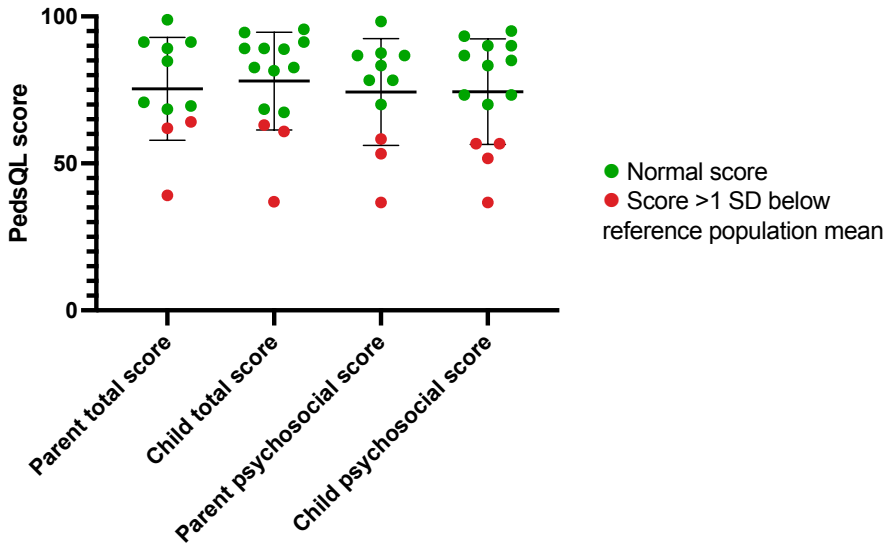


Figure 3.6. The PedsQL scores for the overall HSCR cohort.

Of the 11 children with parent reported scores, 3 (27.3%) children had a total score, and 3 (27.3%) children had a psychosocial score that was more than 1 SD below the reference population mean. Of the 14 children with child reported scores, 3 (21.4%) children had a total score, and 4 (28.6%) children had a psychosocial score that was more than 1 SD below the reference population mean (359). Table 3.19 shows the quality of life scores for the total cohort.

	Parent reported quality of life (n=11)	Child reported quality of life (n=14)
PedsQL total score, mean (SD)	75.40 (17.50)	78.01 (16.61)
Total score >1 SD lower than the reference population mean, n (%)	3 (27.3)	3 (21.4)
PedsQL psychosocial score, mean (SD)	74.32 (18.17)	74.41 (17.98)
Psychosocial score >1 SD lower than the reference population mean, n (%)	3 (27.3)	4 (28.6)

Table 3.19. PedsQL scores for the total HSCR cohort.

3.4.6. Patient reported outcomes – HSCR phenotype

3.4.6.1. Patient characteristics according to HSCR phenotype

Out of the 14 children with HSCR who returned the questionnaires, 12 (85.7%) had recto-sigmoid HSCR and the remaining 2 (14.3%) had extended-segment HSCR. Table 3.20 shows the patient characteristics of this cohort according to HSCR phenotype.

	Recto-sigmoid (n=12)	Extended-segment (n=2)
Age in months, median (IQR)	77 (66-99)	53 (38-68)
Male	10 (83.3)	1 (50.0)
Primary stoma formation	5 (41.7)	2 (100)
Definitive surgery		
Pull-through procedure • Soave • Swenson	12 (100) • 9 (75.0) • 3 (25.0)	1 (50.0) • 1 (100) • 0 (0)
Subtotal colectomy	0 (0)	1 (50.0)

Table 3.20. Patient characteristics according to HSCR phenotype.

3.4.6.2. Bowel function score

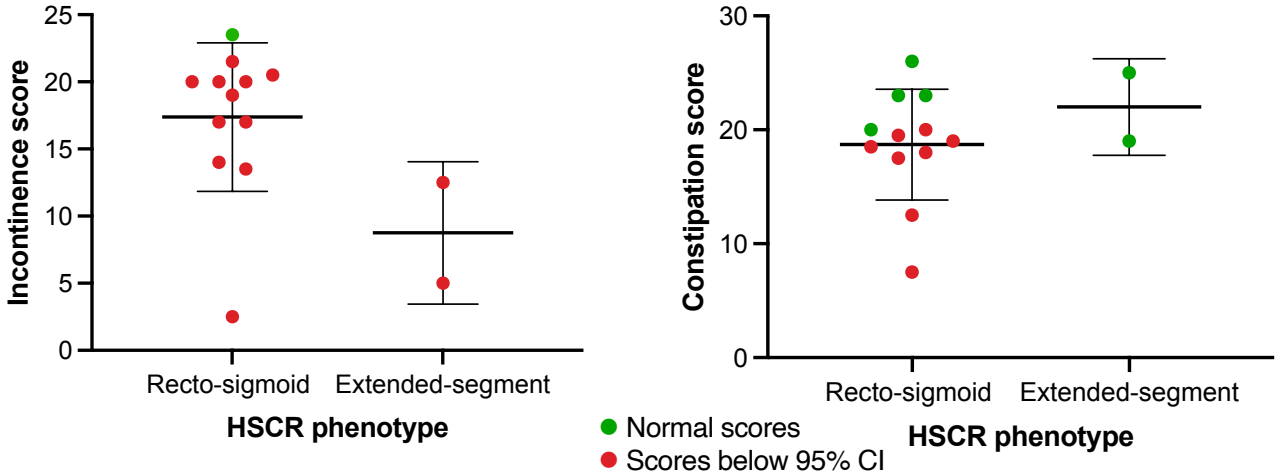
Table 3.21 shows the bowel function scores for this cohort according to HSCR phenotype.

	Recto-sigmoid (n=12)	Extended-segment (n=2)	P value*
Impaired continence, n (%)	11 (91.7)	2 (100)	
Incontinence score, mean (SD)	17.38 (5.29)	8.75 (3.75)	0.06
Constipation, n (%)	8 (66.7)	0 (0)	
Constipation score, mean (SD)	18.71 (4.66	22 (3.0)	0.39

Table 3.21. The bowel function scores of the HSCR cohort according to HSCR phenotype.

*t-test (recto-sigmoid vs extended segment)

Of the 14 children in this HSCR cohort, 12 (85.7%) had recto-sigmoid disease and 2 (14.3%) had extended-segment HSCR. Both children with extended-segment disease met the scoring criteria for impaired continence (100%), however neither met the criteria for constipation. Of the 12 children with recto-sigmoid disease, 11 (91.7%) met the criteria for impaired continence and 8 (66.7%) met the criteria for constipation. Figures 3.7 and 3.8 show the incontinence and constipation scores according to HSCR phenotype.



Figures 3.7 and 3.8. The incontinence and constipation PICS scores according to HSCR phenotype.

3.4.6.3. Quality of life

When comparing the quality of life scores of children with different HSCR phenotypes, there were no significant differences between the scores. Table 3.22 shows the quality of life scores of the HSCR cohort according to HSCR phenotype.

	Recto-sigmoid (n=12)	Extended-segment (n=2)	P value[a]
Child reported quality of life			
PedsQL total score, mean (SD)	80.14 (17.05)	65.21 (2.18)	0.25
Total score >1 SD lower than the reference population mean, n (%)	2 (18.2)	1 (50.0)	
PedsQL psychosocial score, mean (SD)	76.25 (18.65)	63.34 (6.67)	0.37
Psychosocial score >1 SD lower than the reference population mean, n (%)	3 (27.3)	1 (50.0)	
Parent reported quality of life			
PedsQL total score, mean (SD)	77.43 (18.87)	66.31 (2.18)	0.44
Total score >1 SD lower than the reference population mean, n (%)	2 (22.2)*	1 (50.0)	
PedsQL psychosocial score, mean (SD)	75.65 (19.41)	68.33 (10.0)	0.58
Psychosocial score >1 SD lower than the reference population mean, n (%)	2 (22.2)*	1 (50.0)	

Table 3.22. PedsQL scores according to HSCR phenotype

*Percentage of those with a parent reported quality of life questionnaire returned.

[a] t test (recto-sigmoid vs extended-segment)

3.5. Results – ARM cohort

3.5.1. Patient inclusion in study

A total of 206 children with an ARM were identified from the databases and from clinic visits. 19 (9.2%) children were excluded due to having either their initial primary treatment or majority of their follow-up at another centre, 18 (8.7%) children were excluded due to insufficient hospital notes for inclusion in this study, 9 (4.4%) were excluded as they did not undergo surgery for their ARM, 19 (9.2%) children were excluded as they had died and 1 (0.5%) child did not have an ARM but had a urethro-vaginal fistula instead. This left a total of 140 (68.0%)eligible children for clinician reported outcomes to be collected from. Figure 3.9 shows a flow chart of ARM children included in this study.

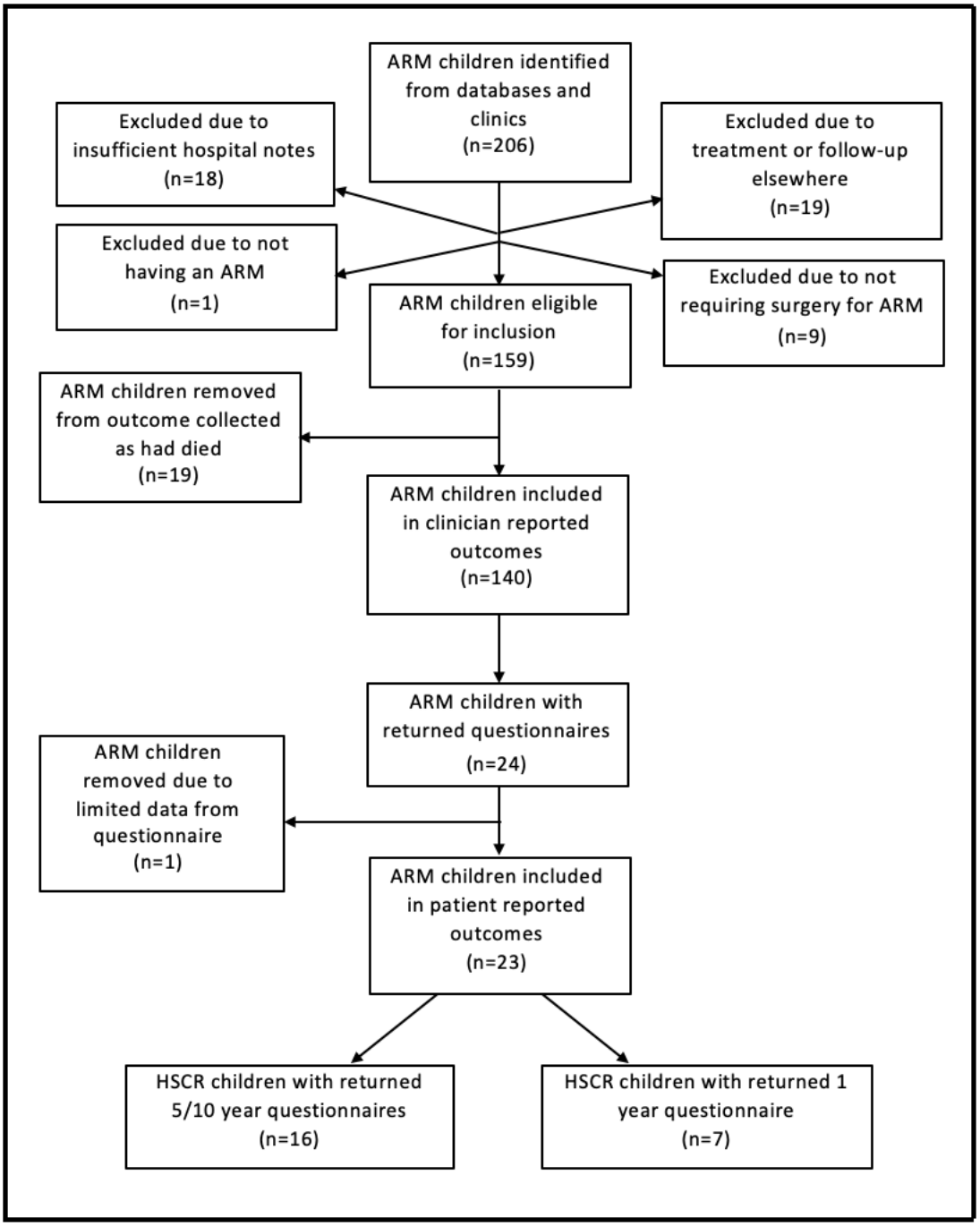


Figure 3.9. A flow chart of ARM children included in this study

3.5.2. Clinician reported outcomes – Overall ARM cohort

3.5.2.1. Patient characteristics

The median age of these 140 children in the ARM cohort was 68.5 months (IQR 33.5-91.5, range 6-122), with 84 (59.6%) children being male. Patients were classified as having either a low, intermediate or high ARM, with 56 (40.0%) children having a low ARM, 50 (35.7%)

children having an intermediate ARM and 34 (24.3%) children having a high ARM. 97 children had at least one additional medical problem associated with VACTERL, 103 (73.6%) children underwent primary stoma formation and 134 (95.7%) children underwent anal reconstruction. Table 3.23 shows the full list of patient characteristics in this cohort, including anal reconstruction operative approach and additional medical problems, such as VACTERL association.

Characteristic	Value n=140 (%)
Median age in months at beginning of data collection (IQR)	68.5 (33.5-91.5)
Male	84 (59.6)
ARM classification	
Low	56 (40.0)
Anal stenosis	6 (4.3)
Recto-perineal fistula	50 (35.7)
Intermediate	50 (35.7)
Rectal atresia with no fistula	16 (11.4)
Recto-bulbar fistula	13 (9.3)
Recto-vestibular fistula	21 (15.0)
High	34 (24.3)
Cloaca	6 (4.3)
Recto-vaginal fistula	1 (0.7)
Recto-prostatic fistula	19 (13.6)
Recto-bladder neck fistula	8 (5.7)
VACTERL associated problem	97 (69.3)
Trisomy 21	2 (1.4)
Vertebral anomalies	11 (7.9)
Sacral agenesis	4 (2.9)
Cord tethering	31 (22.1)
Renal anomaly	50 (35.7)

Characteristic	Value n=140 (%)
Cardiac anomaly	63 (45.0)
Tracheo-oesophageal fistula	20 (14.3)
Limb anomalies	11 (7.9)
Additional neurological problems/syndromes	13 (9.3)
Primary stoma formation	103 (73.6)
Level of stoma formation	
Descending colostomy	96 (93.2)
Other type of colostomy, including transverse colostomy and ileostomy	7 (5.0)
Definitive procedure	
Anal reconstruction	134 (95.7)
Permanent stoma formation as initial management	5 (3.6)
Anal reconstruction operative approach	
Posterior sagittal anorectoplasty	74 (55.2)
Transanal proctoplasty	25 (18.7)
Cut-back	7 (5.2)
Laparoscopic assisted anorectoplasty	15 (11.2)
Mini PSARP	5 (3.7)
Other	8 (5.7)

Table 3.23. ARM patient cohort characteristics

All results in Table 3.23 are reported as number of children and percentages unless stated otherwise, n (%).

3.5.2.1.1. Patient characteristics according to age

Similarly to the HSCR cohort, for clinician reported outcomes collected at the specific time points of 1 year, 5 years and 10 years, there were a different number of patient records that these outcomes were able to be collected from due to the ages of children in the cohort. For the 1 year outcome form, outcomes for all children (n=140) could be collected as the whole cohort had hospital patient notes available from when they were within the age range for this outcome form. For the 5 year outcome form, outcome data was able to be

completed for 89 (63.6%) children and for 10 year follow up, 14 (10.0%) children were able to be included in the outcome collection for this age group. Table 3.24 shows the full list of ARM patient characteristics at 5 and 10 years of age.

Characteristic	5 years (n=89)	10 years (n=14)
Median age in months at beginning of data collection (IQR)	86 (70-102.5)	113.5 (106-120)
Male	52 (58.4)	9 (64.3)
ARM classification		
Low	30 (33.7)	4 (28.6)
Intermediate	35 (39.3)	6 (42.9)
High	24 (27.0)	4 (28.6)
VACTERL associated problems	65 (73.0)	12 (85.7)
Trisomy 21	0 (0)	0 (0)
Vertebral anomalies	8 (9.0)	0 (0)
Cord tethering	23 (25.8)	4 (28.6)
Renal anomaly	39 (43.8)	7 (50.0)
Cardiac anomaly	39 (43.8)	8 (57.1)
Tracheo-oesophageal fistula	15 (16.9)	2 (14.3)
Limb anomalies	9 (10.1)	2 (14.3)
Additional neurological problems/syndromes	10 (11.2)	3 (21.4)
Primary stoma formation	66 (74.2)	13 (92.9)
Level of stoma formation		
Descending colostomy	63 (95.5)	13 (100)
Other type of colostomy, including transverse colostomy or ileostomy	3 (4.5)	0 (0)
Definitive procedure		
Anal reconstruction	84 (94.4)*	11 (78.6)
Permanent stoma formation as initial management	5 (5.6)	3 (21.4)

Characteristic	5 years (n=89)	10 years (n=14)
Anal reconstruction operative approach		
PSARP	51 (60.7)	10 (90.9)
TAP	11 (13.1)	0 (0)
Cut-back	5 (6.0)	0 (0)
Laparoscopic anorectoplasty	10 (11.9)	0 (0)
Other	7 (7.9)	1 (9.1)

Table 3.24. ARM patient characteristics at 5 and 10 year follow-up

*One of these children had not undergone anal reconstruction by 5 year follow-up

All results in Table 3.24 are reported as number of children and percentages unless stated otherwise, n (%).

3.5.2.2. Death

The overall mortality rate for ARM children within this cohort was 12.5% (n=20) with 5 (25.0%) children having a high ARM, 10 (50.0%) children having an intermediate ARM and 5 (25.0%) children having a low ARM. The median age of these patients at time of death was 3.5 months (IQR 1-10, range 0-40). 17 (85.0%) children had at least 1 additional medical problem associated with VACTERL, with 12 (60%) children having a cardiac anomaly. 10 (50%) children had undergone stoma formation and 5 (25%) children had undergone an anoplasty before their death. The hospital patient notes for 6 (30.0%) children did not report a cause of death and 4 (20.0%) deaths were due to multiple severe congenital abnormalities. The cause of death in 2 (10.0%) children was congenital heart disease and sepsis in another 2 (10.0%) children. 2 (10.0%) children died unexpectedly after respiratory tract infections, 2 (10.0%) children died due to renal failure. The causes of death in the remaining 2 (10.0%) children were Wilms tumour in one child and respiratory failure due to an undiagnosed neurodegenerative disorder in the other.

3.5.2.3. Unplanned reoperation

In total, 34/140 (24.3%) children in the ARM cohort required further surgical management, either after initial stoma formation or after anal reconstruction. 12 (8.6%) of these children required 2 additional surgeries and 22 (15.7%) required a single additional surgery. 5 (3.6%)

children underwent a re-do anoplasty only, 2 (1.4%) children underwent a re-do anoplasty followed by stoma closure, 2 (1.4%) children underwent a re-do anoplasty followed by ACE formation, 1 (0.7%) child underwent a re-do anoplasty followed by the formation of a permanent stoma, and 1 (0.7%) child underwent stoma formation before having a re-do anoplasty. This therefore means that the anal construction re-operation rate was 7.9% (n=11) in the overall ARM cohort. 8 (5.7%) children required ACE formation only, and 1 child underwent stoma formation prior to ACE formation. 5 (3.6%) children underwent permanent stoma formation only, 3 (2.1%) children underwent stoma formation and then closure of this stoma, and 2 (1.4%) children underwent permanent stoma formation with these children also requiring refashioning of their stoma either due to prolapse or obstruction. The remaining 4 (2.9%) children underwent one of the following surgeries: total cystectomy and hysterectomy, formation of vesicostomy due to recurrent urinary tract sepsis, urethral dilatation and cystourethroscopy, or laparotomy with division of adhesions causing small bowel volvulus.

Of these 34 children who required further surgical management, 1 (0.7%) child did not undergo anal reconstruction and 1 (0.7%) had their additional surgical management prior to anal reconstruction. This means that out of the 134 children who underwent anal reconstruction, 32 (23.9%) required further surgical management after this surgical management.

3.5.2.4. Permanent stoma

In total 14 (10.0%) children in this ARM cohort required permanent stoma formation, with 9 (6.7%) children out of the 134 who underwent anal reconstruction requiring a permanent stoma, either due to constipation in 7 (77.8%) children, additional neurological problems in 1 (11.1%) child, or the inability to anastomose colon after previous stoma formation in 1 (11.1%) child. All 5 children who did not undergo anal reconstruction required a permanent stoma, either due to having a complex high ARM (40%), significant co-morbidities (40%) or anal stenosis (20%).

In total 11 (7.9%) children required ACE formation, either due to constipation or incontinence, with all of these patients having previously undergone anal reconstruction

surgery. When comparing different ARM classification groups, 1/56 (1.8%) children with a low ARM, 4/50 (8.0%) children with an intermediate ARM (8.0%) and 6/34 (17.6%) children with a high ARM required ACE formation for bowel management.

3.5.2.5. Voluntary bowel movements

3.5.2.5.1. Bowel management

By follow up at 1 year of age, 124 (88.6%) children had undergone anal reconstruction. 44 out of the 140 (31.4%) children in this whole cohort were able to have voluntary bowel movements with no assistance, with 43 of these 44 (97.7%) children having undergone anal reconstruction before this time point. 48 (34.3%) children at 1 year of age had a stoma, therefore 44 out of the 92 (47.8%) children without a stoma were able to have voluntary bowel movements with no assistance. Figure 3.10 shows a pie chart demonstrating the bowel management strategies used at 1 year of age.

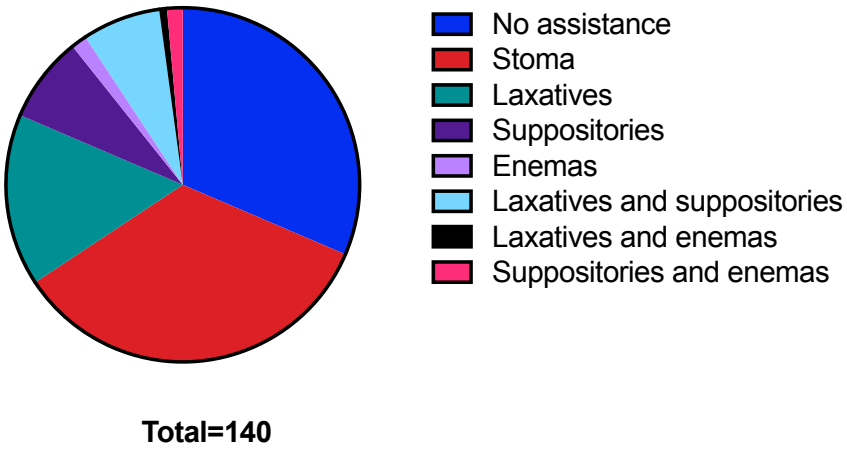


Figure 3.10. A pie chart showing the proportions of children with an ARM using different bowel management strategies at 1 year

By 5 year follow-up, 83/89 (93.3%) had undergone anal reconstruction. 23/89 (25.8%) children followed up at 5 years were able to have voluntary bowel movements with no assistance, with 22 of these 23 (95.7%) children having undergone anal reconstruction by 5 years of age. 21 (23.6%) children had a stoma at 5 years of age, therefore 23 out of the 78 (29.5%) children without a stoma were able to have voluntary bowel movements with no

assistance. A pie chart demonstrating the different bowel management strategies used at 5 years of age is shown in Figure 3.11.

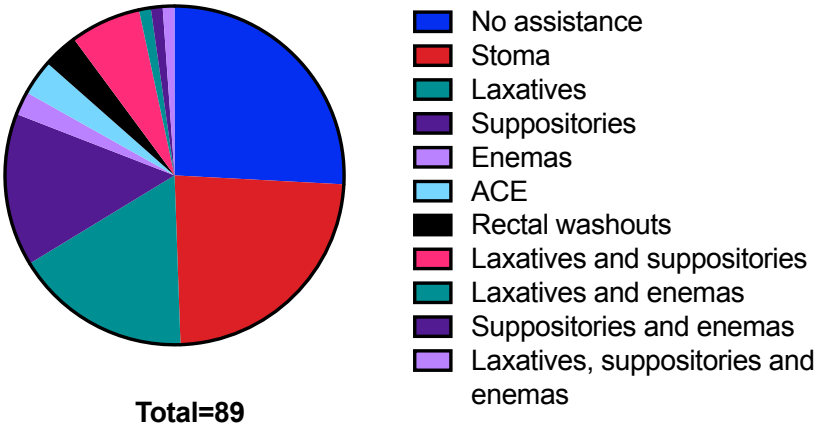


Figure 3.11. A pie chart showing the proportions of children with an ARM using different bowel management strategies at 5 years

By 10 year follow-up, 11/14 (78.6%) children had undergone anal reconstruction. 1/14 (7.1%) children followed up at 10 years were able to have voluntary bowel movements with no assistance, with this patient having an intermediate ARM. As 5 (35.7%) children had a stoma at 10 years of age, 1 out of the 9 (11.1%) children without a stoma were able to have voluntary bowel movements with no assistance. A pie chart demonstrating the bowel management strategies used at 10 years of age is shown in Figure 3.12.

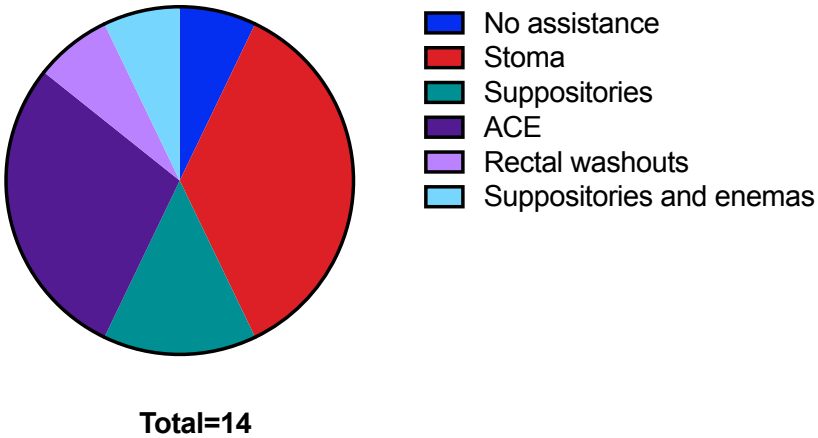


Figure 3.12. A pie chart showing the proportions of children with an ARM using different bowel management strategies at 10 years

3.5.2.5.2. Continence

At 5 years of age, 24/89 (27.0%) children reported soiling, with 23 (25.8%) of these having had anal reconstruction. As 21 (23.6%) children had a stoma at 5 years of age, 24 out of the 78 (30.8%) children without a stoma reported soling.

At 10 years of age 2/14 (14.3%) children reported soiling, with both of these children having had anal reconstruction. As 5 (35.7%) children in the 10 year cohort had a stoma, 2 out of the 9 (22.2%) children without a stoma reported soiling. 1 (7.1%) of these children were classified as having an intermediate ARM and other was classified as having a high ARM. Table 3.25 shows the number of children with an ARM in each age group with soiling.

	1 year (n=140)	5 years (n=89)	10 years (n=14)	P value
Children requiring no assistance for voluntary bowel movements, n (%)	44 (31.4)	23 (25.8)	<4	0.13
Children with soiling, n (%)	N/A	24 (27.0)	<4	0.51

Table 3.25. Comparison of voluntary bowel movement outcomes in different age groups.

3.5.2.6. Urinary incontinence

At 5 years, 52/89 (58.4%) children reported daytime urinary continence in total, and 46/89 (51.7%) children reported night time urinary continence. At 10 years, 11/14 (78.6%) children reported daytime continence in total, with the same patients also reporting night time urinary continence in this age group. When comparing urinary continence across age groups, there were no significant difference for either day or night time continence, p=0.24 and p=0.08, respectively.

3.5.2.7. Non-COS outcomes

3.5.2.7.1. Bowel sensation

Due to the age of patients, bowel sensation was collected at the 5 and 10 year follow-up. At 5 years, 51 (57.3%) children reported an ability to feel when they needed a bowel movement, with 50 of these 51 (98.0%) children having had anal reconstruction. At 10 year

follow-up, 8/14 (57.1%) children reported an ability to feel when they needed a bowel movement, with all of these 8 children having had anal reconstruction.

3.5.2.7.2. Constipation

At 1 year of age, 43/140 (30.7%) children reported constipation, with 39 of these having undergone anal reconstruction prior to follow-up at 1 year. As 48 (34.3%) children had a stoma at 1 year of age, 43 out of the 98 (43.9%) children without a stoma reported constipation.

At follow up at 5 years of age, 35/89 (39.3%) children reported constipation, with all of these patients having previously undergone anal reconstruction. As 21 (23.6%) children had a stoma at 5 years of age, 35 out of the 78 (44.9%) children without a stoma reported constipation.

At 10 years of age, 4 (28.6%) children reported constipation, with all of these patients also having undergone previous anal reconstruction. 5 (35.7%) children had a stoma at 10 years of age, and therefore 4 out of the 9 (44.4%) children without a stoma reported constipation. Table 3.26 shows the constipation rates of ARM children in each age group.

	1 year	5 years	10 years	P value
Proportion of patients able to feel bowel movements n (%)	N/A	51 (57.3%)	8 (57.1%)	>0.99
Proportion of patients with constipation, n (%)	43 (30.7%)	35 (39.3%)	4 (28.6%)	0.37

Table 3.26 Comparison of bowel sensation and constipation rates in each age group in the ARM cohort.

3.5.3. Clinician reported outcomes – ARM phenotype

3.5.3.1. Patient characteristics according to ARM classification

Of the 140 children in the ARM patient cohort, 56 (40.0%) had a low ARM, 50 (35.7%) had an intermediate ARM and 34 (24.3%) had a high ARM. Table 3.27 shows the patient characteristics of this ARM patient cohort according to ARM classification.

	Low ARM (n=56)	Intermediate ARM (n=50)	High ARM (n=34)
Age in months, median (IQR)	54.5 (29.5-89)	77 (30-92)	71.5 (42-98)
Male	32 (57.1)	25 (50.0)	27 (79.4)
VACTERL associated medical problems	26 (46.4)	13 (26.0)	4 (11.8)
Primary stoma formation	31 (55.4)	39 (78.0)	33 (97.1)
Definitive procedure			
Anal reconstruction	54 (96.4)	48 (96.0)	32 (94.1)
Anal reconstruction operative approach			
PSARP	29 (53.7)	31 (64.6)	14 (43.8)
TAP	11 (20.4)	14 (29.2)	0 (0)
Mini PSARP	5 (9.3)	0 (0)	0 (0)
Laparoscopic anorectoplasty	0 (0)	3 (6.3)	12 (37.5)
Open anorectoplasty	0 (0)	0 (0)	3 (9.4)
Other	9 (16.7)	0 (0)	3 (9.4)

Table 3.27. Patient characteristics according to ARM classification.

All results in Table 3.27 are reported as number of children and percentages unless stated otherwise, n (%).

3.5.3.2. Unplanned reoperation

When comparing the number of children requiring additional surgical management between different ARM classification groups, 8/56 (14.3%) children with a low ARM, 11/50 (22.0%) children with an intermediate ARM and 15/34 (44.1%) children with a high ARM required additional surgery. This comparison is shown in Table 3.28.

	Low ARM (n=56)	Intermediate ARM (n=50)	High ARM (n=34)	P value*
Unplanned operation required, n (%)	8 (14.3)	11 (22.0)	15 (44.1)	<0.05
Permanent stoma or ACE formation, n (%)[a]	6 (10.7)	8 (16.0)	11 (32.4)	<0.05

Table 3.28. A comparison of different ARM classifications for unplanned reoperation and permanent stoma formation

*Chi-squared test (Low ARM vs Intermediate ARM vs High ARM)

[a]Permanent stoma formation and ACE formation were combined in order to carry out a statistical test

3.5.3.3. Permanent stoma

When comparing the number of children requiring a permanent stoma in the different ARM classification groups, 5/56 (8.9%) children with a low ARM, 4/50 (8.0%) children with an intermediate ARM and 5/34 (14.7%) children with a high ARM required a permanent stoma to be formed.

3.5.3.4. Voluntary bowel movements

3.5.3.4.1. Bowel management

When comparing different ARM classification groups at 1 year of age, 21 out of the 56 (37.5%) children with a low ARM, 15 out of the 50 (30.0%) children with an intermediate ARM and 8 out of the 34 (23.5%) children with a high ARM required no assistance for

voluntary bowel movements (p=0.37). When comparing patients with different classifications of ARM at 5 years, 14/30 (46.7%) children with a low ARM, 5/35 (14.3%) children with an intermediate ARM, and 4/24 (16.7%) children with a high ARM required no assistance for voluntary bowel movements, which is statistically significant (p<0.05). As only 1 (7.1%) child required no assistance with bowel movements at 10 years of age, a comparison between ARM classifications could not be done.

3.5.3.4.2. Continence

At 5 years of age, 8/30 (26.7%) with a low ARM, 10/35 (28.6%) children with an intermediate ARM and 6/24 (25.0%) with a high ARM in the 5 year ARM cohort reported soiling (p=0.95). At 10 years of age, 0/4 (0%) children with a low ARM, 1/6 (16.7%) children with an intermediate ARM and 1/4 (25.0%) children with a high ARM in the 10 year ARM cohort reported soiling (p=0.59).

3.5.3.5. Urinary incontinence

There were no significant differences in urinary incontinence rates when comparing ARM phenotypes. Table 3.29 shows the number of children in each age group with different ARM classifications reporting urinary continence.

	5 years				10 years			
	Low ARM (n=30)	Intermediate ARM (n=35)	High ARM (n=24)	P value	Low ARM (n=4)	Intermediate ARM (n=6)	High ARM (n=4)	P value
Daytime urinary continence, n (%)	18 (60.0)	24 (68.6)	10 (41.7)	0.12	4 (100)	5 (83.3)	2 (50.0)	0.21
Night time urinary continence, n (%)	17 (56.7)	21 (60.0)	8 (33.3)	0.11	4 (100)	5 (83.3)	2 (50.0)	0.21

Table 3.29. A comparison of urinary continence across different ARM classifications.

3.5.3.6. Non-COS outcomes

3.5.3.6.1. Bowel sensation

Bowel sensation was collected at 5 and 10 years of age due to patients at 1 year of age not being able to report bowel sensation. When comparing patients with different ARM classifications at 5 years of age, 20/30 (66.7%) children with a low ARM, 23/35 (65.7%) children with an intermediate ARM and 8/24 (33.3%) children with a high ARM in this cohort had an ability to feel when they needed a bowel movement, which is a statistically significant difference ($p<0.05$). At 10 years of age, 2/4 (50.0%) children with a low ARM, 5/6 (83.3%) children with an intermediate ARM and 1/4 (25.0%) children with a high ARM in this cohort reported bowel sensation ($p=0.11$).

3.5.3.6.2. Constipation

At 1 year of age, 21/56 (37.5%) children with a low ARM, 20/50 (40.0%) children with an intermediate ARM, and 2/34 (5.9%) children with a high ARM reported constipation at 1 year of age, which is statistically significant different ($p<0.05$). At 5 years of age, 12/30 (40.0%) children with a low ARM, 19/35 (54.3%) children with an intermediate ARM, and 4/24 (16.7%) with a high ARM reported constipation, which is a statistically significant

different (p<0.05). At 10 years of age, 2/4 (50.0%) children with a low ARM, 2/6 (33.3%) children with an intermediate ARM, and 0/4 (0%) children with a high ARM reported constipation in this cohort (p=0.28).

3.5.4. Patient reported outcomes – Overall ARM cohort

3.5.4.1. Patient characteristics

140 children were deemed eligible for inclusion in this study and were contacted via post with a consent form for the study. Of these consent forms sent out, 32 (22.9%) consent forms were returned signed by parents and out of these 32 children with signed consent forms, 24 returned questionnaires. The postal response rate for the ARM patient cohort was therefore 17.1%. 1 child returned some of the questionnaires with very limited data on and therefore was excluded from this study, leaving 23 (16.4%) children.

As children in the 1 year cohort did not complete a bowel function or quality of life questionnaire, these children have been separated into a different group from the 5 and 10 year old cohorts, as was done in the HSCR cohort. Table 3.30 shows the full list of patient characteristics in the two groups of children with an ARM.

Characteristic	1 year (n=7)	5 and 10 years (n=16)
Age in months, median (IQR)	17 (11-20)	67 (44-86)
Male	3 (42.9)	9 (56.3)
ARM classification		
Low	3 (42.9)	6 (37.5)
Recto-perineal fistula	3 (42.9)	5 (31.3)
Anal stenosis	0 (0)	1 (6.3)
Intermediate	2 (28.6)	6 (37.5)
Recto-vestibular fistula	2 (28.6)	2 (12.5)
Rectal atresia with no fistula	0 (0)	3 (18.8)
Recto-bulbar fistula	0 (0)	1 (6.3)

Characteristic	1 year (n=7)	5 and 10 years (n=16)
High	2 (28.6)	4 (25.0)
Recto-bladder neck fistula	1 (14.3)	1 (6.3)
Recto-prostatic fistula	1 (14.3)	2 (12.5)
Cloaca	0 (0)	1 (6.3)
VACTERL associated problem	6 (85.7)	9 (56.3)
Trisomy 21	0 (0)	0 (0)
Vertebral anomalies	1 (14.3)	3 (18.8)
Sacral agenesis	0 (0)	0 (0)
Cord tethering	2 (28.6)	2 (12.5)
Renal anomalies	3 (42.9)	6 (37.5)
Cardiac anomalies	4 (57.1)	6 (37.5)
Tracheo-oesophageal fistula	0 (0)	1 (6.3)
Limb anomalies	0 (0)	1 (6.3)
Additional neurological problems/syndromes	0 (0)	3 (18.8)
Ethnicity		
White: British, Irish, European	7 (100)	14 (87.5)
Mixed race: White/Black Caribbean	0 (0)	1 (6.3)
Other: not stated	0 (0)	1 (6.3)
Primary stoma formation	5 (71.4)	13 (81.3)
Anal reconstruction	7 (100)	16 (100)

Characteristic	1 year (n=7)	5 and 10 years (n=16)
Anal reconstruction operative approach		
PSARP	2 (28.6)	9 (56.3)
TAP	2 (28.6)	2 (12.5)
Laparoscopic assisted anorectoplasty	1 (14.3)	3 (18.8)
Open anorectoplasty	1 (14.3)	0 (0)
Mini PSARP	1 (14.3)	2 (12.5)

Table 3.30. Full list of ARM patient characteristics for all age groups

*One child did not report father information in the 1 year group, therefore these percentages are out of 6 children.

[a]One mother information and one father information were not answered in the 5/10 year cohort, therefore these percentages are out of 15 children.

All results in Table 3.30 are reported as number of children and percentages unless stated otherwise, n (%).

3.5.4.2. Objective score of bowel function

The mean (SD) incontinence score in the ARM cohort was 14.63 (8.51) and the mean (SD) constipation score was 18.63 (4.64). 13 (81.3%) children's scores met the criteria for impaired continence and 8 (50.0%) children's scores met the criteria for constipation, with 6 (37.5%) children meeting the criteria for both impaired continence and constipation.

3.5.4.3. Quality of life

Of the 16 children who returned the questionnaires, all 16 (100%) children returned the PedsQL parent form and 13 (81.3%) children returned the PedsQL child report. Therefore, parent reported PedsQL total scale scores and psychosocial health scores were calculable for all 16 (100%) children and child reported scores were calculable in 13 (81.3%) children.

The mean (SD) parent reported total score was 75.44 (19.81) which was not statistically significantly lower (p=0.79) than the mean (SD) parent reported total score of 80.87 (16.73) from the reference population, and the mean (SD) parent reported psychosocial score was

74.96 (18.27) which was also not significantly lower (p=0.77) than the mean (SD) parent reported psychosocial health score of 80.58 (16.52) from the reference population (359). The mean (SD) child reported total score was 80.40 (13.51) which was not significantly different (p=0.96) than the mean (SD) child reported total score of 79.62 (15.26) from the reference population, and the mean (SD) child reported psychosocial score was 74.41 (17.98) which was not significantly lower (p=0.88) than the mean (SD) child reported psychosocial score of 76.76 (14.87) from the reference population (359). Figure 3.13 shows the PedsQL scores in the ARM patient cohort, showing the mean and standard deviation.

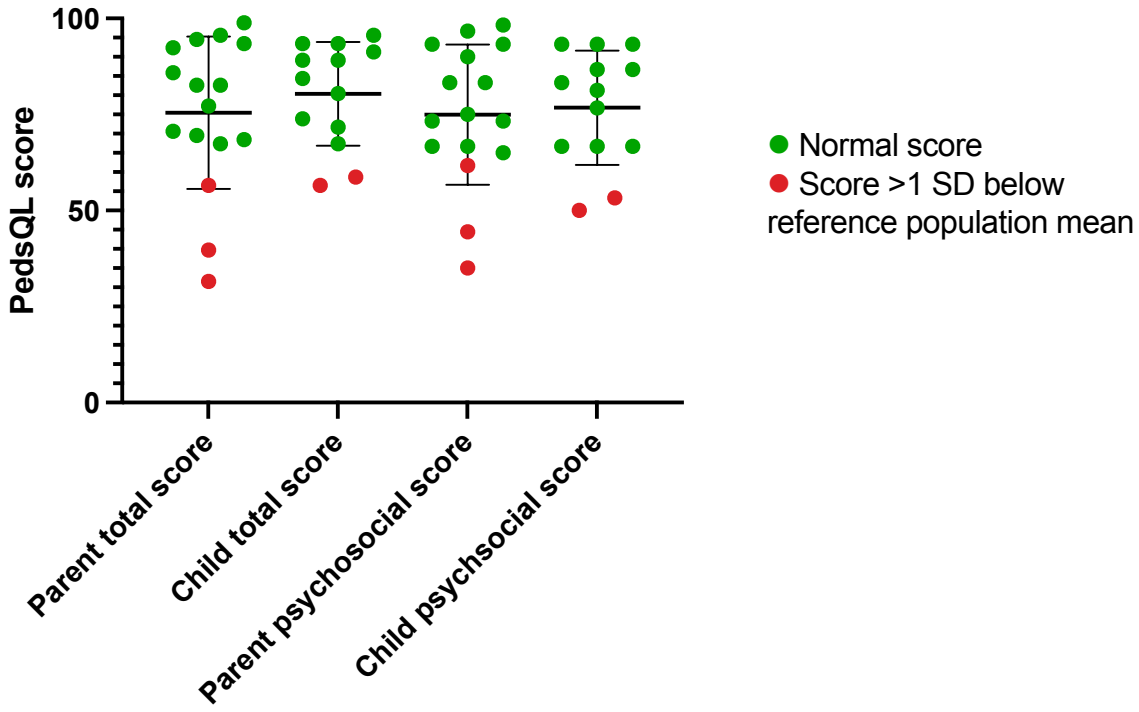


Figure 3.13. The PedsQL scores reported in the total ARM patient cohort.

Of the 16 children with parent reported scores, 3 (18.8%) children had a total score, and 3 (18.8%) children had a psychosocial score that was more than 1 SD below the reference population mean (359). Of the 13 children with child reported scores, 2 (15.4%) children had a total score, and 2 (15.4%) children had a psychosocial score that was more than 1 SD below the reference population mean (359). Table 3.31 shows the quality of life scores for the total cohort.

	Parent reported quality of life (n=16)	Child reported quality of life (n=13)
PedsQL total score, mean (SD)	75.44 (19.81)	80.40 (13.51)
Total score >1 SD lower than the reference population mean, n (%)	3 (18.8)	2 (15.4)
PedsQL psychosocial score, mean (SD)	74.96 (18.27)	76.76 (14.87)
Psychosocial score >1 SD lower than the reference population mean, n (%)	3 (18.8)	2 (15.4)

Table 3.31. The PedsQL scores for the overall ARM patient cohort.

3.5.5. Patient reported outcomes – ARM phenotype

3.5.5.1. Patient characteristics according to ARM classification

Of the 16 children who returned the questionnaires in the 5 and 10 year old cohorts, 6 (37.5%) had a low ARM, 6 (37.5%) had an intermediate ARM and 4 (25.0%) had a high ARM. The patient characteristics for each ARM classification are shown in Table 3.32.

	Low ARM (n=6)	Intermediate ARM (n=6)	High ARM (n=4)
Age in months, median (IQR)	48 (41-62)	76 (72-86)	68.5 (42.5-86.5)
Male	4 (66.7)	2 (33.3)	2 (50.0)
VACTERL associated medical problems	2 (33.3)	4 (66.7)	3 (75.0)
Primary stoma formation	4 (66.7)	5 (83.3)	4 (100.0)
Anal reconstruction operative approach			
PSARP	3 (50.0)	4 (66.7)	2 (50.0)
TAP	1 (16.7)	1 (16.7)	0 (0)
Mini PSARP	2 (33.3)	0 (0)	0 (0)
Laparoscopic assisted anorectoplasty	0 (0)	1 (16.7)	2 (50.0)

Table 3.32. Patient characteristics according to ARM classification.

All results in Table 3.32 are reported as number of children and percentages unless stated otherwise, n (%).

3.5.5.2. Objective score of bowel function

There were no significant differences in bowel function score when comparing the different ARM classifications. Table 3.33 shows the bowel function scores according to ARM classification.

	Low ARM (n=6)	Intermediate ARM (n=6)	High ARM (n=4)	P value
Impaired continence, n (%)	4 (66.7)	6 (100)	3 (75.0)	
Incontinence score, mean (SD)	17.50 (9.05)	13.67 (7.53)	11.75 (7.75)	0.99
Constipation, n (%)	2 (33.3)	4 (66.7)	2 (50.0)	
Constipation score, mean (SD)	18.58 (4.72)	18.75 (4.77)	18.50 (4.30)	0.60

Table 3.33. The bowel function scores according to ARM classification.

*One-way ANOVA test (low ARM vs intermediate ARM vs high ARM)

Of the 16 children in this ARM cohort, 6 (37.5%) had a low ARM, 6 (37.5%) had an intermediate ARM and 4 (25.0%) had a high ARM with the number of children with impaired continence and constipation being shown in Figures 3.14 and 3.15.

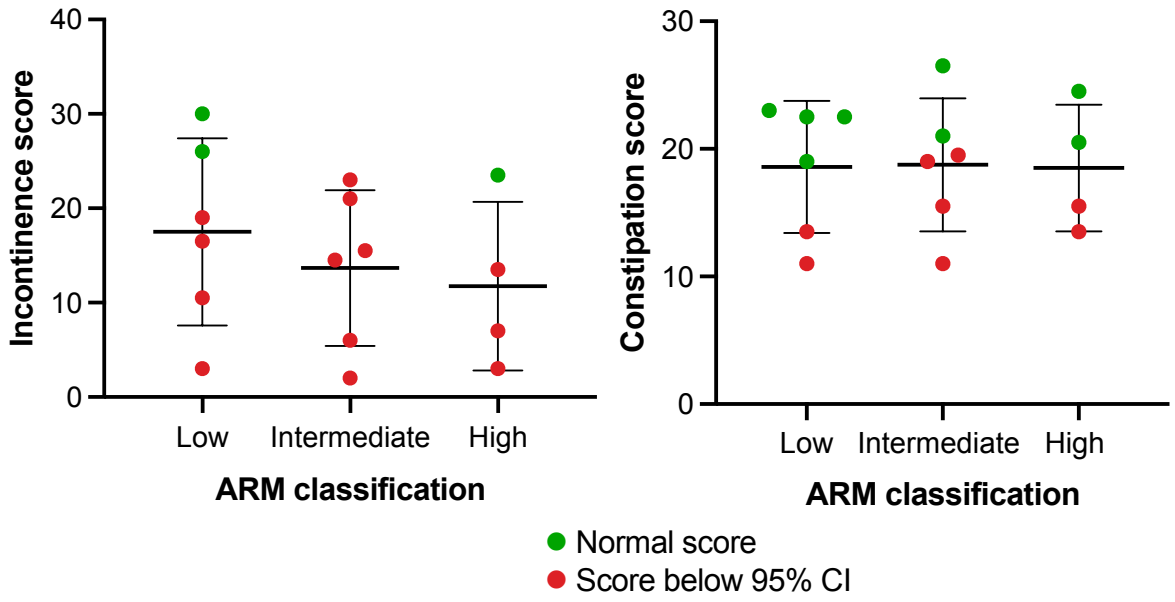


Figure 3.14 and 3.15. The incontinence and constipation PICS scores according to ARM classification.

3.5.5.3. Quality of life

There were no statistically significant differences between quality of life scores when comparing the different ARM phenotypes. Table 3.34 shows the quality of life scores according to ARM phenotype.

	Low ARM (n=6)	Intermediate ARM (n=6)	High ARM (n=4)	P value[a]
Child reported quality of life				
PedsQL total score, mean (SD)	81.22 (13.35)	75.73 (12.07)	92.39 (1.09)	0.34
Total score >1 SD lower than the reference population mean, n (%)	1 (20.0)*	1 (16.7)	0 (0)*	
PedsQL psychosocial score, mean (SD)	77.58 (13.29)	71.67 (14.37)	90.00 (3.33)	0.34
Psychosocial score >1 SD lower than the reference population mean, n (%)	1 (20.0)*	1 (16.7)	0 (0)*	
Parent reported quality of life				
PedsQL total score, mean (SD)	81.16 (12.65)	77.90 (12.73)	63.19 (27.94)	0.37
Total score >1 SD lower than the reference population mean, n (%)	1 (16.7)	0 (0)	2 (50.0)	
PedsQL psychosocial score, mean (SD)	78.61 (10.99)	78.61 (14.06)	64.03 (24.79)	0.41
Psychosocial score >1 SD lower than the reference population mean, n (%)	0 (0)	1 (16.7)	2 (50.0)	

Table 3.34. The quality of life and psychosocial score for each ARM classification.

*Percentage of those with a child reported quality of life questionnaire returned.

[a]One-way ANOVA statistical test

3.6. Discussion

The aim of this retrospective cohort study was to use the standardised core outcome set to determine the outcomes of children with HSCR and ARM. This study was able to identify the outcomes of these children and was also able to compare the outcomes between the different phenotypes of these pathologies and between the different age groups in this patient cohort. The HSCR COS was chosen to be used in this study to determine which outcomes were to be collected for children with either HSCR or ARM, due to there being no existing COS for children with an ARM and the very similar long-term outcomes in both of these conditions.

Of the 106 children in the HSCR cohort, approximately 1 in 5 underwent at least one unplanned reoperation, around a third of the children were unable to maintain voluntary bowel movements without some form of bowel management, such as laxatives or suppositories and just over 1 in 10 required permanent stoma formation. At 5 years of age, faecal incontinence was occurring in just over half of patients with HSCR, with around a quarter of children reporting daytime urinary incontinence. At 10 years of age, the rate of faecal incontinence decreased to around a third of children with HSCR, however, the rate of daytime urinary incontinence seemed to increase to around 40%. In comparison to the previously reported rate of faecal and urinary incontinence in the healthy population, which are 4.4% and 10.5%, respectively, the rates of faecal and urinary incontinence observed in this study were largely increased (360). A previous study assessing the outcomes of children with HSCR after a pull-through procedure reported a constipation rate of 53.3% at just under 5 years of age, which is a lot higher than the constipation rate observed in this study, 20% (361).

Overall, children with extended-segment HSCR tended to have poorer outcomes than children with recto-sigmoid HSCR, however there were a couple of exceptions to this. Constipation and faecal incontinence rates were lower in children with extended-segment HSCR in comparison to children with recto-sigmoid HSCR. However, this may not have been an accurate representation of these children as there was a higher rate of stoma formation in the extended-segment cohort, which would mean these children would not currently

have faecal incontinence or constipation, but may have previously had it leading to stoma formation.

When assessing the patient reported outcomes of children with HSCR, all children met the criteria for either impaired continence or constipation and half of these children met the criteria for both of these outcomes. Although children with extended-segment HSCR scored a large amount lower for the incontinence score than children with recto-sigmoid disease (8.75 vs 17.38), there were only 2 children with extended-segment HSCR meaning statistically significant differences were not found. When assessing the quality of life scores in this HSCR cohort, there were similar child and parent reported scores. The 2 children with extended-segment HSCR had lower average scores for all quality of life scores, however, this also was not statistically significant due to the small number of patients. However, the child scoring the lowest for all four quality of life scores had recto-sigmoid HSCR.

Of the 140 children in the ARM cohort, around a quarter of children required at least one unplanned reoperation, 1 in 10 children required permanent stoma formation and around two thirds of children were unable to maintain voluntary bowel movements without bowel management. At both 5 and 10 years of age, faecal incontinence rates were higher in this study (27.0% and 14.3%) in comparison to the faecal incontinence rate of a healthy population stated as 4.4% (360). Also, the observed urinary incontinence rates in this study at both 5 and 10 years (58.4% and 78.6%), were higher than those observed in a previous study on a healthy population, 10.5%. The constipation rates observed for both 5 and 10 year olds in this study was also higher (39.3% and 28.6%) in comparison with the constipation rate observed in a previous study on healthy children (22.6%) (360).

When assessing the patient reported outcomes of children with an ARM, only 1 child did not meet the criteria for either impaired continence or constipation and 6 children met the criteria for both of these outcomes. Both incontinence and constipation scores remained similar across the different ARM classifications, however when looking at the individual incontinence scores of children classified as having a high ARM, 3 children reported low scores and 1 patient reported a higher score which therefore increased the mean incontinence score. As this cohort had a very small number of children, it is difficult to

assess whether the single child reporting a higher incontinence score is an outlier and bigger studies would therefore be needed to assess this. The average child reported total quality of life score was higher than the average parent reported total quality of life score in this ARM cohort. Also when assessing the high ARM cohort, the child reported total score is higher than the overall average and the parent reported total scores is lower than the overall average (92.39 vs 63.19). This may have been due half of the children in the high ARM cohort not completing the child reported questionnaire, with 1 of these children not being able to complete it due to a lack of cognition. This therefore means that the average total child reported score does not involve these patients but the parent reported score does, leading to a higher total child reported score and a lower total parent reported score.

In both ARM and HSCR cohorts, there was a low rate of ACE formation for bowel management. This may have been due to that fact that this was a relatively young cohort, with previous studies reporting the majority of ACE formations at around 9.2 years of age (362). Therefore, the rate of ACE formation may increase as these children get older and require more effective bowel management strategies suggesting the importance of the continuation of this study in order to establish the total number of children in this cohort needing an ACE formation at some point in their lives.

When comparing children with different ARM classifications, assessing voluntary bowel movements and constipation, there are much higher proportions of children with high ARMs at 1 year of age requiring assistance to maintain voluntary bowel movements (76.5%) than reporting constipation (5.9%). This may have been due to children with a stoma being included in the collection of these outcomes. To understand this difference, a further collection of these outcomes, this time excluding children with a stoma at 1 year of age, showed that 3 out of the 11 (27.3%) children without a stoma required assistance to maintain voluntary movements and 2 out of the 11 (18.2%) children without a stoma reported constipation. This therefore showed similar numbers of children requiring assistance to maintain bowel movements and reporting constipation when excluding children with a stoma. Also, some children reporting constipation may also be soiling and therefore children and families may not be reporting the constipation as they are unaware of it and believe the child is having voluntary bowel movements instead.

3.6.1. Strengths and limitations

Although this study had a broad inclusion criteria to prevent a small sample size, it was a single centre study, and therefore it is not possible to generalise these results across the paediatric population. Clinician reported outcome data was extracted manually from documented patient medical records, meaning there could have been an element of human error.

One strength of this study was the inclusion of patient reported outcomes including objective scores of bowel function and quality of life, however very limited numbers of children returned these questionnaires for the study. Due to a delay in gaining ethical approval for this study, consent forms were only able to be sent out a number of months after originally planned, which limited the time available for the collection of patient questionnaires. This meant that it was not possible to re-contact eligible children for consent and the total postal response rate for the HSCR and ARM cohort was 22.6% and 17.1%, respectively. However, those in the 1 year cohort were not required to complete a bowel function or quality of life score, meaning there was a very limited number of children completing these questionnaires creating a very small sample size for patient reported outcomes and limiting the data analysis able to be done. Due to the limited sample size, there is a risk of responder bias, with children who may have higher quality of life scores and better cognition responding and children with a lower quality of life being more unlikely to respond. The low number of children included in this study also reduces the impact of this study and limits the conclusions which can currently be drawn from it, as what has been found in this study may not be applicable to children with either of these conditions, for example children in other locations receiving different methods of treatment. Future studies could use electronic methods to distribute consent forms and questionnaires in order to get a better response rate and therefore a larger sample size for patient reported outcomes.

One weakness of this study was the limited number operative approaches to the pull-through procedure for children with HSCR. As only 2 distinct procedures were carried out for these children at this centre, the power of the study is reduced in terms of outcomes, as

other pull-through procedure approaches, such as the Duhamel pull-through approach, were not included and therefore outcomes for this approach could not be collected.

There were no pre-treatment bowel function or quality of life scores available for these cohorts, and therefore it was not possible to determine the effects of specific variables on bowel function or quality of life scores reported from patient questionnaires. There were also no healthy controls used in this study meaning scores were compared to the general healthy population scores, however, these scores were not able to be matched according to patient characteristics, such as age or sex.

As the HSCR COS has been used in this study to collect outcomes for both HSCR and ARM children, there may be some drawbacks of using this COS for ARM children outcome reporting. One drawback could be that the HSCR COS was designed involving healthcare professionals and families specifically related to HSCR patients. This could therefore mean that using it for ARM patient outcome reporting could mean that certain outcomes, such as HAEC, may not be relevant to ARM patients. As healthcare professionals and families related to ARM patients have not been included in the development of the HSCR COS, outcomes which are specific to ARM patients or the outcomes people involved in the care of ARM patients would classify as of high importance to the success of ARM management may have not been included. However, as there is no pre-existing COS for ARM patients, and the outcomes of HSCR and ARM patients are very similar, the use of the HSCR COS for ARM patient outcome reporting may be beneficial in ensuring the majority of important outcomes, such as faecal and urinary incontinence, are being reported for these patients.

Future research looking at HSCR and ARM patient outcomes could include an older age range of children and conduct the research over a longer period of time to assess the longer-term outcomes of children and increase the sample size. A multi-centre outcome study could also be done to compare outcomes of different patient cohorts. Adult patients with these conditions could also be included in order to assess sexual function and obstetric outcomes.

3.7. Conclusion

This cohort study highlights the outcomes of children with HSCR and ARM, and suggests how issues can continue for these children many years after diagnosis and surgical management. However, children with less severe phenotypes of these conditions are more likely to have better outcomes than patients with more severe phenotypes. This study is continuing with more children being recruited, and with future analysis aiming to gather information of the longer-term outcomes of children with HSCR and ARM.

4. Conclusions

The systematic review in Chapter 2 highlighted the variability in outcome reporting for HSCR patients, even after the publication of the HSCR COS and explained the need for the use of the COS across all HSCR studies to reduce the risk of reporting bias and improve meta-analysis of these outcomes. This therefore highlighted the need for an outcome study using the HSCR COS and the correct outcome measures for both HSCR and ARM patients, which was completed in Chapter 3.

The data analysis in Chapter 3 of this thesis contributed to the understanding of both clinician and patient reported outcomes for HSCR and ARM patients. This study used the HSCR COS to assess the important outcomes for these patients and also compared the outcomes of patients with different classifications of these conditions. This study has therefore been able to makes suggestions for future research using these methods for a larger cohort of patients.

In conclusion, this thesis has assessed the outcomes of HSCR and ARM patients being reported in previous studies and described both the clinician and patient reported outcomes of these patients. This research has provided an opportunity for future, more wide-spread research and therefore will help with the understanding of longer-term outcomes for HSCR and ARM patients.

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Appendices

Appendix 1: Systematic review search strategy – PubMed

Database: PubMed	
Date: 10/01/22	
Number	Term
1	“Hirschsprung’s Disease”
2	“Hirschsprung Disease”
3	Hirschsprung*
4	recto-sigmoid
5	aganglionosis
6	colon* aganglionosis
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	outcome
9	“quality of life”
10	“bowel function”
11	#8 OR #9 OR # 10
12	#7 AND #11

Appendix 2: Outcomes collected and outcome measures used in all 188 studies

Author (year)	Age at time of assessment (years)	Clinician reported outcomes				Patient reported outcomes			
		COS	Outcome measure	Non-COS	Outcome measure	COS	Outcome measure	Non-COS	Outcome measure
Delgado-Miguel C (2022)	Median: 6.6	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Modified Wingspread system	Perineal rash	N/A
		Unplanned reoperation	N/A	Perioperative complications	Clavien-Dindo classification	Bowel function	Rome IV criteria		
		Permanent stoma	N/A						
		HAEC	Pastor scoring system						
Onishi S (2021)	At 5, 7 and 9	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Evacuation score from Japan Society of Ano-Rectal Malformation Study Group		
						Bowel function	Evacuation score from Japan Society of Ano-Rectal Malformation Study Group		

						Voluntary bowel movements	Evacuation score from Japan Society of Ano-Rectal Malformation Study Group		
Davidson JR (2021)	With learning difficulties: 20 Without learning difficulties: 28	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Rintala bowel function score		
		Unplanned reoperation	N/A			Bowel function	Rintala bowel function score		
		Permanent stoma	N/A			Voluntary bowel movements	Rintala bowel function score		
		HAEC	Review of records			Psychological stress	SF-36 PedsQL GIQLI		
						Urinary incontinence	Modified DanPSS		
						Quality of Life	PedsQL GIQLI		
Bapaye A (2021)	Median: 5.4	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure		
				Readmission	Review of records	Voluntary bowel movements	Subjective measure		
Pecoraro AR (2021)	Median: 0.3	Death with cause specified	N/A	Postoperative hospital stay	N/A				
		HAEC	Review of records	Readmission	Review of records				

Shankar G (2021)	Mean: 5.2	Death with cause specified	N/A			Faecal incontinence	Subjective measure		
		Unplanned reoperation	N/A			Voluntary bowel movements	Subjective measure		
		HAEC	Review of records						
Svetanoff WJ (2021)	Median: 0.9	HAEC	Review of records						
Pini Prato A (2021)	Unspecified	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Wingspread system	Patients' and families' perspectives of symptoms	Modified Visick scoring system
		HAEC	Pastor scoring system						
Nasr A (2021)	Mean: 13.7	Death with cause specified	N/A			Faecal incontinence	Subjective measure		
						Voluntary bowel movements	Subjective measure		
Arafa A (2021)	Between 3-7	Death with cause specified	N/A	Postoperative hospital stay	N/A			Perineal rash	N/A
		HAEC	Review of records	Perioperative complications	Review of records				

Li Q (2021)	Median: 5.1	Unplanned reoperation	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure		
		Permanent stoma	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
		HAEC	Review of records			Urinary incontinence	Subjective measure		
Davidson JR (2021)	Median: 28	Death with cause specified	N/A	Perioperative complications	Clavein-Dindo classification	Faecal incontinence	Rintala bowel function score		
		Unplanned reoperation	N/A			Bowel function	Gastro-intestinal quality of life index		
		Permanent stoma	N/A			Voluntary bowel movements	Rintala bowel function score		
		HAEC	Review of records			Psychological stress	PedsQL GIQLI SF-36 questionnaire		
						Urinary incontinence	Danish prostatic score		
						Quality of life	PedsQL GIQLI		
Kastenberg ZJ	Unspecified	Unplanned reoperation	N/A	Perioperative complications	Review of records	Faecal incontinence	Subjective measure		

(2021)		HAEC	Review of records			Voluntary bowel movements	Subjective measure		
Rentea RM (2021)	Mean: 3.9	Death with cause specified	N/A	Postoperative hospital stay	N/A				
		HAEC	Review of records	Readmission	Review of records				
Peng C (2021)	Median: 11.1	Death with cause specified	N/A			Faecal incontinence	Rintala bowel function score		
		Unplanned reoperation	N/A			Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		
Zbaida R (2021)	Mean: 6	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Krickenbeck classification		
		Permanent stoma	N/A	Perioperative complications	Review of records	Bowel function	Krickenbeck classification		
						Voluntary bowel function	Krickenbeck classification		
Yuan Y (2021)	Mean: 8.1			Anorectal manometry	Anorectal manometry readings	Faecal incontinence	Rintala bowel function score		
						Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		

Telborn L (2021)	Median: 4.3			Growth and nutritional status	Subjective measure	Faecal incontinence	Subjective measure		
						Voluntary bowel movements	Subjective measure		
Loganathan AK (2021)	Mean: 7	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Rintala bowel function score	Patients' and families' perspectives of symptoms	Family impact module
		Unplanned reoperation	N/A	Growth and nutritional status	Height and weight	Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		
						Psychological stress	PedsQL		
						Quality of life	PedsQL		
Apfeld JC (2021)	All younger than 2	Death with cause specified	N/A	Perioperative complications	Review of records				
		Unplanned reoperation	N/A						
		HAEC	Review of records						

Kim S-H (2021)	Mean: 6.3	Death with cause specified	N/A	Readmission	Review of records	Faecal incontinence	Rintala bowel function score		
		Unplanned reoperation	N/A			Bowel function	Rintala bowel function score		
		HAEC	Review of records			Voluntary bowel movements	Rintala bowel function score		
Allin BSR (2020)	Median 6.8	Death with cause specified	N/A			Faecal incontinence	Subjective measure		
		Unplanned reoperation	N/A			Bowel function	Pediatric incontinence/ constipation scoring system		
		Permanent stoma	N/A			Voluntary bowel movements	Subjective measure		
		HAEC	Review of records			Psychological stress	PedsQL		
						Urinary incontinence	Subjective measure		
						Quality of life	PedsQL		
Verkuijl SJ (2022)	Median: 17	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Rome IV criteria		
		Unplanned reoperation	N/A			Bowel function	Rome IV criteria		
		Permanent stoma	N/A			Voluntary bowel movements	Rome IV criteria		

		HAEC	Review of records			Psychological stress	CHQ-CF87 WHOQOL-100		
						Quality of life	CHQ-CF87 WHOQOL-100		
Askarpour S (2021)	Unspecified	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A
		Unplanned reoperation	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
		HAEC	Review of records						
Youn JK (2021)	Median: 18.6	Death with cause specified	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure	Perineal rash	N/A
		Unplanned reoperation	N/A	Growth and nutritional status	Height and weight				
		Permanent stoma	N/A						
		HAEC	Review of records						
Yan J-Y (2020)	Mean: 8.4	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Rintala bowel function score	Perineal rash	N/A
		Unplanned reoperation	N/A	Growth and nutritional status	Height and weight	Bowel function	Rintala bowel function score		
		Permanent stoma	N/A			Voluntary bowel movements	Rintala bowel function score		

		HAEC	Review of records						
Gunadi IG (2021)	Median: 2.6	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Krickenbeck classification		
		HAEC	Review of records	Growth and nutritional status	Subjective measure	Bowel function	Krickenbeck classification		
						Voluntary bowel movements	Krickenbeck classification		
Lin Z (2021)	Mean: 0.4			Postoperative hospital stay	N/A				
				Perioperative complications	Review of records				
Lin Z (2021)	Mean: 0.5	Death with cause specified	N/A	Postoperative hospital stay	N/A				
		HAEC	Review of records	Perioperative complications	Review of records				
Kabbash MM (2021)	Mean: 5.5	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure		
				Perioperative complications	Review of records				
Chen F (2021)	Mean: 7.5	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Heikkinen defecation function score		
		Unplanned reoperation	N/A	Perioperative complications	Review of records	Bowel function	Heikkinen defecation function score		

		HAEC	Review of records			Voluntary bowel movements	Heikkinen defecation function score		
Hoel AT (2021)	Median: 29					Faecal incontinence	Subjective measure		
						Voluntary bowel movements	Subjective measure		
						Psychological stress	Subjective measure		
Liu Q (2021)	Mean: 1.6	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Wexner scoring system	Perineal rash	N/A
						Bowel function	Wexner scoring system	Patients' and families' perspectives of symptoms	Self-rating Anxiety scale
						Voluntary bowel movements	Wexner scoring system		
						Psychological stress	PedsQL		
						Quality of life	PedsQL		
Roorda D (2021)	Median: 8	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure		
		Unplanned reoperation	N/A	Readmission	Review of records	Voluntary bowel movements	Subjective measure		

		HAEC	Review of records	Perioperative complications	Review of records				
Davidson JR (2021)	Median: 29					Sexual function	Erectile hardness score		
						Fertility	Subjective measure		
						Sexual quality of life	Sexual quality of life questionnaire		
Mohamed W (2021)	Median: 0.9	HAEC	Review of records	Postoperative hospital stay	N/A	Voluntary bowel movements	Subjective measure	Perineal rash	N/A
				Perioperative complications	Review of records				
Gabriela GC (2020)	Median: 6.4	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Subjective measure		
		HAEC	Review of records	Growth and nutritional status	Height and weight	Voluntary bowel movements	Subjective measure		
Fosby MV (2020)	Median: 8.1 then 15.4	Death with cause specified	N/A			Faecal incontinence	Krickenbeck classification		
		Permanent stoma	N/A			Bowel function	Krickenbeck classification		
						Voluntary bowel movements	Krickenbeck classification		
Khamroev UA (2020)	Mean: 0.5	Unplanned reoperation	N/A			Faecal incontinence	Questionnaire for long-term results		

		HAEC	Review of records			Bowel function	Questionnaire for long-term results		
						Voluntary bowel movements	Questionnaire for long-term results		
Watanabe T (2020)	Median: 2.5	Death with cause specified	N/A	Postoperative hospital stay	N/A				
		Unplanned reoperation	N/A	Perioperative complications	Review of records				
Saysoo MR (2020)	Aged over 6					Faecal incontinence	HSCR/Anorectal malformation quality of life questionnaire		
						Bowel function	HSCR/Anorectal malformation quality of life questionnaire		
						Voluntary bowel movements	HSCR/Anorectal malformation quality of life questionnaire		
						Psychological stress	HSCR/Anorectal malformation quality of life questionnaire		
						Quality of life	HSCR/Anorectal malformation quality of life questionnaire		

Brooks LA (2020)	At 1 and 2	Death with cause specified	N/A			Faecal incontinence	Rintala bowel function score		
		HAEC	Review of records			Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		
						Psychological stress	Rintala bowel function score		
						Quality of life	Rintala bowel function score		
Granstrom AL (2020)	Median: 19			Cancer diagnosis	Review of records				
Pruitt LCC (2020)	Unspecified	Death with cause specified	N/A	Postoperative hospital stay	N/A				
		Unplanned reoperation	N/A						
		Permanent stoma	N/A						
		HAEC	Review of records						
Espeso L (2020)	Mean: 11	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Krickenbeck classification		
		HAEC	Review of records	Growth and nutritional status	Height and weight	Bowel function	Krickenbeck classification		

						Voluntary bowel movements	Krickenbeck classification		
						Psychological stress	HSCR/Anorectal malformation quality of life questionnaire		
						Urinary incontinence	HSCR/Anorectal malformation quality of life questionnaire		
						Quality of life	HSCR/Anorectal malformation quality of life questionnaire		
Ali S (2020)	Mean: 1.1			Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A
				Growth and nutritional status	Weight	Voluntary bowel movements	Subjective measure		
Peters NJ (2020)	Mean: 7.7	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Clinical bowel function scoring system	Perineal rash	N/A
		HAEC	HD-associated EC score			Bowel function	Clinical bowel function scoring system		
						Voluntary bowel movements	Clinical bowel function scoring system		

						Psychological stress	Quality of life scoring criteria for children with faecal incontinence		
						Quality of life	Quality of life scoring criteria for children with faecal incontinence		
Svetanoff WJ (2020)	Unspecified	HAEC	Review of records	Postoperative hospital stay	N/A				
				Readmission	Review of records				
Stenstrom P (2020)	Median: 12	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Rintala bowel function score	Perineal rash	N/A
		Unplanned reoperation	N/A	Growth and nutritional status	Subjective measure	Bowel function	Rintala bowel function score		
		Permanent stoma	N/A			Voluntary bowel movements	Rintala bowel function score		
		HAEC	Review of records						
Gunadi (2020)	Unspecified	Death with cause specified	N/A	Growth and nutritional status	Height and weight				

Dai Y (2020)	Median: 3.8	Death with cause specified	N/A	Growth and nutritional status	Height and weight	Faecal incontinence	Holschneider incontinence score	Patients' and families' perspectives of symptoms	Parental self-efficacy in the management of home care of children with HD or ARM
						Bowel function	Holschneider incontinence score		
						Voluntary bowel movements	Holschneider incontinence score		
						Psychological stress	PedsQL		
						Quality of life	PedsQL		
Meng X (2020)	Mean: 4.5	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Stooling survey from El-Sawaf et al.	Perineal rash	N/A
				Perioperative complications	Review of records	Bowel function	Stooling survey from El-Sawaf et al.		
						Voluntary bowel movements	Stooling survey from El-Sawaf et al.		

Oh C (2020)	Median: 6.23	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Krickenbeck classification		
		Unplanned reoperation	N/A			Bowel function	Krickenbeck classification		
		HAEC	Review of records			Voluntary bowel movements	Krickenbeck classification		
Mille E (2020)	Mean: 10.3	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Krickenbeck classification	Patients' and families' perspectives of symptoms	Adolescents' health and perceived health and Kidscreen 10
				Readmission	Review of records	Bowel function	Krickenbeck classification	Intelligence	Wechsler Children's intelligence scale
				Growth and nutritional status	Height and weight	Voluntary bowel function	Krickenbeck classification	Behaviour	Child behaviour check list
						Psychological stress	Spielberg state-trait anxiety inventory questionnaire		
						Quality of life	Adolescents' health and perceived		

							health and Kidscreen 10		
Quiroz HJ (2020)	Groups of <1, 1-6, 7-12 and 13-18	Death with cause specified	N/A	Postoperative hospital stay	N/A				
		Unplanned reoperation	N/A	Readmission	Review of records				
		HAEC	Review of records	Perioperative complications	Review of records				
Townley OG (2020)	Mean: 5.4	Unplanned reoperation	N/A			Faecal incontinence	Pediatric incontinence/ constipation scoring system		
		Permanent stoma	N/A			Bowel function	Pediatric incontinence/ constipation scoring system		
						Voluntary bowel movements	Pediatric incontinence/ constipation scoring system		
						Psychological stress	PedsQL		
						Quality of life	PedsQL		
Schlund D (2020)	Mean: 36	Death with cause specified	N/A	Postoperative hospital stay	N/A				
		Unplanned reoperation	N/A	Readmission	Review of records				

				Perioperative complications	Review of records				
Tang J (2020)	Mean: 0.4	Death with cause specified	N/A	Postoperative hospital stay	N/A				
				Perioperative complications	Review of records				
				Growth and nutritional status	Height and weight				
Pini Prato A (2020)	Median: 3.4	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Wingspread score	Perineal rash	N/A
		Unplanned reoperation	N/A	Perioperative complications					
		Permanent stoma	N/A						
		HAEC	Review of records						
Zhuansun D (2020)	Mean: 11.9	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Stooling survey from El-Sawaf et al.		
				Perioperative complications		Bowel function	Stooling survey from El-Sawaf et al.		
						Voluntary bowel movements	Stooling survey from El-Sawaf et al.		
						Psychological stress	Quality of life scoring criteria for children		

							with fecal incontinence		
						Quality of life	Quality of life scoring criteria for children with fecal incontinence		
Zhu J (2020)	Between 3 and 6					Faecal incontinence	Krickenbeck classification		
						Bowel function	Krickenbeck classification		
						Voluntary bowel movements	Krickenbeck classification		
Halleran DR (2020)	Median: 2.8	Death with cause specified	N/A	Readmission	Review of records				
		HAEC	Review of records						
Yan J (2020)	Mean: 4.9	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Rintala bowel function score	Perineal rash	N/A
		HAEC	Review of records	Perioperative complications	Review of records	Bowel function	Rintala bowel function score		
				Growth and nutritional status	Height and weight	Voluntary bowel movements	Rintala bowel function score		
Zhang X (2020)	Mean: 2	Unplanned reoperation	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A

		HAEC	2009 HAEC scoring system	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
Xu P-P (2019)	Mean: 0.5	HAEC	Review of records	Postoperative hospital stay	N/A	Voluntary bowel movements	Subjective measure	Visibility of scar	Manchester Scar Scale
				Perioperative complications	Review of records				
Elsherbeny M (2019)	Mean: 2	Unplanned reoperation	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
		HAEC	Review of records						
Adamou H (2019)	21 and 22			Postoperative hospital stay	N/A	Voluntary bowel movements	Subjective measure		
				Growth and nutritional status	Height and weight				
Youn JK (2019)	Median: 4.8			Growth and nutritional status	Weight	Faecal incontinence	Holschneider incontinence score		
				Anorectal manometry	Anorectal manometry readings	Bowel function	Wexner constipation score		
						Voluntary bowel movements	Wexner constipation score		

						Psychological stress	Quality of life score for defecation		
						Quality of life	Quality of life score for defecation		
Roorda D (2019)	Mean: 3.2	Death with cause specified	N/A	Readmission	Review of records	Voluntary bowel movements	Subjective measure		
		Unplanned reoperation	N/A	Perioperative complications	Review of records				
Hoff N (2019)	Median: 0.2	Unplanned reoperation	N/A	Postoperative hospital stay	N/A				
		Permanent stoma	N/A	Readmission	Review of records				
		HAEC	Review of records	Perioperative complications	Review of records				
Amin L (2019)	Mean: 19	Death with cause specified	N/A			Psychological stress	Subjective measure		
Berrios CD (2019)	Mean: 38					Faecal incontinence	Rintala bowel function score	Patients' and families' perspectives of symptoms	Illness Perceptions questionnaire
						Bowel function	Rintala bowel function score		

						Voluntary bowel movements	Rintala bowel function score		
						Psychological stress	Psychological adaptation scale		
						Quality of life	Quality of life index		
Fusaro F (2019)	Median: 6.7	Death with cause specified	N/A						
		Unplanned reoperation	N/A						
		Permanent stoma	N/A						
		HAEC	Review of records						
Louis-Borrione C (2019)	Mean: 7.1	HAEC	Review of records	Perioperative complications	Review of records	Faecal incontinence	Jorge-Wexner fecal incontinence score		
						Bowel function	Jorge-Wexner fecal incontinence score		
						Voluntary bowel movements	Subjective measure		
Ashjaei B (2019)	Mean: 8.1	Unplanned reoperation	N/A	Perioperative complications	Review of records				

Meinds RJ (2019)	Median: 18	Unplanned reoperation	N/A	Perioperative complications	Review of records	Faecal incontinence	Rome IV criteria		
		Permanent stoma	N/A			Bowel function	Defecation and faecal incontinence questionnaire		
		HAEC	Review of records			Voluntary bowel movements	Rome IV criteria		
						Psychological stress	CHQ-CF87 WHOQOL-100		
						Quality of life	CHQ-CF87 WHOQOL-100		
Gustafson E (2019)	Mean: 37.8	Death with cause specified	N/A	Growth and nutritional status	Height and weight	Faecal incontinence	Miller's incontinence score	Sexual function	Subjective measure
		Permanent stoma	N/A			Bowel function	Miller's incontinence score	Sexual quality of life	Subjective measure
						Voluntary bowel movements	Miller's incontinence score		
						Psychological stress	SF-36 questionnaire		
						Urinary incontinence	Subjective measure		
						Quality of life	SF-36 questionnaire		

Ghorbanpour M (2019)	Mean: 0.3	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure		
		HAEC	Review of records	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
Askarpour S (2019)	Unspecified	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Holschneider incontinence score		
		HAEC	Review of records			Bowel function	Holschneider incontinence score		
						Voluntary bowel movements	Subjective measure		
Gupta DK (2019)	Mean: 3.6	Unplanned reoperation	N/A	Perioperative complications	Review of records	Faecal incontinence	Subjective measure		
		Permanent stoma	N/A			Voluntary bowel movements	Subjective measure		
		HAEC	Review of records						
Obata S (2019)	Unspecified	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Subjective measure		
		Unplanned reoperation	N/A			Voluntary bowel movements	Subjective measure		
		HAEC	Review of records						

Hedbys J (2019)	Median: 7	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Rintala bowel function score	Perineal rash	N/A
		Permanent stoma	N/A	Perioperative complications	Review of records	Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		
Sekioka A (2019)	Mean: 0.1	Permanent stoma	N/A						
Freedman-Weiss MR (2019)	Mean: 0.1	Death with cause specified	N/A	Postoperative hospital stay	N/A				
		Unplanned reoperation	N/A	Readmission	Review of records				
				Perioperative complications	Review of records				
				Growth and nutritional status	Weight				
Jiao C (2019)	Mean: 1	HAEC	Review of records	Perioperative complications	Review of records	Faecal incontinence	Subjective measure		
						Voluntary bowel movements	Subjective measure		
Obata S (2019)	Unspecified	Death with cause specified	N/A						
		Unplanned reoperation	N/A						
		Permanent stoma	N/A						

		HAEC	Review of records						
Drissi F (2019)	Mean: 32	Permanent stoma	N/A			Faecal incontinence	HSCR/Anorectal malformation quality of life questionnaire	Educational level and income	Subjective measure
						Bowel function	HSCR/Anorectal malformation quality of life questionnaire		
						Voluntary bowel movements	HSCR/Anorectal malformation quality of life questionnaire		
						Psychological stress	HSCR/Anorectal malformation quality of life questionnaire		
						Urinary incontinence	HSCR/Anorectal malformation quality of life questionnaire		
						Quality of life	HSCR/Anorectal malformation quality of life questionnaire		
Sola R Jr (2019)	Unspecified	Death with cause specified	N/A	Readmission	Review of records	Faecal incontinence	Subjective measure	Feeding issues	Subjective measure

		Unplanned reoperation	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
		HAEC	Review of records						
Zhu T (2019)	Less than 1	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure		
				Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
Peng CH (2018)	Median: 6.8	Unplanned reoperation	N/A			Faecal incontinence	Subjective measure		
		Permanent stoma	N/A			Voluntary bowel movements	Subjective measure		
Zheng Z (2018)	Mean: 1.1	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A
		HAEC	Severity scoring system	Perioperative complications	Review of records	Bowel function	Long term prognosis survey following pull-through		
						Voluntary bowel movements	Subjective measure		
Gunadi (2018)	Unspecified	HAEC	Delphi score system			Voluntary bowel movements	Krickenbeck classification		

Xi Z (2018)	Mean: 1.6					Faecal incontinence	HD anal function criteria		
						Bowel function	HD anal function criteria		
						Voluntary bowel movements	HD anal function criteria		
						Psychological stress	TACQOL scale		
						Quality of life	TACQOL scale		
Widyasari A (2018)	Mean: 2.5			Perioperative complications	Review of records	Faecal incontinence	Krickenbeck classification		
				Growth and nutritional status	Weight	Bowel function	Krickenbeck classification		
						Voluntary bowel movements	Krickenbeck classification		
Chung PHY (2018)	Median: 4.3	HAEC	Review of records	Anorectal manometry	Anorectal manometry readings	Faecal incontinence	Rintala bowel function score		
						Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		

Sood S (2018)	Median: 14.5	Permanent stoma	N/A	Perioperative complications	Review of records	Faecal incontinence	Baylor continence scale	Patients' and families' perspectives of symptoms	Fecal incontinence and constipation quality of life questionnaire
		HAEC	Review of records			Bowel function	Baylor incontinence scale		
						Voluntary bowel movements	Cleveland clinic constipation scoring system		
						Psychological stress	PedsQL		
						Urinary incontinence	Vancouver symptom score		
						Quality of life	PedsQL		
Yokota K (2018)	Median: 3.8	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A
				Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
Neuvonen MI (2018)	Median: 12	Permanent stoma	N/A			Faecal incontinence	Rintala bowel function score		
		HAEC	Review of records			Bowel function	Rintala bowel function score		

						Voluntary bowel movements	Rintala bowel function score		
Roorda D (2018)	Median: 16.5	Death with cause specified	N/A			Faecal incontinence	HSCR/Anorectal malformation quality of life questionnaire		
		Unplanned reoperation	N/A			Bowel function	HSCR/Anorectal malformation quality of life questionnaire		
		Permanent stoma	N/A			Voluntary bowel movements	HSCR/Anorectal malformation quality of life questionnaire		
		HAEC	Review of records			Psychological stress	CHQ-CF87 WHOQOL-100		
						Urinary incontinence	HSCR/Anorectal malformation quality of life questionnaire		
						Quality of life	CHQ-CF87 WHOQOL-100		
Miyano G (2018)	At 1, 3, 5, 7 and 10	HAEC	Review of records	Perioperative complications	Review of records	Faecal incontinence	Postoperative bowel function evaluation score	Perineal rash	N/A
						Bowel function	Postoperative bowel function		

							evaluation score		
						Voluntary bowel movements	Postoperative bowel function evaluation score		
Huang WK (2018)	Mean: 6.3	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Subjective measure		
		HAEC	Review of records	Growth and nutritional status	Weight	Voluntary bowel movements	Subjective measure		
Tran VQ (2018)	Mean: 16.1	HAEC	Review of records	Perioperative complications	Review of records	Faecal incontinence	Wingspread score		
				Anorectal manometry	Anorectal manometry readings	Bowel function	Rome III criteria		
						Voluntary bowel movements	Rome III criteria		
Zhang X (2018)	Median: 5.2	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Holschneider incontinence score	Perineal rash	N/A
		Unplanned reoperation	N/A	Perioperative complications	Review of records	Bowel function	Holschneider incontinence score		
		HAEC	Review of records	Growth and nutritional status	Height and weight	Voluntary bowel movements	Holschneider incontinence score		

Zhang J (2017)	At 0.25, 0.5, 2 and 5	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Rintala bowel function score		
				Perioperative complications	Review of records	Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		
Lof Granstrom A (2017)	Median: 19	Death with cause specified	N/A						
Bjornland K (2017)	Median: 9.5	Unplanned reoperation	N/A	Perioperative complications	Review of records	Faecal incontinence	Rintala bowel function score		
		Permanent stoma	N/A			Bowel function	Rintala bowel function score		
		HAEC	Review of records			Voluntary bowel function	Rintala bowel function score		
Bradnock TJ (2017)	Under 0.5	Death with cause specified	N/A						
		Unplanned reoperation	N/A						
		Permanent stoma	N/A						
Neuvonen M (2017)	Median: 18	Death with cause specified	N/A			Urinary incontinence	Danish prostatic symptom score	Sexual function	Erectile hardness score
		Unplanned reoperation	N/A					Fertility	Subjective measure

		Permanent stoma	N/A					Sexual quality of life	Subjective measure
		HAEC	Review of records						
Onishi S (2017)	Median: 25	Death with cause specified	N/A			Faecal incontinence	Evacuation score defined by Japan society of Ano-rectal malformation study group	Sexual function	Subjective measure
						Bowel function	Evacuation score defined by Japan society of Ano-rectal malformation study group	Fertility	Subjective measure
						Voluntary bowel movements	Evacuation score defined by Japan society of Ano-rectal malformation study group	Sexual quality of life	Subjective measure
						Urinary incontinence	Subjective measure		
						Quality of life	Subjective measure		

De la Torre L (2017)	Mean: 7					Faecal incontinence	Subjective measure		
						Voluntary bowel movements	Subjective measure		
Collins L (2017)	Mean: 6.4	Permanent stoma	N/A	Perioperative complications	Review of records	Faecal incontinence	Baylor continence scale	Patients' and families' perspectives of symptoms	Fecal incontinence and constipation quality of life questionnaire
						Bowel function	Baylor continence scale		
						Voluntary bowel movements	Cleveland clinic constipation scoring system		
						Psychological stress	PedsQL		
						Urinary incontinence	Vancouver symptom score		
						Quality of life	PedsQL		
Cheng S (2017)	Median: 2.7	HAEC	HAEC grade system	Postoperative hospital stay	N/A				
				Readmission	Review of records				

				Perioperative complications	Review of records				
Hasserius J (2017)	Median: 7	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Rintala bowel function score	Perineal rash	N/A
		Unplanned reoperation	N/A	Perioperative complications	Review of records	Bowel function	Rintala bowel function score		
		Permanent stoma	N/A			Voluntary bowel movements	Rintala bowel function score		
Graneli C (2017)	Median: 5	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Rintala bowel function score	Perineal rash	N/A
				Readmission	Review of records	Bowel function	Rintala bowel function score	Feeding issues	Subjective measure
				Perioperative complications	Review of records	Voluntary bowel movements	Rintala bowel function score		
Bing X (2017)	Mean: 3.5			Postoperative hospital stay	N/A	Faecal incontinence	Rintala bowel function score	Perineal rash	N/A
				Perioperative complications	Review of records	Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		
Yasui Y (2017)	Mean: 10.6			Perioperative complications	Review of records	Faecal incontinence	Evacuation score defined by Japan society of Ano-rectal		

							malformation study group		
				Anorectal manometry	Anorectal manometry readings	Bowel function	Evacuation score defined by Japan society of Ano-rectal malformation study group		
						Voluntary bowel movements	Evacuation score defined by Japan society of Ano-rectal malformation study group		
Lu C (2017)	Mean: 0.3	HAEC	HAEC grading system	Perioperative complications	Review of records	Faecal incontinence	Pediatric incontinence/ constipation scoring system	Perineal rash	N/A
						Bowel function	Pediatric incontinence/ constipation scoring system		
						Voluntary bowel movements	Pediatric incontinence/ constipation scoring system		
Neuvone n MI	Median: 15	Permanent stoma	N/A			Faecal incontinence	Rintala bowel function score	Patients' and	PedsQL

(2017)								families' perspectives of symptoms	
		HAEC	Review of records			Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		
						Psychological stress	PedsQL GIQLI SF-36 questionnaire		
						Quality of life	PedsQL GIQLI		
Church JT (2017)	Mean: 4.8	Unplanned reoperation	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
		HAEC	Review of records						
Thakkar HS (2017)	Median: 6	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Rintala bowel function score	Feeding issues	Subjective measure
		Unplanned reoperation	N/A	Anorectal manometry	Anorectal manometry readings	Bowel function	Rintala bowel function score		
		Permanent stoma	N/A			Voluntary bowel movements	Rintala bowel function score		
		HAEC	Review of records						

Stenstrom P (2017)	Median: 9.5	Unplanned reoperation	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Rintala bowel function score	Feeding issues	Subjective measure
		Permanent stoma	N/A	Perioperative complications	Review of records	Bowel function	Rintala bowel function score		
		HAEC	Review of records	Growth and nutritional status	Height and weight	Voluntary bowel movements	Rintala bowel function score		
Tannuri AC (2017)	Mean: 10.4					Faecal incontinence	Holschneider incontinence score		
						Bowel function	Holschneider incontinence score		
						Voluntary bowel movements	Holschneider incontinence score		
						Psychological stress	Assessment of quality of life in children and adolescents with fecal incontinence		
						Quality of life	Assessment of quality of life in children and adolescents with fecal incontinence		
Dingemans A	Median: 6.7	Unplanned reoperation	N/A	Perioperative complications	Review of records	Faecal incontinence	Subjective measure		

(2017)		Permanent stoma	N/A			Bowel function	Krickenbeck classification		
		HAEC	Review of records			Voluntary bowel movements	Krickenbeck classification		
Bischoff A (2017)	Mean: 6.1	Unplanned reoperation				Faecal incontinence	Subjective measure		
		Permanent stoma				Voluntary bowel movements	Subjective measure		
Ghosh DN (2017)	Median: 1.3	Unplanned reoperation	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
		HAEC	Review of records						
Ladi-Seyedian SS (2017)	Mean: 7.2			Anorectal manometry	Anorectal manometry readings	Faecal incontinence	Subjective measure		
						Bowel function	Rome III criteria		
						Voluntary bowel movements	Rome III criteria		
Adiguzel U (2017)	Median: 0.3	Unplanned reoperation	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A
		Permanent stoma	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		

		HAEC	Review of records	Anorectal manometry	Anorectal manometry readings				
Taguchi T (2017)	Unspecified					Voluntary bowel movements	Subjective measure	Feeding issues	Subjective measure
Lukac M (2016)	Unspecified	Unplanned reoperation	N/A	Perioperative complications	Review of records				
		HAEC	Review of records						
Onishi S (2016)	Median: 8.5	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Evacuation score defined by Japan Society of Ano-Rectal Malformation Study Group		
				Perioperative complications	Review of records	Bowel function	Evacuation score defined by Japan Society of Ano-Rectal Malformation Study Group		
						Voluntary bowel movements	Evacuation score defined by Japan Society of Ano-Rectal		

							Malformation Study Group		
Kwendakwema N (2016)	Median: 2.4	HAEC	Review of records	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
Granstrom AL (2016)	Median: 25							Educational level and income	Subjective measure
Ouladsaiad M (2016)	Mean: 6	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Pediatric incontinence/ constipation scoring system	Perineal rash	N/A
				Perioperative complications	Review of records	Bowel function	Pediatric incontinence/ constipation scoring system		
						Voluntary bowel movements	Pediatric incontinence/ constipation scoring system		
Guerra J (2016)	Mean: 0.3	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A
				Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
Li Q (2016)	Median: 3.5	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A

		Unplanned reoperation	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
		HAEC	Review of records	Growth and nutritional status	Height and weight				
Xia X (2016)	Mean: 19.7	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A
				Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure	Visibility of scar	Subjective measure
Xia X (2016)	Mean: 4.8	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Stooling survey from El-Sawaf et al.	Visibility of scar	Subjective measure
		HAEC	Review of records	Perioperative complications	Review of records	Bowel function	Stooling survey from El-Sawaf et al.		
						Voluntary bowel movements	Stooling survey from El-Sawaf et al.		
Nam SH (2015)	Median: 9.9			Postoperative hospital stay	N/A	Faecal incontinence	Krickenbeck classification		
				Perioperative complications	Review of records	Bowel function	Krickenbeck classification		
						Voluntary bowel movements	Krickenbeck classification		
Xiong X (2015)	Mean: 26.8					Faecal incontinence	Rintala bowel function score		

						Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		
						Psychological stress	WHO QOL-BREF		
						Quality of life	WHO QOL-BREF		
Miyano G (2015)	Median: 7	HAEC	Review of records	Perioperative complications	Review of records	Faecal incontinence	Postoperative fecal continence	Perineal rash	N/A
						Bowel function	Postoperative fecal continence		
						Voluntary bowel movements	Postoperative fecal continence		
Aubdoolah TH (2015)	Mean: 1	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A
		HAEC	Review of records	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure	Visibility of scar	Manchester Scar Scale
Khazdouz M (2015)	Median: 5.5	HAEC	Review of records			Faecal incontinence	Subjective measure		
						Voluntary bowel movements	Subjective measure		

Granstrom AL (2015)	Median: 28	Unplanned reoperation	N/A	Perioperative complications	Review of records	Faecal incontinence	Miller's incontinence score		
		Permanent stoma	N/A	Growth and nutritional status	Height and weight	Bowel function	Miller's incontinence score		
						Voluntary bowel movements	Miller's incontinence score		
						Psychological stress	SF-36 GIQLI		
						Urinary incontinence	Subjective measure		
						Quality of life	GIQLI		
Amerstorfer EE (2015)	Median: 13.5	Unplanned reoperation	N/A	Perioperative complications	Review of records	Faecal incontinence	Rintala bowel function score		
		HAEC	Review of records	Growth and nutritional status	Height and weight	Bowel function	Rintala bowel function score		
						Voluntary bowel movements	Rintala bowel function score		
						Psychological stress	Quality of life scoring criteria for children with fecal incontinence		
						Quality of life	Quality of life scoring criteria		

							for children with fecal incontinence		
Hukkinen M (2015)	Mean: 6.8	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Subjective measure	Feeding issues	Subjective measure
		Unplanned reoperation	N/A	Growth and nutritional status	Height and weight	Voluntary bowel movements	Subjective measure		
		Permanent stoma	N/A						
		HAEC	Review of records						
Khalil M (2015)	Mean: 5.9			Perioperative complications	Review of records	Faecal incontinence	Subjective measure		
				Growth and nutritional status	Height and weight	Voluntary bowel movements	Subjective measure		
						Psychological stress	PedsQL		
						Quality of life	PedsQL		
Stensrud KJ (2015)	Median: 8.8			Anorectal manometry	Anorectal manometry readings	Faecal incontinence	Krickenbeck classification		
						Bowel function	Krickenbeck classification		
						Voluntary bowel movements	Krickenbeck classification		

Neuvonen MI (2015)	Mean: 15	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Miller's incontinence score	Feeding issues	Subjective measure
		Unplanned reoperation	N/A	Growth and nutritional status	Height and weight	Bowel function	Miller's incontinence score		
		Permanent stoma	N/A			Voluntary bowel movements	Miller's incontinence score		
		HAEC	Review of records						
Wester T (2015)	Mean: 6.8	Unplanned reoperation	N/A			Faecal incontinence	Subjective measure	Feeding issues	Subjective measure
		Permanent stoma	N/A			Voluntary bowel movements	Subjective measure		
		HAEC	Review of records						
Shrestha MK (2014)	Mean: 3	Unplanned reoperation	N/A	Perioperative complications	Review of records	Faecal incontinence	Subjective measure	Perineal rash	N/A
		Permanent stoma	N/A			Voluntary bowel movements	Subjective measure		
		HAEC	Review of records						
YK S (2014)	Mean: 0.03	Death with cause specified	N/A	Perioperative complications	Review of records				
		Unplanned reoperation	N/A						

		Permanent stoma	N/A						
		HAEC	Review of records						
Sulkowski JP (2014)	Mean: 2	Unplanned reoperation	N/A	Readmission	Review of records				
		HAEC	Review of records	Perioperative complications	Review of records				
Yeh YT (2014)	Median: 9	Death with cause specified	N/A	Growth and nutritional status	Height and weight	Faecal incontinence	Subjective measure	Perineal rash	N/A
		Unplanned reoperation	N/A			Voluntary bowel movements	Subjective measure	Feeding issues	Subjective measure
		Permanent stoma	N/A						
		HAEC	Review of record						
Ralls MW (2014)	Mean: 18.7	Unplanned reoperation	N/A	Perioperative complications	Review of records	Faecal incontinence	Stooling survey from El-Sawaf et al.		
		Permanent stoma	N/A			Bowel function	Stooling survey from El-Sawaf et al.		
		HAEC	Review of records			Voluntary bowel movements	Stooling survey from El-Sawaf et al.		
Han-Geurts IJ	Median: 7.3	Unplanned reoperation	N/A			Faecal incontinence	Subjective measure		

(2014)		HAEC	Review of records			Voluntary bowel movements	Subjective measure		
Basson S (2014)	Median: 10.8	Unplanned reoperation	N/A			Voluntary bowel movements	Subjective measure		
		Permanent stoma	N/A						
Mabula JB (2014)	Median: 0.7	Death with cause specified	N/A	Urinary tract infection	Review of records	Faecal incontinence	Subjective measure	Perineal rash	N/A
		Unplanned reoperation	N/A	Perioperative complications	Review of records				
		Permanent stoma	N/A						
Zhang JS (2014)	Median: 12.2	HAEC	Review of records	Perioperative complications	Review of records	Faecal incontinence	Subjective measure		
				Anorectal manometry	Anorectal manometry readings	Voluntary bowel movements	Subjective measure		
Nasr A (2014)	Mean: 3	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A
				Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
Spataru R (2014)	Mean: 3.1			Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure		
				Perioperative complications	Review of records				

Mathur MK (2014)	At 0.1 and 0.3			Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure	Perineal rash	N/A
				Perioperative complications	Review of records				
Hukkinen M (2014)	Median: 3.2	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Miller's incontinence score	Perineal rash	N/A
				Readmission	Review of records	Bowel function	Miller's incontinence score	Feeding issues	Subjective measure
				Perioperative complications	Review of records	Voluntary bowel movements	Miller's incontinence score	Visibility of scar	Subjective measure
						Urinary incontinence	Subjective measure		
More K (2014)	Mean: 1	Death with cause specified	N/A	Postoperative hospital stay	N/A			Intelligence	Griffiths Mental Development Scale
		HAEC	Review of records	Perioperative complications	Review of records			Behaviour	Ages and Stages Questionnaire
				Growth and nutritional status	Height and weight				
Wang L (2014)	Mean: 22	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Rintala bowel function score	Sexual function	Subjective measure

						Bowel function	Rintala bowel function score	Sexual quality of life	Subjective measure
						Voluntary bowel function	Wexner constipation score		
						Psychological stress	GI quality of life index		
						Quality of life	GI quality of life index		
Ksia A (2013)	Unspecified	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Holschneider incontinence score	Perineal rash	N/A
				Perioperative complications	Review of records	Bowel function	Holschneider incontinence score		
						Voluntary bowel movements	Holschneider incontinence score		
Granstrom AL (2013)	Mean: 7.4	HAEC	Review of records	Perioperative complications	Review of records	Faecal incontinence	Subjective measure		
						Voluntary bowel movements	Subjective measure		
Levitt MA (2013)	Unspecified	Unplanned reoperation	N/A	Readmission	Review of records	Faecal incontinence	Subjective measure	Sexual function	Subjective measure
		Permanent stoma	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		

		HAEC	Review of records						
Tang ST (2013)	Mean: 0.25	HAEC	Review of records	Postoperative hospital stay	N/A	Voluntary bowel movements	Subjective measure	Perineal rash	N/A
				Perioperative complications	Review of records				
Van de Ven TJ (2013)	Median: 4.2	Death with cause specified	N/A	Postoperative hospital stay	N/A	Voluntary bowel movements	Subjective measure		
		Unplanned reoperation	N/A	Perioperative complications	Review of records				
		HAEC	Review of records						
Demirbag S (2013)	Mean: 3.5	HAEC	Review of records	Anorectal manometry	Anorectal manometry readings	Faecal incontinence	Subjective measure	Perineal rash	N/A
						Voluntary bowel movements	Subjective measure		
El-Sawaf M (2013)	At 0.1, 0.25, 0.5 and 1	Death with cause specified	N/A						
		HAEC	El Halabi criteria						
Miyano G (2013)	Mean: 11.6	Death with cause specified	N/A	Readmission	Review of records			Visibility of scar	Subjective measure
		Unplanned reoperation	N/A	Perioperative complications	Review of records				

		HAEC	Review of records						
Zhu T (2013)	Mean: 2.6	HAEC	Review of records	Perioperative complications	Review of records	Faecal incontinence	Subjective measure	Perineal rash	N/A
						Voluntary bowel movements	Subjective measure	Visibility of scar	Subjective measure
Stensrud KJ (2012)	Mean: 8.5	Unplanned reoperation	N/A	Perioperative complications	Review of records	Faecal incontinence	Krickenbeck classification		
		Permanent stoma	N/A			Bowel function	Krickenbeck classification		
						Voluntary bowel movements	Krickenbeck classification		
						Psychological stress	Subjective measure		
Aworanti OM (2012)	Mean: 4.6	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Pediatric incontinence/ constipation scoring system		
		Permanent stoma	N/A			Bowel function	Pediatric incontinence/ constipation scoring system		
		HAEC	Review of records			Voluntary bowel movements	Pediatric incontinence/ constipation scoring system		

Al-Jazaeri A (2012)	Mean: 0.6	Death with cause specified	N/A						
		Unplanned reoperation	N/A						
		Permanent stoma	N/A						
Yang L (2012)	Mean: 4.7	HAEC	Teitelbaum and Coran criteria	Postoperative hospital stay	N/A	Faecal incontinence	Wingspread score	Perineal rash	N/A
				Perioperative complications	Review of records	Bowel function	Rome II criteria		
						Voluntary bowel movements	Rome II criteria		
						Urinary incontinence	Subjective measure		
Li N (2012)	Mean: 2.8					Bowel function	Kohno's rating scale		
Zakaria OM (2012)	Mean: 1.9	HAEC	Review of records	Postoperative hospital stay	N/A	Faecal incontinence	Wingspread score	Perineal rash	N/A
				Perioperative complications	Review of records	Bowel function	Wingspread score		
				Anorectal manometry	Anorectal manometry readings	Voluntary bowel movements	Wingspread score		
Kothari PR	Mean: 3.8	Unplanned reoperation	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure		

(2012)		HAEC	Review of records	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
				Growth and nutritional status	Height and weight				
Sheng Q (2012)	Mean: 2.5	Unplanned reoperation	N/A	Anorectal manometry	Anorectal manometry readings	Faecal incontinence	Krickenbeck classification		
		HAEC	Review of records			Bowel function	Krickenbeck classification		
						Voluntary bowel movements	Krickenbeck classification		
Nah SA (2012)	Median: 6.8	Death with cause specified	N/A	Postoperative hospital stay	N/A	Faecal incontinence	Subjective measure		
		Unplanned reoperation	N/A	Perioperative complications	Review of records	Voluntary bowel movements	Subjective measure		
		Permanent stoma	N/A						
		HAEC	Review of records						
Urushihara N (2012)	Mean: 5.6	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Subjective measure		
		Unplanned reoperation	N/A			Voluntary bowel movements	Subjective measure		

		HAEC	Review of records			Urinary incontinence	Subjective measure		
Sharma S (2012)	Mean: 4.6			Perioperative complications	Review of records				
Dagorno C (2020)	Mean: 8.5	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Subjective measure	Perineal rash	N/A
		Unplanned reoperation	N/A			Voluntary bowel movements	Subjective measure	Feeding issues	Subjective measure
		Permanent stoma	N/A						
		HAEC	Review of records						
Urla C (2018)	Median: 7	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Wildhaber score	Perineal rash	N/A
		Unplanned reoperation	N/A	Growth and nutritional status	Height and weight	Bowel function	Wildhaber score		
		Permanent stoma	N/A			Voluntary bowel movements	Wildhaber score		
						Psychological stress	Barrena scoring system		
						Quality of life	Barrena scoring system		

Broch A (2019)	Median: 15	Death with cause specified	N/A			Faecal incontinence	Subjective measure		
		Unplanned reoperation	N/A			Voluntary bowel movements	Subjective measure		
		Permanent stoma	N/A						
Pini Prato A (2019)	Median: 7	Death with cause specified	N/A	Perioperative complications	Review of records	Faecal incontinence	Wingspread score	Perineal rash	N/A
		Unplanned reoperation	N/A						
		Permanent stoma	N/A						
		HAEC	El Halabi criteria						

Appendix 3: Information leaflet and consent form for cohort study

Long term outcomes for patients with Hirschsprung's Disease and Anorectal Malformations

Information for Parents

We are inviting you to take part in a study looking at the long-term effects of your child being born with an Anorectal Malformation or Hirschsprung's Disease. This leaflet provides information about what the study involves and the reasons for performing the study. Please take your time to think about this and if you have any questions or would like any further information before deciding whether to participate then please ask us. It is worthwhile spending some time to think about whether you would like to take part and it can be helpful to discuss this with others.

What is the purpose of the study?

We know that people with Anorectal Malformations and Hirschsprung's Disease can develop a range of problems with their bowels in both the short and the long term. We hope to be able to better determine the factors that may lead to more problems and assess the effect of these bowel problems on people's quality of life. This will help us to better inform others of what they may be able to expect in the future and will help to guide the management of people born with Anorectal Malformations and Hirschsprung's Disease. This study complements the NETS^{2HD} study which you may be aware of. This was a national study looking at all children born with Hirschsprung's Disease in 2010-2012. This study uses the same questionnaires but in addition to NETS^{2HD}, will be asking older children and adults about their experiences too. If your child was a part of the NETS^{2HD} study, you will not be sent questionnaires before they are 9 years old.

Why have I been chosen?

As someone whose child has been born with an Anorectal Malformation or Hirschsprung's, your input and experience is very important. You and your child have individual experiences of what has happened and therefore your input is very important.

What will be involved?

If you agree to take part in the study you will be given questionnaires to complete. You will be given the age-appropriate questionnaires at the point that your child enters the study and then subsequent questionnaires at two further time points, 5 and 10 years after the first questionnaire. The questionnaires will take approximately an hour to complete and will cover questions on quality of life and bowel function. We will collect background information about your child including the age and type of operation that they have had and subsequent treatments that they have required.

Do we have to take part?

No, it is completely up to you and your child as to whether you take part. You or your child can also opt-out of the study at any point and your child's care will not be affected by either of these situations.

What will happen to us if we do decide to take part?
If you do decide to take part you will be taken through a consent form, and so will your child if they are old enough. You will be given the questionnaires to complete with your child either in hospital or at home and post or email back to us. The research nurse will be available for any questions that you may have. There will be the opportunity to discuss any concerns or questions with your clinical team at an outpatient appointment or over the telephone. Future questionnaires will be posted or emailed out to you depending on your preference.

What are the possible disadvantages or risks of taking part?
You may find some of the questions difficult to answer or that they may bring up memories that are hard to deal with. We are on-hand to discuss this with you and if you feel that your child needs to talk to a psychologist then we will refer you to that service.

What are the potential benefits of taking part?
There will be no direct benefit to you or your child in taking part, however we will be asking people who are now adults themselves who have had an Anorectal Malformation or Hirschsprung's Disease the same questionnaires (age appropriate) and their participation may give us further knowledge that will be useful for you and your child.

Will my participation in the study be kept confidential?
Yes, your child's name will not be disclosed outside of the hospital.

What will happen to the results of the study?
We will publish the results of this work in medical and scientific journals. If you would like to know the results please inform us.

Who is organising and funding the research?
This study is being organised and led by Mr Baillie, Mr Kenny and Miss Almond at Alder Hey Children's Hospital. They are not being paid for running this study. The study will be funded by the Alder Hey Paediatric Surgery Charity.

Who has reviewed the study?
This study has been reviewed by the Research Review Committee at Alder Hey Hospital and the Liverpool Research Ethics Committee.

What will happen to data about my child?
Alder Hey Children's Hospital is the sponsor for this study based in the United Kingdom. We will be using information from you, your child and their medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Alder Hey Children's Hospital will keep identifiable information about you for 10 years.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you

or your child withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting Miss Almond at the address below.

Alder Hey Children's Hospital will use your name, NHS number and contact details to contact you and your child about the research study, and make sure that relevant information about the study is recorded for your child's care, and to oversee the quality of the study. Individuals from Alder Hey Children's Hospital and regulatory organisations may look at your child's medical and research records to check the accuracy of the research study. The only people in Alder Hey who will have access to information that identifies you will be people who need to contact you to send out questionnaires or audit the data collection process. The people who analyse the information will not be able to identify you or your child and will not be able to find out your name, NHS number or contact details.

Contact for further information:
Miss S Almond
Consultant Paediatric Surgeon
Alder Hey Children's Hospital
East Prescot Road
Liverpool
L14 5AB
Tel: 0151 2933693

If you are unhappy with the way in which this research is conducted or would like to make a complaint, the Patient Advice and Liaison Service (PALS) is available to discuss this with you. Their contact details are:

PALS,
Alder Hey Children's NHS Foundation Trust,
Eaton Road,
Liverpool,
L12 2AP
Tel: 0151 282 4907

Parent Information Leaflet and Consent v4 05/10/2021 IRAS: 219338
Patient's Initials: _ _ _

Patient's Date of Birth: _ _/ _ _/ _ _ _ _

Long term outcomes for patients with Hirschsprung's Disease and Anorectal Malformations

Parent Consent form

	Please initial box
1. I confirm that I have read and understand the information sheet v4 dated 05/10/2021 for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2. I understand that participation is voluntary and that I am free to withdraw my child at any time, without giving a reason, and without my child's care or legal rights being affected.	
3. I understand that relevant sections of any of my child's medical notes and data collected during the study may be looked at by responsible individuals where it is relevant to my child taking part in this research. These include individuals representing the trial team, trial sponsor (Alder Hey hospital), regulatory authorities or from other NHS bodies and the Independent Ethics Committee. I give permission for these individuals to have access to my child's records and to collect, store, analyse and publish information from this research even if I withdraw him/her from the study. I understand that my child's name will be kept confidential.	
4. I consent to the data collected to be processed and reported for medical research purposes.	
5. I agree for my child's data on NHS hospital admissions to be collected from routine NHS care records	
6. I agree to medical personnel responsible for my child's welfare being informed on my participation in this study.	
7. I agree for my child to take part in the above study.	
8. Optional: I agree that I may be contacted again in the future in relation to this study.	Yes …… No

_____ Name of Patient

_____	_____	_____
Name of Parent	Signature	Date

_____	_____	_____
Researcher	Signature	Date

original copy for participant, copy for site file, copy for patient notes