A journey from clinical data to clinical care for anorectal malformation patients across Europe and Australia: methodological implications of registries and epidemiological comparisons

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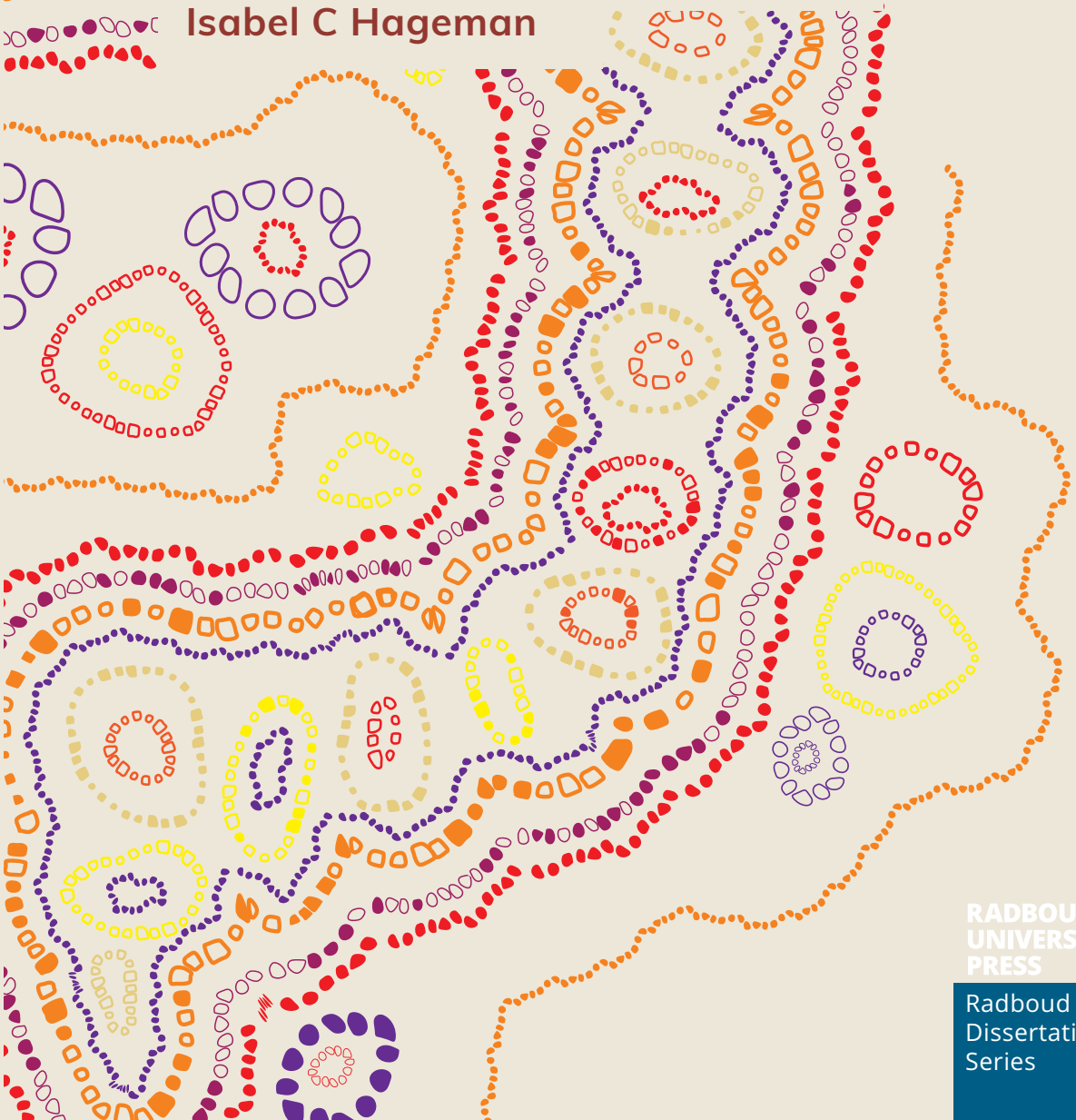

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from Radboud University Nijmegen
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according to the decision of the Doctorate Board
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Thursday, December 5, 2024
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PART 1

Background, key components, and challenges of rare disease patient registries

CHAPTER 1

General introduction

Background

Rare disease patient registries

Patient registries have the potential to solve one of the main challenges of research in rare diseases, where small sample sizes often lead to limited possibilities, and existing data are scarce, scattered, and mostly derived from single-centre studies. Registries are organized systems that use observational study methods to collect data to evaluate specified outcomes for a population defined by a particular disease or condition [1]. They are useful tools when randomized controlled trials are difficult to conduct, and collect observational data outside of experimental or controlled settings, also known as real-world data [2]. The rise of these patient registries, as well as policies protecting the collected data, allow for different centres and countries to collaborate and share data to enhance research possibilities. Registries may also accommodate registry randomized controlled trials: trials that are embedded into the existing infrastructure of a registry, delivering answers to key clinical questions efficiently with great generalizability of results [3]. Rare disease patient registries have become increasingly popular, with more than 800 rare disease registries in or affiliated with Europe listed in a recent report [4]. International collaboration and centralization of data through a registry platform may not only facilitate research, but also allows for exchange of expertise, and establishment of new, or reinforcement of existing partnerships. Furthermore, collecting clinical data from different centres with varying practices may provide a rich source to evaluate and standardize care, ultimately aiming to improve health-related outcomes. However, the establishment of a registry is just a first step, and measures to ensure the quality, utility, relevance, and sustainability are challenges that continuously need to be considered from initiation onwards [5-7].

Anorectal malformations

Anorectal malformations (ARM) encompass a spectrum of complex congenital defects where the development of the rectum and anus is affected, requiring specialized reconstructive surgery and long-term bowel management [8, 9]. A wide range of ARM types exist (**Figure 1**), and since 2005 they are classified according to the Krickenbeck system with major clinical groups including perineal fistula, recto-bulbar or recto-prostatic urethral fistula, recto-bladder neck fistula, vestibular fistula, cloaca, anal atresia without fistula, and anal stenosis, and rare variants such as rectal atresia, rectovaginal fistula, H-type fistula, or pouch colon [10, 11].

Vestibular fistula and cloaca only present in females, whereas recto-bulbar, recto-prostatic, and recto-bladder neck fistulas only present in males.

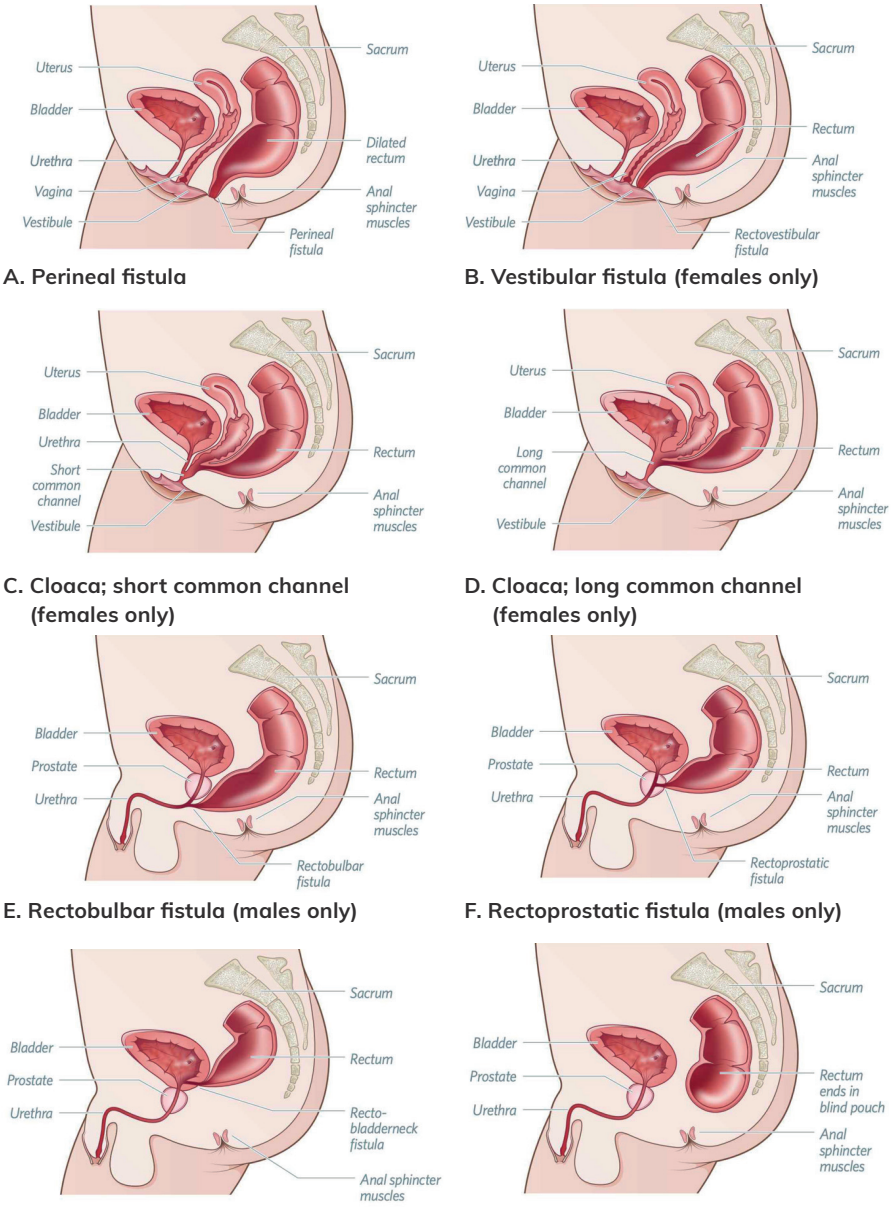

Figure 1: Types of anorectal malformations.

Reused with permission from The Royal Children's Hospital Colorectal and Pelvic Reconstruction Service

Furthermore, ARM patients often present with congenital anomalies in other organ systems, such as genital, spinal, vertebral, cardiac, tracheo-oesophageal, renal, or limb anomalies, either individually or as part of the VACTERL association [12, 13]. As many as 80% of ARM patients have one or more associated anomalies, emphasizing the importance of rigorous diagnostic screening [14-17]. Different ARM types require different surgical approaches, but most patients undergo a surgical reconstruction commonly known as the posterior sagittal anorectoplasty (PSARP), first described in 1982, and about half of the patients receive a prior temporary enterostomy [18]. Other variations to this technique include the anterior sagittal anorectoplasty (ASARP) in 1992 and the laparoscopically assisted anorectoplasty (LAARP) in 2000 [19, 20]. Although outcomes have improved over the years, the quality of life of ARM patients continues to be affected from childhood into adolescence and adulthood both physically, with poor bowel functioning such as faecal incontinence and constipation, and psychosocially with impaired mental and sexual health [21-26].

Anorectal malformation patient registries

Although ARM patients are highly impacted by their condition, research into ARM is often limited because of its rarity, with a prevalence of only 1 in 3000 to 5000 live births [4, 27-29]. Therefore, joint efforts of multiple paediatric surgical centres to communally collect and combine data in online patient registries may be a solution to overcome these challenges. Several initiatives, such as the Anorectal Malformation Network Consortium (ARM-Net) comprising a voluntary group of European paediatric surgeons, epidemiologists, geneticists, and patient representatives (www.arm-net.eu), and later the European Reference Network (ERN) eUROGEN, a virtual network where specialist healthcare providers are connected to share knowledge and expertise on highly specialized surgery for rare urogenital diseases and complex conditions, have developed patient registries collecting real-world clinical data of patients with complex colorectal conditions, including ARM [30, 31]. Another example is the multi-centre registry of the Pediatric Colorectal and Pelvic Learning Consortium of the Nationwide Children's Hospital in Columbus, Ohio in the United States, established in 2016, collecting demographic, diagnostic, treatment and complication data from patients with colorectal conditions including ARM [32]. Furthermore, on the other side of the globe, large specialized centres have their own registries, such as The Royal Children’s Hospital (RCH) in Melbourne, Australia, including patients who have undergone surgical

repair for an ARM or Hirschsprung disease (HD) at Department of Paediatric Surgery of the RCH, in a Colorectal Database [33].

Aims and objectives

The aim of this thesis was to investigate the translation from data to clinical care for ARM patients across Europe and Australia in terms of methodological implications and epidemiological comparisons, to ultimately improve health-related outcomes. To accomplish this, several research questions were investigated:

1. What are the key components, main challenges, and quality measurements for the formation, use, and maintenance of patient registries for rare diseases in medical research and improvement of care?
2. How can real-world data from patient registries be utilized to describe and compare clinical and surgical characteristics of ARM patients across Europe and Australia?
3. How can the knowledge and experience gained facilitate the establishment of new, and the improvement of existing registries for patients with colorectal conditions?

Data sources and study populations

The study populations to investigate the aforementioned research questions have been derived from two data sources: the European Anorectal Malformation Network (ARM-Net) Consortium registry and the Australian RCH Colorectal Database.

ARM-Net registry

The ARM-Net registry was established in 2011 by a group of European paediatric surgeons, epidemiologists, psychologists, clinical geneticists, and patient advocacy groups, forming the ARM-Net Consortium [30, 34]. Patients diagnosed with ARM and treated primarily or secondarily in one of the ARM-Net Consortium participating centres are included in the registry. A lead paediatric surgeon per participating centre is responsible for data collection on patient demographics, disease characteristics including ARM type, diagnostic screening, associated anomalies, surgical details,

complications, and one-year follow-up functional outcomes. The registry is web-based, and data are collected and stored on a webserver based in Germany. Patients treated before 2011 were included retrospectively, and patients treated in 2011 onwards, and whenever a new centre joined the Consortium, were included prospectively. Local ethical requirements, including informed consent, are variable per centre and country and have been met for each participating centre by deidentifying and pseudonymizing all patient data before collection. At moment of writing, more than 3,000 ARM patients have been registered from 34 centres in 13 countries. Data from all patients registered until March 1st, 2023, have been extracted and used in three studies in this thesis (Chapters 4, 5 and 6). Furthermore, metadata on the ARM-Net registry structure and data collection methods have been extracted and evaluated as may be read in Chapter 3, and have served as a foundation for Chapter 7.

RCH Colorectal Database

Patients with ARM or HD treated at the Department of Paediatric Surgery of the RCH in Melbourne, Australia, are included in the Colorectal Database, a patient registry adapted from Nationwide Children's Hospital in Ohio, United States. The RCH Colorectal Database was established in 2015 and collects data on patient demographics, care pathways, diagnostic screening, associated anomalies, surgical and medical history, complications, treatments, and parent- or patient-reported functional outcomes including quality of life. Data are collected in the online web-based Research Electronic Data Capture (REDCap) platform. The RCH Colorectal Database retrospectively includes all ARM, HD, and chronic constipation patients currently or previously treated at the RCH Department of Paediatric Surgery, and all new patients prospectively. Currently, more than 500 ARM patients have been included in the Colorectal Database. Ethical approval was obtained from the RCH Human Research Ethics Committee (HREC) and all patients included have provided verbal consent recorded in a departmental log. Use of the collected data for research purposes requires separate ethics approval. Data from all ARM patients registered until March 1st, 2023, have been extracted and used for the study described in Chapter 6, for which ethics approval was granted (HREC/93070/RCHM-2023).

Outline of this thesis

This thesis explored the journey from research methodologies, epidemiology, and clinical implications of rare diseases, and specifically ARM, by 1) studying how to build and audit rare disease registries, 2) analysing existing ARM registries, 3) building a novel registry, and 4) finalizes with a general discussion.

Part 1: Background, key components, and challenges of rare disease patient registries

Part 1 assesses the key components and pitfalls of registries from a methodological point of view. To gain a better understanding of existing rare disease registries, a qualitative systematic review aimed to describe the literature on the challenges in design, quality management, and maintenance of rare disease patient registries was conducted and is presented in Chapter 2. With the knowledge gained from this investigation, the structure, components, and data collection procedures of the ARM-Net registry were evaluated in an extensive quality assessment described in Chapter 3.

Part 2: Clinical and surgical characteristics of anorectal malformation patients in Europe and Australia

Data collected in the ARM-Net and RCH Colorectal registries were extracted to describe the included ARM patients from an epidemiological and clinical perspective. In Chapter 4, a general overview of the clinical and surgical characteristics of all ARM patients of the ARM-Net registry is provided and discussed. In Chapter 5, the important clinical outcome of surgical complications in ARM patients was studied. By delving further into reconstruction- and enterostomy-related complications, patient- and treatment-related risk factors were identified. Chapter 6 uses the ARM-Net registry patient cohort as the European comparator against Australian ARM patients, derived from the RCH Colorectal Database, to evaluate differences in terms of patient characteristics and surgical approaches.

Part 3: Innovation through collaboration: novel registries for patients with anorectal malformations

With the knowledge and experience gained from reviewing the literature, diving into the European activities around rare disease research, and evaluating the ARM-Net registry, a similar registry for ARM and Hirschsprung disease patients in the Pacific was developed, and the design

and objectives of the Australia New Zealand Congenital Colorectal Registry (ANZCCoRe) are presented in Chapter 7.

Part 4: General discussion and future perspectives

A general discussion conjoining the different themes and findings of the studies included in this thesis, their clinical implications, and possibilities for future research are outlined in Chapter 8. Chapter 9 presents an English and Dutch summary of the research conducted in this thesis.

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CHAPTER 2

A systematic overview of rare disease patient registries: challenges in design, quality management, and maintenance

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Abstract

Patient registries serve to overcome the research limitations inherent in the study of rare diseases, where patient numbers are typically small. Despite the value of real-world data collected through registries, adequate design and maintenance are integral to data quality. We aimed to describe an overview of the challenges in design, quality management, and maintenance of rare disease registries.

A systematic search of English articles was conducted in PubMed, Ovid Medline/Embase, and Cochrane Library. Search terms included “rare diseases, patient registries, common data elements, quality, hospital information systems, and datasets”. Inclusion criteria were any manuscript type focused upon rare disease patient registries describing design, quality monitoring or maintenance. Biobanks and drug surveillances were excluded.

A total of 37 articles, published between 2001 and 2021, met the inclusion criteria. Patient registries covered a wide range of disease areas and covered multiple geographical locations, with a predisposition for Europe. Most articles were methodological reports and described the design and setup of a registry. Most registries recruited clinical patients (92%) with informed consent (81%) and protected the collected data (76%). Whilst the majority (57%) collected patient-reported outcome measures, only few (38%) consulted PAGs during the registry design process. Few reports described details regarding quality management (51%) and maintenance (46%).

Rare disease patient registries are valuable for research and evaluation of clinical care, and an increasing number have emerged. However, registries need to be continuously evaluated for data quality and long-term sustainability to remain relevant for future use.

Background

Patient registries, organized systems that use observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease or condition, are powerful tools to evaluate outcomes when randomized controlled trials are difficult to conduct [1]. Therefore, patient registries have the potential to solve one of the main challenges of research in rare diseases, where small sample sizes often lead to limited possibilities. With the low prevalence consequential to rare diseases, patient data are scarce and scattered. However, the rise of large online databases and data protection policies allow different centres and different countries to collaborate and share data to enhance research possibilities. Rare disease registries have become increasingly popular: more than 800 rare disease registries were listed in a December 2021 report of registries in or affiliated with Europe [2].

In line with the increasing number of patient registries for rare diseases, the European Union Committee of Experts on Rare Diseases (EUCERD) published recommendations in 2013 on patient registration and data collection. They emphasize interoperability with other registries through use of ontological coding language and minimum common data sets, involvement of patients in registry governance, and adaptability and sustainability for registry continuation [3]. However, with the exception that quality should be assured, no constructive descriptions on measures for quality were outlined, even though experts agree that registries should always be created using well-established quality criteria, and quality should be one of the most important elements in design and maintenance of a registry [4, 5]. Fortunately, many European registries do dedicate attention to data quality, but comprehensive quality assurance plans are not yet common practice [6].

In 2015, the Cross-border Patient Registries Initiative (PARENT) published specific methodological guidelines for governance of patient registries, delving deeper into the quality dimensions of a patient registry [7]. PARENT categorized the quality dimensions into governance, data quality, information quality, and ethical and legal issues regarding data privacy and protection. However, with the increasing number and widely varying types of (online) registries, guidelines on management and infrastructure on (re) use of data were necessary, and the FAIR principles were born in 2016 [8].

The four principles of findability, accessibility, interoperability and reusability (FAIR) aimed to navigate the expanding terrain of big data and electronic data capturing in research and have also been successfully applied and implemented in rare disease registries [8, 9]. The Italian National Centre of Rare Diseases recognized the need for guidelines specifically for data quality management in rare disease patient registries. Together with other European countries, they published recommendations aligned with the FAIR principles in 2018, focusing not only on establishment of registries, but also on maintenance and sustainability [10].

The design, development, and establishment of a registry comprises a multitude of aspects: technicalities of coding language and data capturing programs; ethical and legal issues to ensure data privacy and protection whilst simultaneously enabling data sharing and reuse; governance and managerial aspects attending to the different interests of patients, clinicians, researchers, policy makers, pharmaceutical companies, and other stakeholders. Initiatives worldwide provide support to the development of rare disease registries. The European Registration of Rare Disease Patients (EPIRARE) project aims to address regulatory, ethical and technical issues associated with the registration of rare disease patients in Europe, and the American Patient Registry Item Specifications and Metadata (PRISM) Library for rare diseases centralizes important questions and answers when creating a new registry [11, 12].

However, the establishment of a registry is just a first step, and although several guidelines have been published, the quality of patient registries remains a challenge, and data quality and bias are amongst the limitations of using patient registry data [13]. Utility, relevance, and sustainability are also amongst the issues that continuously need to be addressed. In this review, we aimed to describe the literature that pertains to the design, quality management, and maintenance of rare disease patient registries to learn from and improve existing registries, and to act as a basis for the setup of new registries.

Methods

A systematic search for English language publications in Medline (Ovid), Embase (Ovid), Pubmed, and Cochrane Library was conducted. Search items included “rare diseases”, “patient registries”, “common data

elements", "quality", "hospital information systems" and "datasets", in free text and keyword (MeSH) versions (See **Supplementary File 1** for full search methods). There was no time frame limit on publication date of the literature search. After removing duplicates, studies were screened across two stages. In the first stage, all titles and abstracts of all studies were screened against the inclusion criteria. In the second stage, the potentially relevant studies underwent full text screening. Using Covidence systematic review software, one person (ICH) completed all screening [14].

Inclusion criteria:

- No restriction on types of studies
- Subjects must be human and have a rare disease
- Study must involve a patient registry, defined as an organized system that uses observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease or condition [1]
- Study must include a description of a registry component such as setup/design, maintenance/sustainability, and/or quality monitoring/assurance
- Aim of the registry must at least include either surveillance or, gaining knowledge on the understanding of natural history, evolution, risk and/or outcomes of a specific disease

Exclusion criteria:

- Study only describing results with patient data extracted from a registry
- Study involves a registry that does not collect clinical data (e.g., biobanks)
- Study involves a registry that is designed for the sole purpose to develop or evaluate (pharmacological) products

The primary data points for extraction of this literature review were at least one description of:

i. Design or setup of a registry:
    b. use of informed consent (yes/no)
    c. use of a set of common data elements (yes/no)
    d. the (electronic) data capturing system/interface (e.g., REDCap)
    e. use of ontology/diagnostic codes (yes/no)
    f. collection of patient-reported outcomes (yes/no)
    g. involvement of patient advocacy groups (PAGs) in the design (yes/no)

h. description of governance or structure of management (e.g., coordinating centres, dedicated working group, electoral selection, stakeholders)
i. description of data protection and sharing, (e.g., data access policies, anonymization processes)
j. method of patient recruitment (through clinic, PAGs, insurance records, pharmacy bills, voluntarily through social media/websites, other)

ii. Quality management or assurance of a registry (yes/no), such as quality assessment measures, audits, data entry training programs, site monitoring
iii. Maintenance or sustainability of a registry (yes/no), such as long-term or specific end goals, funding, partnerships, or collaborations

Secondary data points included general characteristics, including article type and aim, characteristics of the patient registry, year launched, country of coordinating entity, population description, inclusion criteria, number of registered patients at time of publications, aim of the registry, and type of data collected.

A data extraction template was created in Covidence systematic review software to collect relevant information according to the aforementioned datapoints [14]. The data were exported to Microsoft Excel 2016 for analysis [15]. Only data published in the articles were collected, with no approaches made to the registry developers and/or websites.

Results

A literature search in the four databases resulted in a total of 1070 records. With the removal of 390 duplicates, 680 records were eligible for title and abstract screening. After title and abstract screening, 165 records were selected for full text screening. Forty articles were selected for inclusion, with subsequent exclusion of 3 articles due to insufficient data, resulting in a total of 37 articles [16-52] (**Figure 1**).

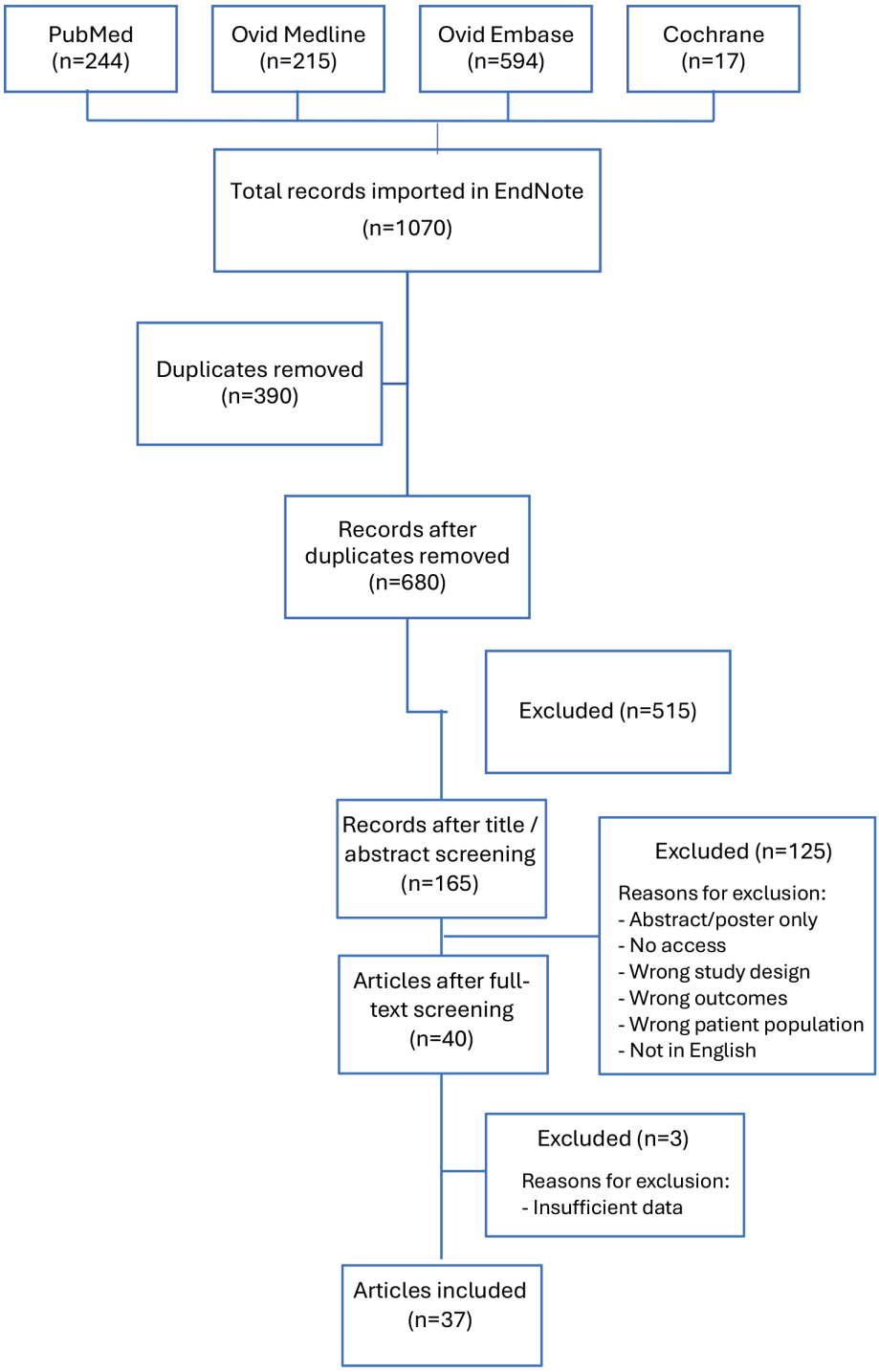

Figure 1: PRISMA flow chart

The characteristics of the selected studies and respective registries are displayed in **Table 1**. Registries were launched between 2001 and 2021 with a geographical coverage of national (10/37, 27%), continental (limited to one continent; 8/37, 22%), or global (across multiple continents; 19%), and with most of their coordinating entities in the United States (8/37, 22%), United Kingdom (8/37, 22%), or Germany (7/37, 19%) (**Figures 2 and 3**). Number of cases included at time of publication ranged from 0 to more than 30,000 cases. The time between the launch of the registry and the year of publication of the article was median 3 years (range 1-12 years). Most of the registries (23/37; 62%) covered a multitude of related diseases, and 14/37 (38%) registries focused on a single specific disease only. All registries included multiple participating centres, except one single centre-based registry [21].

The majority (36/37, 97%) of the articles described elements of the design, 19/37 (51%) described some form of quality management, and 17/37 (46%) had a description of registry maintenance. A summary of these main findings can be found in **Table 2**, and a detailed overview per registry in **Supplementary File 2**.

Registry design

The aims of the registries, as reported, were providing subjects for clinical studies (32%), evaluating or improving clinical care (24%), describing epidemiology (22%) improving the understanding of natural history (19%), evaluating or improving health-related outcomes (16%), creating collaborations or clinical networks (16%), describing clinical characteristics of a disease (14%), evaluating therapies or interventions (8%), and providing evidence for management decisions (3%). Five registries had no clear description of their aim.

The type of data collected was mostly sociodemographic data (e.g., sex, date of birth or age, country of birth), diagnosis, medical history (e.g., signs and symptoms, date of onset, diagnostic tests, physical examination), care pathway (e.g., treatment centre, number of visits, date of contact, physician), and treatment history (e.g., interventions, drugs). Other data collected were health-related outcomes (e.g., quality of life, disability, adverse events), research information (e.g., participation in trials), genetics, and biobank specimens.

Table 1: Characteristics of included articles and respective registries

First author	Publication Year	Registry name
Ali [6]	2020	European Registries for Rare Endocrine Conditions (EuRRECa)
Alvis [7]	2020	Colombian registry of haemophilia and other coagulopathies
Bassanese [8]	2021	European Rare Kidney Disease Registry (ERKReg)
Bellgard [9]	2012	Australian National Duchenne Muscular Dystrophy Registry
Beswick [20]	2016	Cole-Reagins Registry for Sinonasal Cancer (CORSICA)
Blankshain [21]	2016	The University of Illinois at Chicago (UIC) Neuro-Ophthalmology Registry
Chalmers [22]	2017	European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) registry
Clarke [23]	2011	Fabry Outcome Survey (FOS)
De Antonio [24]	2019	French myotonic dystrophy registry (DM-Scope)
Eades-Perner [25]	2007	European registry of primary immunodeficiencies (ESID)
Evangelista [26]	2016	UK FSHD registry
Feenstra [27]	2006	European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations (ECARUCA)
Finkel [28]	2020	Registry of Patients with a Diagnosis of Spinal Muscular Atrophy (RESTORE Registry)
Fischer [29]	2014	PedNet Haemophilia registry
Guien [30]	2018	French National FSHD Registry
Hilber [31]	2012	National Registry of MD and FSHD
Jaussaud [32]	2006	The French 'observatoire' on Gaucher's disease (FROG)
Javaid [33]	2016	Rare UK Diseases Study (RUDY) platform
Khatami [34]	2016	The European Narcolepsy Network (EU-NN) database
Kingswood [35]	2014	TuberOus SClerosis registry to increase disease Awareness (TOSCA)
Mallbris [36]	2007	Swedish Hereditary Angioedema Registry (Sweha-Reg)
Marques [37]	2020	Portuguese inherited retinal dystrophies registry (IRD-PT)
Mercier [38]	2019	Desmoid Tumor Research Foundation (DTRF) Patient Registry
Ng [39]	2011	UK Primary Sjogren's Syndrome Registry (UKPSSR)
Nurok [40]	2010	International lymphangioleiomyomatosis (LAM) Registry
Opladen [41]	2016	International Working Group on Neurotransmitter Related Disorders (iNTD)
Opladen [42]	2021	Unified European Registry for Inherited Metabolic Disease (U-IMD registry)
Orbach [43]	2021	Paediatric Rare Tumours Network -European Registry (PARTNER)
Osara [44]	2017	Newborn Screening (NBS) Connect

Disease area(s)	Country*	Coverage†	Launch	n‡
Rare endocrine conditions	United Kingdom	Continental	2018	5500
Hemophilia and other coagulopathies	Colombia	National	2015	4395
Rare kidney diseases	Germany	Continental	2019	7607
Duchenne and Becker's muscular dystrophy	Australia	National	2010	/
Malignancy of the paranasal sinuses	United States	National	/	/
Neuro-ophthalmic diseases	United States	National	/	/
Bronchiectasis	United Kingdom	Continental	2015	>8000
Fabry disease	Sweden	Global	2001	1616
MD	France	National	2008	2970
Primary immunodeficiencies	Germany	Continental	2004	2386
FSHD	United Kingdom	Regional	2012	518
Rare chromosome aberrations	United Kingdom	Continental	2003	~4000
SMA	United States	Global	2018	64
Hemophilia	Netherlands	Global	2004	1094
FSHD	France	National	2013	638
MD and FSHD	United States	National	2002	1611
Gaucher's disease	France	National	2005	0
Rare disorders of the musculoskeletal system or blood vessels	United Kingdom	Regional	2014	380
Narcolepsy and other hypersomnias	Switzerland	Continental	2008	1079
Tuberous sclerosis complex	United Kingdom	Global	2011	2216
Hereditary angioedema	Sweden	National	2007	/
Inherited retinal dystrophies	Portugal	National	2017	1800
Desmoid tumors	United States	Global	2017	329
Primary Sjogren's Syndrome	United Kingdom	Regional	2009	500
Lymphangioleiomyomatosis	United States	Global	2010	/
Primary and secondary neurotransmitter-related disorders	Germany	Global	2014	95
inherited metabolic diseases	Germany	Continental	2019	1193
Very rare paediatric tumors	Italy	Global	2016	/
Inherited metabolic disorders	United States	National	2012	442

First author	Publication Year	Registry name
Patel [45]	2010	North American Skull Base Society (NASBS) database
Pechmann [46]	2019	SMA patient registry (SMArtCARE)
Reincke [47]	2006	German Acromegaly Registry
Roy [48]	2015	Belgian Neuromuscular Disease Registry
Seidel [49]	2017	Global Rare Fungal Infection Registry (FungiScope™)
Spahr [50]	2021	MyeliNeuroGene Database
Tingley [51]	2020	Canadian Inherited Metabolic Diseases Research Network (CNMDRN) database
Viviani [52]	2015	European Cystic Fibrosis Society Patient Registry (ECFSPR)

*Abbreviations: MD, myotonic dystrophy; FSHD, facioscapulohumeral muscular dystrophy; SMA, spinal muscular atrophy. * Country of coordinating entity † Geographical coverage ‡ Number of participants included in registry at time of publication*

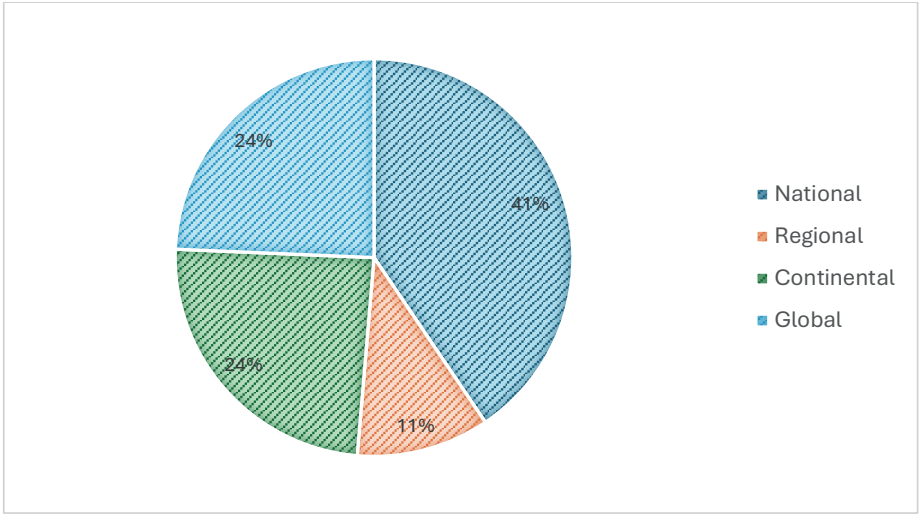

Figure 2: Geographical coverage of included registries

Disease area(s)	Country*	Coverage†	Launch	n‡
Skull base tumors treated with craniofacial surgery	United States	Continental	2004	/
SMA	Germany	Regional	2017	/
Acromegaly	Germany	National	2003	1543
Neuromuscular diseases	Belgium	National	2008	3424
Rare invasive fungal diseases	Germany	Global	2003	794
Rare diseases	Canada	National	2011	1000
Inherited metabolic diseases	Canada	National	2012	798
Cystic fibrosis	United Kingdom	Continental	2003	>30000

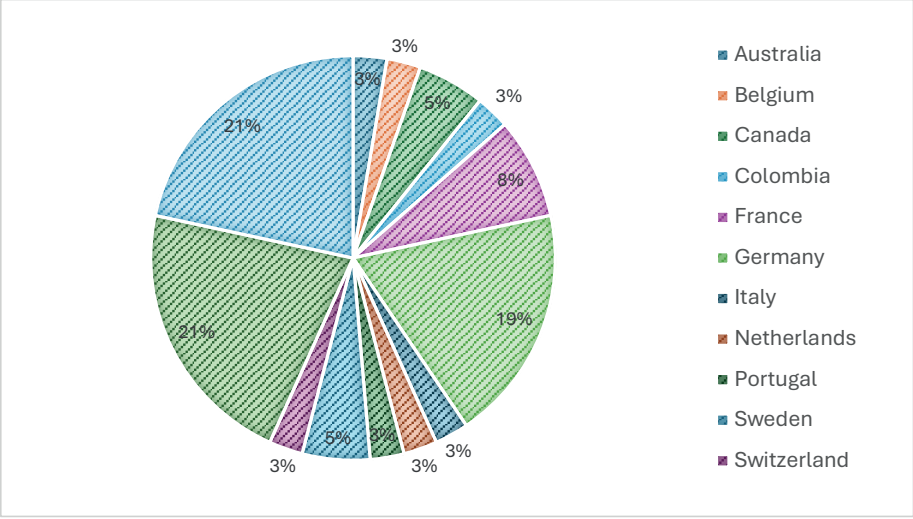

Figure 3: Countries of coordinating entities of included registries

Table 2: Summary of main findings on design, quality management, and maintenance of included registries

Registry attribute	**Frequency**	
Aims	*N/37*	*%*
Providing subjects for clinical studies	12	32
Evaluating/improving clinical care	9	24
Describing epidemiology	8	22
Improving the understanding of natural history	7	19
Evaluating/improving health-related outcomes	6	16
Creating collaborations or clinical networks	6	16
Describing clinical characteristics of disease	5	14
Evaluating therapies or interventions	3	8
Providing evidence for management decisions	1	3
Unclear	5	14
Recruitment method		
Clinic	34	92
PAGs	6	16
Voluntarily*	6	16
Other†	1	3

	Yes		*No*		*Unclear*	
	N/37	*%*	*N/37*	*%*	*N/37*	*%*
Informed consent	30	81	2	5	5	14
Core data set	8	22	27	73	2	5
Coding language	9	24	24	65	4	11
PROMS collection	21	57	3	8	13	35
PAG involvement	14	38	19	51	4	11
Governance description	21	57	11	30	5	14
Data security description	28	76	6	16	3	8
Quality monitoring	19	51	15	41	3	8
Maintenance description	17	46	18	49	2	5
Funding description	30	81	5	14	2	5

Abbreviations: PROMS, patient-reported outcome measures; PAG, patient advocacy groups.
** e.g., through social media, websites† e.g., mandatory by law*

Participants were recruited mostly through clinical care (34/37, 92%). For one national registry, all participants were registered by law through health care providers and health payers (e.g., insurance companies [17]. The majority of the registries collected informed consent (30/37, 81%) and described some form of data access, data sharing, or data protection strategies (28/37, 76%). The main findings on design description of the included registries are described in **Table 2**. In terms of development, 8/37 (22%) used a common or core data set and 9/37 (24%) used an ontological coding language such as the International Statistical Classification of Diseases (ICD) [53], Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) [54], Online Mendelian Inheritance in Man (OMIM) [55], Human Phenotype Ontology (HPO) [56], Human Genome Variation Society (HGVS) [57], or Orphanet Rare Disease Ontology (ORDO) [58]. Electronic data capture software programs were poorly reported, but most of the registries had an online web portal programmed using HTML and Javascript technologies, such as Research Electronic Data Capture (REDCap). In terms of governance, nearly half (16/37, 43%) of the registries had no or unclear descriptions on the included stakeholders or members of the governing body or structure of management. Whilst many (21/37, 57%) of the registries collected patient-reported outcome measures (PROM), only few (15/37, 38%) consulted PAGs of their respective disease areas during the design of the registry. PROMs collected in the registries included general quality of life (e.g., Pediatric Quality of Life Inventory [59], Short Form 36 [60], World Health Organisation Quality of Life questionnaire [61]), health-related quality of life (e.g., European Quality of Life-5 Dimension 5 Levels [62]), disease-specific quality of life (e.g., Acromegaly Quality of Life Questionnaire [63], Sinonasal Outcome Test-22 [64], Individualised Neuromuscular Quality of Life Questionnaire [65]), pain (e.g., McGill Pain Questionnaire [66], PainDetect [67]), patient experience (Hospital Anxiety and Depression Scale [68]), burden of disease (e.g., Zarit Burden Interview [69], Work Productivity and Activity Impairment Questionnaire [70], Nottingham Activities of Daily Living score activity [71]), sleep quality (e.g., Pittsburgh Sleep Quality Index [72], Epworth Sleepiness Scale [73]), and symptom assessment (e.g., Composite Autonomic Symptom Scale [74], Profile of Fatigue and Discomfort and Sicca Symptoms Inventory [75, 76]).

Registry quality

About half (19/37, 51%) of all registries mentioned some description of quality maintenance, but measures varied widely. The described quality measures could generally be divided into assessment at the system input

level, during data collection, and assessment at the user level, before or after data collection. Measures of assessment at the system input level included automated quality assurance checks (e.g., error alerts for duplicate records, predefined ranges for numeric data, calculation checks for dates), closed-ended items, validating data types (string vs. numeric), and mandatory data elements or items. At the user level, before data collection, measures described were data input training and support, prerequisite credentials of capability or knowledge, and selection of patients through predefined inclusion and exclusion criteria. After data collection, measures such as periodical quality monitoring (or auditing or peer-reviewing), performed by specific members of the governing body, a dedicated data management team, or independent professionals were described. Of the 19 registries that described some form of quality maintenance, 14 registries mentioned quality monitoring at least once during the lifetime of the registry.

Registry maintenance

Similar to quality management, approximately half (17/37, 46%) of the included registries had a clear description of maintenance of the registry (**Table 2**). Descriptions of funding, long-term goals, or sustainability were considered descriptions of maintenance. Sources of funding were frequently described (30/37; 81%) and varied from federal or European Union authoritative bodies (18/30; 60%), private pharmaceutical or technical companies (12/30; 40%), research institutes, societies, or foundations (10/30; 33%), PAGs (3/30; 10%), and private philanthropy (1/30; 3%). Clear long-term or end-goals included descriptions such as predefined follow-up or recruitment periods and aims in gaining of understanding or developments of treatments. Only two registries mentioned the malleability of a registry, recognizing how it may evolve over time through feedback, new knowledge and technologies, and capacity to expand [38, 48]. Another interesting measure for maintenance and sustainability described was a financial compensation per registered patient, to encourage regular and continuous updating of data [25].

Discussion

The majority of registries included in the review registered clinical patients from all over the world, with the United States, United Kingdom, and Germany in the lead as coordinating entities. A wide variety of rare diseases were covered, with an apparent representation of (neuro)muscular

diseases. Most registries were developed for the provision of participants for scientific research. Most patient registration used informed consent, and often data security policies were in place as per the General Data Protection Regulation (GDPR) of the European Union [77]. Only a minority of registries used ontological coding systems. Although patient-reported outcome measures were frequently collected by the registries in this review, PAGs had not equally been consulted during the developmental process. Elements on registry design were most frequently described, but less attention was paid to descriptions on quality management and maintenance.

The findings in this review highlight the imbalance between designing and sustaining a registry, challenged by difficulties in collecting quality data and the continued relevance of a registry. These results are in line with the findings of other similar studies [1, 6, 11, 12, 78, 79]. With an average of only three years between launch of the registry and its publication, long-term functionality of the registries is questionable. Funding is frequently described in the included registries, with a large portion of the registries maintained by private pharmaceutical or technological companies. This may also influence maintenance, as this type of funding could contribute to greater registry visibility as part of regulated industry requirements [1]. Furthermore, registries with industry funding also frequently have policies in place to ensure long-term sustainability and are more likely to be of high quality [78]. Although sustainability of a registry may be supported by adequate funding, it does not necessarily constitute longevity, as funding may not be renewed after a certain period of time.

There are several limitations to this study. Firstly, the inclusion criteria and definitions of specific datapoints might not always have been an accurate representation of the included registries. Certain datapoints, for example regarding a description on data access policies, might have been regarded as absent despite the respective registry still having these policies. Secondly, the selected search terms required studies describing the design, quality management, or maintenance of a rare disease patient registry. Some articles, including those describing a registry and its collected data, which focused primarily on their results rather than on the framework of the registry, might have been missed due to absence of important key words. Therefore, the strict inclusion criteria limited the results to articles with sufficient detail regarding methodology. On the other hand, this highlights the importance of complete and detailed descriptions of methodological

aspects when publishing the introduction of a registry. Lastly, as this is a qualitative study in nature, no meta-analysis of the collected data could be conducted.

The rise of many new rare disease registries and a lacking focus on improving and sustaining existing ones leads to the production of data that is not always usable nor shareable. One of the reasons to increase data quality in existing rare disease patient registries is to reduce duplicate efforts and production of excessive data. Several measures have been developed to improve these issues, such as promoting interoperability between registries with the sets of common and domain-specific data elements of the European Commission Joint Research Centre (JRC) [80, 81]. Another measure to tackle the different forms of data collection is through the use of standardized coding languages, such as ICD, SNOMED CT, and ORDO [53, 54, 58]. The use of ontologies is not only important to promote interoperability, but also to facilitate the technological developments to link registries and facilitate overarching research access [82]. Importantly, of the registries included in this review, only a minority have implemented these measures. Furthermore, although these measures are a refinement of quality data collection and in accordance with the FAIR principles, which do facilitate maintenance and sustainability, these measures are nevertheless also part of registry design. Although the JRC common and domain-specific data sets are good suggestions to promote interoperability, registries generally want to collect additional disease-specific or patient-reported data and, ideally, collect data through several points of follow-up over a long period of time.

Concerningly, a survey on the main activities and methodological, technical and regulatory issues of European rare disease registries conducted more than a decade ago presented findings not dissimilar to the findings in this review [83]. Quality assurance and sustainability are amongst the key issues addressed, and despite the guidelines and recommendations published in the past 10 years, are still issues that newly established registries face. Therefore, the important question is how to improve existing registries. Possibilities include periodical quality monitoring, recurrent evaluation of user feedback, implementation of coding languages, monetary incentives and mandatory items to promote complete data entry, assessments of data capturing, revision of research aims, and long-term sources of funding. However, application of multiple adequate maintenance strategies remains

an important issue, with several registries describing the challenges of maintaining a registry, such as ensuring continuous data entry, assuring quality, and securing further funding [35, 37, 39, 48]. It is important to recognize that once a registry has been developed and collecting data, its design is not set in stone, and continuous evaluations and efforts to improve are necessary. Nevertheless, the limited number of registries describing any strategies on sustainability and maintenance over a longer term, and the few that recognize the challenges demonstrate how this area is still largely undermined. Therefore, strategies and protocols on maintenance and management should play an equally large role as structure design when developing a registry.

The present review illustrates that the current registries are still largely behind in complying with the 2013 guidelines on patient registration and data collection, and the field of rare disease registries has made limited improvements in the past decade. Only a minority of the registries promoted interoperability through the use of coding language and minimum common data sets, there was little involvement of patients in registry governance, and few considered sustainability strategies for registry continuation [3].

Conclusions

With this review we described that rare disease patient registries commonly describe the elements of registry design but pay less attention to quality management and maintenance. These important finding highlight the challenges of developing and maintaining a high quality and sustainable registry. Considerations during design should be made as to what is ideal and what is feasible. Lastly, recommendations on measures to improve existing databases to remain relevant and valuable for rare disease research are warranted.

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Supplementary File 1: Search strategy

SEARCH STRING 1: Pubmed

1.	"Rare Diseases"[Title/Abstract] OR "Rare Diseases"[MeSH Terms]	16993
2.	"Common Data Elements"[Title/Abstract] OR "quality"[Title/Abstract] OR "Data Accuracy"[MeSH Terms] OR "quality assurance, health care"[MeSH Terms] OR "Common Data Elements"[MeSH Terms]	1436434
3.	"patient registry"[Title/Abstract] OR "patient registries"[Title/Abstract] OR "registry"[Title/Abstract] OR "Registries"[Title/Abstract] OR "database"[Title/Abstract] OR "Registries"[MeSH Terms] OR "Hospital Information Systems"[MeSH Terms] OR "Datasets as Topic"[MeSH Terms] OR "Information Storage and Retrieval"[MeSH Terms] OR "databases, factual"[MeSH Terms]	683384
4.	#1 AND #2 AND #3	
5.	#4 AND english[la]	**244**

SEARCH STRING 2: Ovid Medline

1.	exp Rare Diseases/	12356
2.	(rare adj diseases).tw,kf,hw.	17004
3.	Common Data Elements/ or Data Accuracy/ or (Quality Assurance, Health Care/ or "Quality of Health Care"/)	133717
4.	quality.tw,kf.	1157952
5.	(common adj data adj elements).tw,kf.	433
6.	Registries/	98937
7.	(patient adj registr*).tw,kf.	3840
8.	registry.tw,kf.	127059
9.	"Datasets as Topic"/ or exp Hospital Information Systems/ or exp "Information Storage and Retrieval"/	229136
10.	database.tw,kf.	347460
11.	(1 or 2) and (3 or 4 or 5) and (6 or 7 or 8 or 9 or 10)	229
12.	limit 11 to english language	**215**

SEARCH STRING 3: Ovid Embase

1.	exp rare disease/	41988
2.	"rare diseases".tw,kf,dq.	11152
3.	data accuracy/ or quality control/ or health care quality/	437785
4.	quality.tw,kf,dq.	1624357
5.	"common data elements".tw,kf,dq. or common data elements/	751
6.	exp register/	173384
7.	"patient registr*".tw,kf,dq.	7179
8.	data base/	242810
9.	exp hospital information system/	25623
10.	information processing/ or information retrieval/ or information storage/	283147
11.	"database".tw,kf,dq.	545626
12.	(1 or 2) and (3 or 4 or 5) and (6 or 7 or 8 or 9 or 10 or 11)	606
13.	limit 12 to english language	**594**

SEARCH STRING 4: Cochrane

1.	MeSH descriptor: [Rare Diseases] explode all trees	32
2.	(rare NEXT diseases):ti,ab,kw	236
3.	MeSH descriptor: [Data Accuracy] this term only	30
4.	MeSH descriptor: [Common Data Elements] this term only	0
5.	MeSH descriptor: [Quality of Health Care] explode all trees	470218
6.	(quality):ti,ab,kw	186154
7.	(common NEXT data NEXT elements):ti,ab,kw	19
8.	MeSH descriptor: [Registries] this term only	908
9.	(registry):ti,ab,kw	17598
10.	(patient NEXT registr*):ti,ab,kw	367
11.	MeSH descriptor: [Datasets as Topic] this term only	19
12.	MeSH descriptor: [Hospital Information Systems] explode all trees	581
13.	MeSH descriptor: [Information Storage and Retrieval] explode all trees	601
14.	(database):ti,ab,kw	15467
15.	(#1 OR #2) AND (#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	**21**

Supplementary File 2: Main findings on design, quality management, and maintenance of included registries

First author	Informed consent	Core data set	Coding language	PROMS collection	PAG involvement
Ali[1]	Yes	Yes	Yes	Yes	Yes
Alvis[2]	No	No	Unclear	No	Yes
Bassanese[3]	Yes	Yes	Yes	Unclear	Yes
Bellgard[4]	Yes	No	Yes	No	Yes
Beswick[5]	Yes	Yes	No	Yes	No
Blankshain[6]	Yes	No	Yes	No	No
Chalmers[7]	Yes	Yes	No	Yes	Yes
Clarke[8]	Yes	Yes	No	Yes	No
De Antonio[9]	Yes	Yes	No	Yes	Yes
Eades-Perner[10]	Yes	Yes	Yes	Yes	No
Evangelista[11]	Yes	Unclear	No	Yes	Yes
Feenstra[12]	Yes	No	Yes	No	Yes
Finkel[13]	Yes	No	No	Yes	No
Fischer[14]	Yes	No	No	No	No
Guien[15]	Yes	No	No	Yes	Yes
Hilber[16]	Yes	No	Yes	Yes	Unclear
Jaussaud[17]	Yes	No	No	Yes	No
Javaid[18]	Yes	No	No	Yes	No
Khatami[19]	Unclear	No	No	No	No
Kingswood[20]	Yes	No	No	Yes	Unclear
Mallbris[21]	Yes	No	No	Yes	No
Marques[22]	Yes	No	Yes	No	No
Mercier[23]	Yes	No	Unclear	Yes	No
Ng[24]	No	No	No	Yes	Yes
Nurok[25]	Unclear	No	No	No	Unclear
Opladen[26]	Yes	No	No	Unclear	No
Opladen[27]	Yes	Yes	Yes	Yes	Yes
Orbach[28]	Yes	Unclear	Unclear	No	Unclear
Osara[29]	Yes	No	No	Yes	Yes
Patel[30]	Unclear	No	No	No	No
Pechmann[31]	Yes	No	Unclear	Yes	Yes
Reincke[32]	Unclear	No	No	Yes	No
Roy[33]	Yes	No	No	No	No
Seidel[34]	Unclear	No	No	No	No
Spahr[35]	Yes	No	No	Yes	No
Tingley[36]	Yes	No	No	No	No
Viviani[37]	Yes	No	No	Unclear	Yes

Abbreviations: PROMS, patient-reported outcome measures; PAG, patient advocacy groups
**Patients recruited into the registry either through their clinic, patient advocacy groups, voluntarily (e.g., through social media/websites), other (e.g., by law)*

Governance description	Data security description	Recruitment method*	Quality monitoring	Maintenance description	Funding description
Yes	Yes	Clinic	Yes	Unclear	Yes
Yes	Yes	Other	Yes	Yes	Unclear
Yes	Yes	Clinic	Unclear	No	Yes
Unclear	Yes	Clinic	No	No	Yes
Yes	Yes	Clinic	No	No	Yes
No	No	Clinic	No	No	No
Yes	Yes	Clinic	No	No	Yes
No	Yes	Clinic	Yes	No	Yes
Yes	Yes	Clinic	Yes	No	Yes
Yes	Yes	Clinic	Yes	Yes	Yes
Yes	Yes	Clinic; PAG; voluntary	Yes	No	Yes
Yes	Yes	Clinic	Yes	No	Yes
Yes	Unclear	Clinic	No	Yes	Yes
No	Yes	Clinic	Yes	No	Yes
Yes	Yes	Clinic; PAG; voluntary	No	Yes	Yes
No	Yes	Clinic	Yes	No	Yes
Yes	Yes	Clinic; PAG; voluntary	No	No	Yes
Yes	No	Clinic	No	Yes	No
Yes	Yes	Clinic	Yes	No	Yes
Yes	No	Clinic	No	Yes	Yes
Unclear	Yes	Clinic; PAG; voluntary	No	No	No
Unclear	Yes	Clinic	Unclear	No	Yes
No	Yes	PAG; voluntary	No	Yes	Yes
No	Unclear	Clinic	Yes	Yes	Yes
Yes	Yes	Clinic	Yes	Yes	Yes
Yes	Yes	Clinic	No	Yes	Unclear
Yes	Yes	Clinic	No	No	Yes
No	Yes	Unclear	No	Yes	Yes
No	Yes	Clinic; PAG; voluntary	Unclear	Yes	Yes
No	Unclear	Clinic	No	No	No
Unclear	Unclear	Clinic	Yes	Yes	Yes
Yes	Unclear	Clinic	Yes	Yes	Yes
Yes	Yes	Clinic	Yes	Yes	Yes
No	Unclear	Clinic	Yes	No	Yes
No	Yes	Clinic	Yes	Unclear	No
Unclear	Yes	Clinic	Yes	Yes	Yes
Yes	Yes	Clinic	Yes	Yes	Yes

CHAPTER 3

A quality assessment of the ARM-Net registry design and data collection

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Abstract

Registries are important in rare disease research. The Anorectal Malformation Network (ARM-Net) registry is a well-established European patient registry collecting demographic, clinical, and functional outcome data. We assessed the quality of this registry through review of the structure, data elements, collected data, and user experience.

Design and data elements were assessed for completeness, consistency, usefulness, accuracy, validity, and comparability. An intra- and inter-user variability study was conducted through monitoring and re-registration of patients. User experience was assessed via a questionnaire on registration, design of registry, and satisfaction.

We evaluated 119 data elements, of which 107 were utilized and comprised 42 string and 65 numeric elements. A minority (37.0%) of the 2278 included records had complete data, though this improved to 83.5% when follow-up elements were excluded. Intra-observer variability demonstrated 11.7% incongruence, while inter-observer variability was 14.7%. Users were predominantly paediatric surgeons and typically registered patients within 11-30 minutes. Users did not experience any significant difficulties with data entry and were generally satisfied with the registry, but preferred more longitudinal data and patient-reported outcomes.

The ARM-Net registry presents one of the largest ARM cohorts. Although its collected data are valuable, they are susceptible to error and user variability. Continuous evaluations are required to maintain relevant and high-quality data, and to achieve long-term sustainability. With the recommendations resulting from this study, we call for rare disease patient registries to take example and aim to continuously improve their data quality to enhance the small, but impactful, field of rare disease research.

Background

Anorectal malformations (ARM) are congenital defects involving the anus and rectum and have an estimated prevalence in Europe of 20 to 33 per 100,000 live births [1, 2]. With the rarity of this disease, data are scarce and scattered. Therefore, patient registries, as information systems that gather clinical data from different health care centres, play a pivotal role in rare disease research [3, 4].

The ARM Network (-Net) Consortium, a group of dedicated European paediatric surgeons, epidemiologists, geneticists, and patient advocacy groups, was established in 2010 [5]. The ARM-Net Consortium has contributed significantly to the field of ARM, with its consensus and publications to harmonize diagnostic classifications, interventional approaches, and psychosocial follow-up [6-8]. Furthermore, it has facilitated ARM patients and their families to provide input and collaborate with clinicians to enhance colorectal care (www.arm-net.eu).

The ARM-Net Consortium also established the ARM-Net patient registry, for which paediatric surgeons identified the data elements to be collected and these were converted and developed into an online interface. Since 2010, this project of dedicated volunteers has successfully registered more than 2200 ARM patients across Europe. The original intention of the registry was to prospectively collect anonymized data on all consecutive patients of the participating centres to surveil epidemiology of ARM and create a screening list of potential subjects for studies in ARM research. However, as the registry developed and grew over the years, it has also served purpose to collect data and conduct research on health-related outcomes for this patient group, including longitudinal data. Several important studies have been conducted with the collected data to improve clinical care for ARM [5, 9-15]. Identification of risk factors for unfavourable outcomes, interpretation variation in diagnostics, and different management approaches are amongst the significant contributions resulting from the ARM-Net patient registry.

Although the registry collects valuable information, it has been apparent that not all collected data are useful for documentation purposes, nor directly useable for research. Data cleaning and supplying of missing information are both necessary. Additionally, due to the design of the registry,

requested data on individual patients was intentionally limited, as not to discourage surgeons to register their data. As a consequence, potentially relevant information for research purposes is not currently captured in the registry, leading to disparate pieces of information in different places, or unavailability all together. Although these existing hurdles influence the usability and experience with the registry, both from a clinical and a research perspective, the registry has not undergone fundamental changes since its initial setup.

The registry in its current form is very valuable, but it has outgrown its original purpose over its lifetime. Therefore, updates and improvements are warranted for the registry to continue to be of high quality and sustainable for long-term use. For this reason, this study aimed to assess the quality of the ARM-Net registry through analysis of the structure and data elements, collected data, and user experience. More importantly, registries often exhaust their funding on initial setup or engaged investigators may disperse over time, resulting in few resources left for continued maintenance and delivery of high-quality data [4, 16]. For this reason, this report aimed to highlight the need for other rare disease patient registries to continuously self-evaluate and adapt to remain relevant, both for clinical and research purposes.

Methods

This quality assessment is based on published methods for undertaking quality evaluation of rare disease registries, including assessment of data with the dimensions of quality, monitoring, intra- and inter-user variability studies, requesting and providing feedback and recommendations, and producing a quality evaluation report [4, 17-22]. Therefore, the ARM-Net registry quality assessment consisted of three parts: critical analysis of the registry structure and data elements; monitoring of collected data for user variability; and an ARM-Net registry user questionnaire to evaluate user experience. All data were collected in Microsoft Excel 2016 (v16.62, Microsoft Corporation, Redmond, Washington, United States) and, where applicable, analysed in Stata (v17.0, StataCorp, College Station, Texas, United States).

Assessment of registry structure and data elements

All 119 data elements in nine categories and accompanying value labels were given a reference number (Supplementary File 1). For each data element and accompanying data of 2287 records, the number of missing data, actions for cleaning, actions for analysis, and suggestions for improvements were recorded as well as assessment of accuracy, completeness, consistency, usefulness, and validity [4, 18-22]. Completeness analysis of records was conducted, and completion rate was considered 100% if data was entered for each element. This analysis excluded the automatically created elements (n=8, as these were never missing), unused elements (n=4), completion check elements (n=2), and non-applicable elements if not performed (n=17, e.g., stoma bowel section if patient has no stoma). The remaining free text string elements for further specifications (n=24) were also excluded, as these were not mandatory to complete and therefore cannot be regarded as missing data if left blank. A total of 64 elements were included in the completeness analysis. Completeness analysis was also conducted for data elements irrespective of records, meaning completion rate was calculated for each data element and regarded as 100% if there were data for 2287 records. Completeness of one-year follow-up data elements excluded the records of patients whose reconstructive surgery was performed less than one year before date of data extraction from the ARM-Net registry for the current study. Median completion rate for all elements was calculated, excluding the previously specified elements.

Intra- and inter-user variability

A monitoring session to study intra- and inter-user variability was conducted on ten patients previously registered by a single paediatric surgeon responsible for the registration of patients at the Radboud University Medical Centre (Radboudumc). The ten patients were randomly selected based on varying Krickenbeck type [8, 23], sex, and age to ensure a sample of patients appropriately reflecting the ARM population. All patients were treated at the Department of Paediatric Surgery at the Radboudumc, with sufficient time since reconstructive surgery, so as one-year follow-up data should be available for both first- and second-time registration. The selected patients were registered by a paediatric surgeon (HJJS) for a second time at least one year after first registration for intra-user variability of the database (User 1A vs. User 1B), and by a second user (junior doctor, ICH), for evaluation of differences between the first and the second user for inter-user variability (User 1 vs. User 2). During second-time registration,

User 1 was blinded from their first registration in the ARM-Net registry. For data collection, a copy of the ARM-Net registry was built in Research Electronic Data Capture (REDCap; v12.5.16, Vanderbilt University, Nashville, Tennessee, United States), so as not to affect the existing ARM-Net registry. Certain data elements, such as elements with multiple answers, were coded and exported differently, resulting in a total number 148 data elements per user per patient. Of these 148 elements, five were automatically created by the system and 27 data elements were free text string elements, resulting in 116 data elements included in the analysis. Closed-ended data elements were considered as either congruent or incongruent. Open-ended free text data elements were analysed for differences in interpretation, which were categorized per subject. The absolute total of discrepancies in the collected data and the number of data elements with discrepancies were reported. Differences between intra- and inter-user variations were tested for significance using independent Students' t-tests and considered statistically significant at a p-value of <0.05.

ARM-Net registry user questionnaire

In collaboration with paediatric surgeons (SKK, IdB, HJJS), ARM researchers (MT, IALMvR), and ARM-Net data managers (IALMvR, EJ), the ARM-Net registry user questionnaire was developed and aimed at all ARM-Net users who contribute patients to the registry. It consisted of items on current and future purposes of the registry, maintenance, satisfaction with collected elements and desired changes, ease of use, limitations, and general satisfaction (Supplementary File 2). The questionnaire was built in Castor EDC (v2022.3.0.0, Castor, Amsterdam, The Netherlands) and sent out to all 32 users responsible for data input at their respective centres. Users were given a minimum period of two months, with three reminders, to complete the questionnaire. Percentages of response are presented without decimals, as the total absolute number of users that have completed the questionnaire is less than 100.

Results

Assessment of registry structure and data elements

There were 119 data elements, of which eight were automatically created by the electronic data capturing (EDC) system of the ARM-Net registry. Seven involved time and person creating, modifying, and locking records.

One was a unique identifier to anonymize the data and prevent duplicate entries, generated by entering the date of birth of the patient and the year of birth of the patient's mother. Four elements included in the data dictionary were not present in the registry interface and were therefore not used in data collection. Of the remaining 107 utilizable elements, there were 42 string and 65 numeric data elements (Supplementary Table 1). The data elements could be categorized into several groups: automatically created administrative, patient demographics, ARM diagnosis, family history of congenital abnormalities, genetic testing and availability of biosamples, associated anomalies, surgical procedures and associated complications, one-year follow-up data, and completion of the record checks (**Table 1**). The majority (63.6%) of the 107 utilized data elements were dedicated to associated anomalies and surgery.

Table 1: Overview of number of data elements per category

Category	Number of data elements
Administrative	8
Demographics	10
ARM diagnosis	2
Family history	10
Genetic testing and biosamples	5
Associated anomalies	49
Surgery and complications	19
Completion check	2
One-year follow-up	12
Not used	*4*
Total	**119**

Complete data was available for only 37.0% of records. However, when excluding the one-year follow-up data elements (n=10) completion rate improved to 83.5% (**Figure 1A**). Irrespective of record completeness, median completion rate per data element was 99.6% (IQR 99.3-99.6%), with a median completion rate of 58.6% (IQR 51.1-63.3%) for the one-year follow-up data elements only (**Figure 1B**) for patients with a reconstruction more than one year before data extraction.

Completeness of data elements does not necessarily equal useful data. For many of the elements, there is the option to select 'Unknown'. For the data

elements on family history of congenital malformations in the parents of the patient, 34.4% and 32.3% of records had 'Unknown' answers for father and mother, respectively. The remaining data elements on family history of siblings and extended family members had an even higher proportion, with a median of 72.8% (IQR 72.4-84.5%) of records 'Unknown'. This raises the question of relevancy of these elements when information on extended family members is seemingly often unavailable.

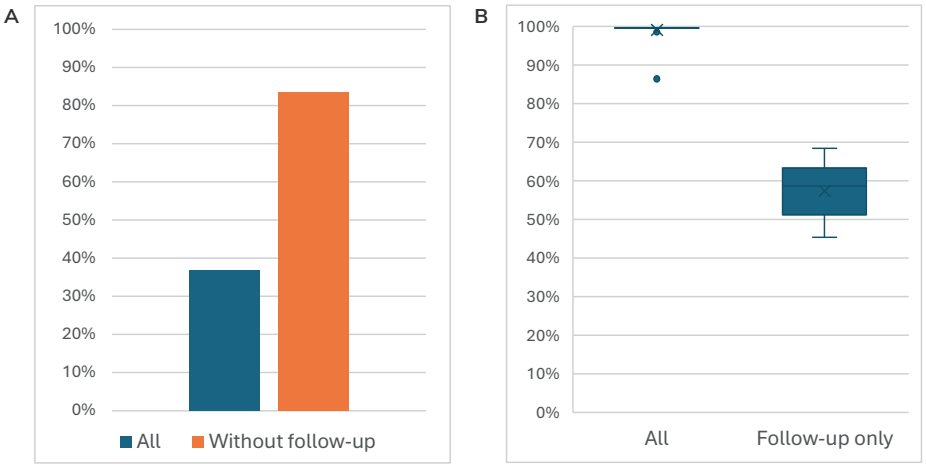

Figure 1: Completion rates

A. Proportion of records with complete data for all data elements and without follow-up elements. **B.** Median completion rate per data element of all data elements and follow-up data elements only

There were 27/107 (25.2%) elements that were free text fields, allowing a user to add an additional description of a previously chosen answer, or when the option 'Other' was selected. For these data elements, there were 61 to 577 different answers entered per item. From the collected data it was evident that the free text elements are utilized more often than the option 'Other' is selected, presumably because the existing answer options in the corresponding single-choice question were not sufficient or satisfactory. This was especially interesting for the free text element on Krickenbeck classification, which was utilized for 283 records, whilst the answer option 'Other' for the closed-ended Krickenbeck element was only selected for 20 records. Another reason free text elements were used was to register information that could not be collected elsewhere, such as prematurity, birth weight, order of birth, and method of conception.

The majority of single-choice data elements on associated anomalies collected data on whether the respective organ system was 'Abnormal' or 'Normal', whether it was 'Not checked', or whether this information was 'Unknown'. Although these data elements have subsequent free text fields for descriptions, users did not always utilize them. When information was provided in these fields, it often required extensive cleaning and human interpretation.

Intra- and inter-user variability

Both User 1 and 2 registered 10 patients, entering 116 data elements per patient, totalling 1160 entered datapoints per user. Discrepancies between first- and second-time registration (User 1A and User 1B) for a single user demonstrated that there is intra-user variability, with 11.7% of collected data incongruent. Similarly, the number of discrepancies between User 1 and User 2 showed that there is also inter-user variability, with 14.7% of collected data differing between the users (**Table 2**). The number of intra-user and inter-user discrepancies were not statistically different (136 vs. 170; p≥0.20). The discrepancies were found in 61 and 70 of the 116 data elements for intra- and inter-user variability, respectively. To determine which data elements might be specifically sensitive to intra- or inter-user variability, the number of data elements with three or more discrepancies in the 10 patients registered were determined, but the difference in intra- and inter-user variation (15.5% vs. 23.3%, respectively), was not statistically significant.

Table 2: Intra- and inter-user variation

	User 1A vs. User 1B Intra-user variation	**User 1 vs. User 2 Inter-user variation**	**P-value†**
Total real discrepancies *(n=1160*)*	136 (11.7%)	170 (14.7%)	0.20
Data elements with discrepancies in ≥1 record(s) *(n=116)*	61 (52.6%)	70 (60.3%)	0.24
Data elements with discrepancies in ≥3 records *(n=116)*	18 (15.5%)	27 (23.3%)	0.20

** 116 data elements per patient, with 10 patients resulting in a total of 1160 datapoints.*
† Independent Students' t-test to test for significant differences between the variations.

For intra-user variation, elements with discrepancies were found in the categories of, in order of frequency, associated anomalies (n=57), surgery and complications (n=30), family history (n=17), one-year follow-up (n=15),

genetic testing and biosamples (n=9), patient demographics (n=6), and diagnosis (n=2). The three data elements with the most discrepancies were “Brain abnormality” (n=10), “Other gastrointestinal abnormality” (n=8), and “DNA sample” (n=6). For the first two elements, the discrepancies resulted mostly from ‘Normal’ chosen at first-time registration, contrary to ‘Not checked’ chosen at second-time registration. For “DNA sample”, discrepancies came from missing data.

The data elements subject to inter-user variability fell, in order of frequency, into the categories of associated anomalies (n=101), one-year follow-up (n=26), surgery and complications (n=22), genetic testing and biosamples (n=13), family history (n=3), diagnosis (n=3), and patient demographics (n=2). Similar to the results of intra-user variation, the three data elements with the most discrepancies found were “Other gastrointestinal abnormality” (n=10), “Spinal canal / cord specification” (n=8), and “DNA sample” (n=6). The discrepancies for “Other gastrointestinal abnormality” were mostly because User 1 selected ‘Normal’, whereas User 2 entered ‘Not Checked’. “Spinal canal / cord specification” mostly had discrepancies because the data were missing by the first user, and the same was for “DNA sample”. This might be because the original ARM-Net registry has ‘Unknown’ as the default answer when untouched, contrary to the REDCap version, where there were no default answers and non-selection resulted in missing data.

ARM-Net registry user questionnaire

The ARM-Net registry user questionnaire had a response rate of 75% (24/32) with complete information provided by 23/24 respondents. The results of the questionnaire could be categorized in current and future design of the ARM-Net registry, registration of patients, and satisfaction (**Table 3**). The initial purpose of the registry was surveillance of all consecutive ARM patients in participating centres. Over a third (38%) of users have indeed selected this as the current purpose, while only 13% believed this is a future purpose of the registry. Most users (54%) believed the current purpose of the registry was for clinical research and would like the future purpose to shift to improving clinical care (71%).

The majority of users wanted to collect patient-recorded outcome measures (PROMs) and to expand the follow-up period, currently at 5 years, to at least until adulthood, up to lifelong. The current registry data element with

most votes for removal from the registry was DNA sample, followed by eye/ear abnormalities, family history, and facial dysmorphic features. Of all users, 21% selected 'Other' for removal of an item, which comprised of removal of no data elements (15%), removal of free text option for DNA sample (3%), and removal of the dermatological problems data element (3%). Users were willing to collect more items, with prematurity and birthweight, cardiac abnormality consequences, and expansion of diagnostic tests as frequently chosen. Other data elements users suggested for inclusion were incontinence scales, dilatation regimens, date of stoma placement, menstrual outflow obstruction, methods of conception, and PROM questionnaires on patient/parent satisfaction, quality of life, sexual function, urinary function, and incontinence/constipation. The majority of users made use of the free text fields and supported the need to keep this option to gather specific information, rather than just using an 'Other' option without the availability of specification in a free text field.

Patients were mostly registered by their treating paediatric surgeon (71%) and registration took approximately 11-30 minutes (61%) for most users. A patient was registered when the paediatric surgeon remembered to do so (61%), and follow-up entry was remembered with a manual note in the patient's medical file (35%). Users were generally satisfied (65%) and found the ARM-Net registry easy to use (65%), rating the registry with an overall mean grade of 7.4 on a scale of 1 to 10, with 1 being useless and 10 being perfect. Users were largely not willing to pay a yearly fee for maintenance of the registry (65%). Those who would pay entered a fee ranging from 25 to 500 euros a year, with 50 euros as the most common answer.

Table 3: Responses of ARM-Net registry user questionnaire

Design									
Item	**Answer options and response rate* (%)**								
Current purpose of the registry	Surveillance of all ARM-patients (38%)			Improvement of clinical care (8%)			**Scientific research (54%)**		
Future purpose of the registry	Surveillance of all ARM-patients (13%)			**Improvement of clinical care (71%)**			Scientific research (17%)		
Collection of PROMs	No (22%)						**Yes (78%)**		
Pay a fee for maintenance	**No (65%)**						Yes (35%)		
Expand follow-up period	No (13%)						**Yes (87%)**		
Use of user manual	No, I did not know there was a manual (22%)	**No, I know how to register a patient (35%)**		Yes, only for the first patient (13%)		Yes, occasionally (30%)		Yes, always (0%)	
Helpfulness of user manual	No (13%)			Yes (39%)			**Not applicable (48%)**		
Delete item	Family history (18%)	**DNA sample (27%)**		Throat/lung/tho-rax abnormalities (15%)	Eye/ear abnormalities (24%)		Facial dysmorphic features (18%)	Other (21%)	
Collect more items	No (30%)						**Yes (70%)**		
Add item	Order of birth (6%)	**Prematurity and birth weight (49%)**	Kidney function (eCRF / creatinine) (30%)	Voiding cystoure-throgram (36%)	Cystoscopy (27%)	Echocardio-gram (21%)	Cardiac abnormality consequences (42%)	Constipation based on Rome IV criteria (33%)	Other (21%)
Use of free text fields	Never (4%)		Rarely (26%)		**Sometimes(65%)**		Always (4%)		
Keeping free text fields	**I would like to keep the "free text" option to know the exact information (78%)**				I am happy to only have the option "other" without an explanation / specification (22%)				

Table 3: Continued

Design						
Item	**Answer options and response rate* (%)**					
Registration						
Who registers a patient	**Only me (paediatric surgeon) (71%)**	Another colleague (paediatric surgeon, always the same one) (13%)	Other colleagues (paediatric surgeons, different ones) (0%)	Another specialist or nurse, nurse practitioner, research nurse, case manager (4%)	Me and another colleague (13%)	I don't know (0%)
How long does registration take	≤10 minutes (13%)	**11-30 minutes (61%)**	31-60 minutes (22%)	>60 minutes (4%)		
When is a patient registered	Directly after a consultation/visit (0%)	I plan a separate time slot (39%)	**When I remember to do so (61%)**			
How to remember follow-up entry	I don't, I usually forget (22%)	I note a reminder in patient file **(35%)**	I set a reminder in my calendar (13%)	Someone else reminds me (13%)	I don't know (17%)	
Satisfaction						
Satisfaction	Not satisfied (0%)	Somewhat satisfied (30%)	**Satisfied (65%)**	Very satisfied (4%)		
Difficulty	Difficult (4%)	Somewhat difficult (13%)	**Easy(65%)**	Very easy (17%)		
Overall grade (1-10)	**7.4**					

Abbreviations: ARM, anorectal malformation; PROMs, patient-reported outcome measures.* The answer options presented reflect the possible options provided to the users, with the users' most commonly selected answer in bold.

Discussion

The current study evaluated the quality of the ARM-Net registry through a critical analysis of the structure and data elements, the collected data, and the user experience. Most data elements were dedicated to collecting information on associated anomalies and surgery. A quarter of the data elements were free text fields, resulting in a very high number of up to nearly 600 different answers submitted for a single field, varying from further specifications of previous data elements to information that cannot be registered anywhere else in the registry. This suggests that the registry has outgrown its initial purpose, and that existing data elements and answer options are not fully satisfactory. Unsatisfactory data elements and answer options result in room for interpretations and frequent use of free text fields, making the registry vulnerable to mistakes and imputation errors. The user experience questionnaire also confirmed this, where the majority of users opted to use free text fields and suggested the addition of several data elements currently missing in the registry.

According to the ARM-Net registry user questionnaire, most users registering patients were paediatric surgeons, but still the registry has apparent tendency for differences in data collection, or intra-user and inter-user variability. Up to 15% of collected data was incongruent between users and between different timepoints of registration by a single user. This shows that discrepancies in data collection exist not only between different users, but also equally for the same user. The most common discrepancies were either due to missing data or interpretation differences. Absence of clear documentation in the patient's medical file can either be interpreted as a specific item not checked for or considered as normal. Additionally, irrespective of intra- or inter-user variability, the discrepancies mostly occur in the category of associated anomalies, surgery and complications, and one-year follow-up, indicating that the elements in these categories should be evaluated for improvement to minimize imputation errors or left missing. Several data elements that fall in these categories were also selected by the users in the questionnaire to be removed.

Although implemented after first initiation of the registry due to wishes from the paediatric surgeons, one-year follow-up data entry is still an evident weakness of the registry, with the number of complete records being only 37%, while increasing to over 80% when excluding follow-up data elements.

Nevertheless, most users reported that more follow-up data should be collected and preferred to expand the follow-up period to at least until adulthood. Incompleteness of data is clearly an issue and might be explained by the fact that users indicated that patient registration was mostly done when they remembered to do so, and there is no reliable notification to enter follow-up data other than a note in the patient medical file, which, with a completion rate of around 60% per data element, is visibly unreliable and insufficient. Additionally, the limited clinical relevance or predictive value of clinical outcome at one year follow-up presumably limits surgeons to complete the data. Therefore, expanding the follow-up period not only has more clinical relevance, but surgeons may also be more inclined to complete these data.

The user questionnaire aimed to gain an insight on changes that users would like to see and how they experience patient registration, but also to clarify certain incongruencies in the collected data. Both user satisfaction and ease of use were highly regarded by the users. Interestingly, it was apparent that many users preferred the availability of free text elements to continue in the future. However, from a research and data management perspective, free text elements are difficult to analyse and require extensive data cleaning. This demonstrates that there is a discrepancy between what the ARM-Net registry users, mostly paediatric surgeons or otherwise clinical staff, ideally prefer to collect, and what is ideal from a data research perspective. Furthermore, it was also clear that the users would like to move towards a more clinically oriented and patient-centred registry from their preference to remove dysmorphia- and hereditary-related items and start collecting PROMs. Engagement of patients will enhance the registry's scope and longevity, and provide valuable insight into a patient's life [19]. PROMs are paramount to consider when aiming to improve clinical care, in line with the users' preferred future purpose of the ARM-Net registry.

The current study has several limitations. Firstly, the evaluation of the structure of the registry, its data elements, and the collected data was performed based on the available literature, rather than an existing methodology, which has yet to be developed. Considering that patient registries can vary widely in their covered condition, purpose, structure, and lifetime, no single method can encompass all aspects of a registry evaluation. However, the critical analysis in the current study is based on well-recognized components of data quality assessments in patient registries, such as quality dimensions of accuracy, validity, completeness,

consistency, usefulness, and prevention of duplicate entries [4, 18-22]. A second limitation is that the intra- and inter-user variability study only included two different users, with different levels of training, registering a small sample of 10 patients. Ideally, quality monitoring should be repeated across all participating centres in the different countries, with different paediatric surgeons, and covering a larger patient sample. Nevertheless, the small sample of patients with two users from the same centre and identical instructions on patient registration, does not invalidate the findings of variability in the current form of data collection. In order to confirm the degree of variability, evaluation of intra- and inter- user variability is needed on a larger scale across all participating centres.

A third limitation may be the representativeness of the ARM-Net registry user questionnaire. The users who completed the questionnaire were responsible for data collection in large surgical centres and cumulatively registered more than 80% of all records. Therefore, it is unlikely that they are not representative of ARM-Net registry users. Finally, the user questionnaire is not a standardized survey, but rather tailored specifically to the issues data managers experienced with the ARM-Net registry and reviewed by paediatric surgeons, ARM researchers, and ARM-Net data managers, which although not validated, we believe is sufficient for the purpose of this study.

Despite the lack of a systematic quality assessment process for registries, which has yet to be developed, this study has followed the recommendations of evaluation according to quality indicators and dimensions, site monitoring, and a questionnaire [18]. Furthermore, we have conducted several methods previously described on how to conduct a registry quality assessment, including an intra- and inter-user variability study, providing feedback and recommendations, and writing the present data quality report [17]. Therefore, the present quality assessment encompasses all the available methods to evaluate the ARM-Net registry appropriately.

Recommendations for improving the quality of the ARM-Net registry and other rare disease registries

Three areas of the ARM-Net registry were identified as requiring improvement: 1) structure of data collection, 2) completion of data, and 3) clinical value of data. Firstly, addition and removal of data elements,

expansion of answer options, nested further specification items dependent on selected answer options, default answers or error messages when items left blank to prevent missing data, and a reduction of free text fields should be considered. Data collected via free text elements should be evaluated to create additional answer options and elements, as the existing elements and answer options seem not to be satisfactorily sufficient. Data elements with large amounts of missing data or frequent 'Unknown' answers should be considered for removal. To decrease the data cleaning burden and improve quality, free text fields should only be available when additional specifications are expected to be valuable. Expanding answers options and minimizing the availability of free text fields should also reduce intra- and inter-user variation and leaves less room for interpretation differences. Furthermore, system-automated data accuracy checks, such as calculations of surgery date after date of birth, should be implemented.

Secondly, completeness of follow-up data entry should be improved. One-year follow-up data entry might not have reached 100% completion rate as there may have been patients that have undergone their reconstructive surgery less than one year ago. Yet, more than 70% of the patients in this analysis whose records have missing data have undergone their reconstruction before 2020, suggesting that the time since reconstruction does not explain low completion rate. Another, more plausible explanation, is that users must independently remember to enter one-year follow-up data, without proper notification. To improve completeness for one-year follow-up, users should be automatically reminded by the EDC system if data is required a year after reconstruction. Although data for the remaining (closed-ended) elements in the registry was nearly complete, overall completeness should be improved by making the appropriate data elements mandatory to be filled in once starting the registration of a patient.

Thirdly, taking feedback from the users into account, it is recommended to conduct a critical evaluation of the clinical value of the current data elements. For example, current data on diagnostic tests, and whether additional diagnostic procedures (e.g., voiding cystourethrogram, cystoscopy, echocardiogram) should be considered. Additionally, the registry should improve the structure of data collection on whether the ARM is part of a syndrome. The list of syndromes should be elaborated and these, as well as the individual ARM types, should have corresponding standardized ontology codes, such as Orphanet Rare Disease Ontology

(ORDO), Online Mendelian Inheritance in Man (OMIM), or the International Classification of Diseases (ICD) [24-26]. Furthermore, to improve the value of the follow-up data and based on user suggestions, the follow-up period should be extended to at least five years but ideally to lifelong, as ARM is a condition that continues to affect patients throughout their lives. Particularly because transitional, adult, and old-age outcome data are extremely scarce or incomplete for rare congenital diseases such as ARM. Long-term outcomes and longitudinal data collection should be facilitated through standardized case report forms at specific, predetermined time points, with automated reminders before and, if registration not completed, warning reminders after.

It is not only the ARM-Net registry that can benefit from this quality assessment, as there are many suggestions that are applicable to all rare disease patient registries. A recent systematic review [25] highlighted that many registries struggle with quality management and maintenance. Like the suggestions resulting from this study, protocolized periodical monitoring procedures, evaluations of user feedback, implementation of coding languages, and mandatory fields to promote completeness are amongst the recommendations to improve existing registries. Additionally, monetary incentives per registration, revision of research aims, and securing long-term sources of funding are important aspects to maintenance strategy [25].

Most importantly, registry developers and maintainers should recognize that no registry will be perfect from its establishment, and they should continuously be evaluated for improvement. Registries, even if they have been running for more than a decade such as the ARM-Net registry, are malleable and should consider changes and updates resulting from periodical quality assessments to remain relevant. Sustainability of registries is key and with this study, the authors call for other rare disease patient registries to take example to enhancing the small, but impactful field of rare disease research.

Conclusion

The ARM-Net registry collects information that is undeniably very valuable demonstrated by its consensus statements and publications. However, as the registry has outgrown its original purpose, data quality remains a challenge with vulnerability to error and tendency to intra- and inter-user variability. Nevertheless, users were satisfied with the ARM-Net registry. This quality assessment resulted in suggestions for improvement for the ARM-Net registry as well as other rare disease patient registries in general. Periodical critical (self-) evaluation is key to continuously improving data quality in the aspiration for a registry to be sustainable and remain relevant for future research and clinical care.

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Supplementary files

Supplementary File 1: ARM-Net data dictionary

#	Category	Name data element	Format	Type
1	Administrative	@_id	String	Automatic
2		@_creation_time	String	Automatic
3		@_modification_time	String	Automatic
4		@_lock_time	String	Automatic
5		@_creation_user_id	Numeric	Automatic
6		@_modification_user_id	Numeric	Automatic
7		@_lock_user_id	Numeric	Automatic
8		pid	String	Automatic
9	Demographics	bin_dob_child	String	Date
10		bin_dob_mother	String	Text
11		bin_birthtime	String	*not used*
12		bin_twins	Numeric	Radio
13		bin_country	String	Dropdown

Value Labels	
	'1' 'Yes' '0' 'No'
	' '-' 'AF' 'Afghanistan' 'AX' 'Aland Islands' 'AL' 'Albania' 'DZ' 'Algeria' 'AS' 'American Samoa' 'AD' 'Andorra' 'AO' 'Angola' 'AI' 'Anguilla' 'AQ' 'Antarctica' 'AG' 'Antigua and Barbuda' 'AR' 'Argentina' 'AM' 'Armenia' 'AW' 'Aruba' 'AU' 'Australia' 'AT' 'Austria' 'AZ' 'Azerbaijan' 'BS' 'Bahamas' 'BH' 'Bahrain' 'BD' 'Bangladesh' 'BB' 'Barbados' 'BY' 'Belarus' 'BE' 'Belgium' 'BZ' 'Belize' 'BJ' 'Benin' 'BM' 'Bermuda' 'BT' 'Bhutan' 'BO' 'Bolivia' 'BA' 'Bosnia and Herzegovina' 'BW' 'Botswana' 'BV' 'Bouvet Island' 'BR' 'Brazil' 'IO' 'British Indian Ocean Territory' 'BN' 'Brunei' 'BG' 'Bulgaria' 'BF' 'Burkina Faso' 'BI' 'Burundi' 'KH' 'Cambodia' 'CM' 'Cameroon' 'CA' 'Canada' 'CV' 'Cape Verde' 'KY' 'Cayman Islands' 'CF' 'Central African Republic' 'TD' 'Chad' 'CL' 'Chile' 'CN' 'China' 'CX' 'Christmas Island' 'CC' 'Cocos Islands' 'CO' 'Colombia' 'KM' 'Comoros' 'CG' 'Congo' 'CD' 'Congo, Democratic Republic of the' 'CK' 'Cook Islands' 'CR' 'Costa Rica' 'CI' 'Cote d Ivoire' 'HR' 'Croatia' 'CU' 'Cuba' 'CY' 'Cyprus' 'CZ' 'Czech Republic' 'DK' 'Denmark' 'DJ' 'Djibouti' 'DM' 'Dominica' 'DO' 'Dominican Republic' 'EC' 'Ecuador' 'EG' 'Egypt' 'SV' 'El Salvador' 'GQ' 'Equatorial Guinea' 'ER' 'Eritrea' 'EE' 'Estonia' 'ET' 'Ethiopia' 'FK' 'Falkland Islands' 'FO' 'Faroe Islands' 'FJ' 'Fiji' 'FI' 'Finland' 'FR' 'France' 'GF' 'French Guiana' 'PF' 'French Polynesia' 'TF' 'French Southern Territories' 'GA' 'Gabon' 'GM' 'Gambia' 'GE' 'Georgia' 'DE' 'Germany' 'GH' 'Ghana' 'GI' 'Gibraltar' 'GR' 'Greece' 'GL' 'Greenland' 'GD' 'Grenada' 'GP' 'Guadeloupe' 'GU' 'Guam' 'GT' 'Guatemala' 'GG' 'Guernsey' 'GN' 'Guinea' 'GW' 'Guinea-Bissau' 'GY' 'Guyana' 'HT' 'Haiti' 'HM' 'Heard Island and McDonald Islands' 'HN' 'Honduras' 'HK' 'Hong Kong' 'HU' 'Hungary' 'IS' 'Iceland' 'IN' 'India' 'ID' 'Indonesia' 'IR' 'Iran' 'IQ' 'Iraq' 'IE' 'Ireland' 'IM' 'Isle of Man' 'IL' 'Israel' 'IT' 'Italy' 'JM' 'Jamaica' 'JP' 'Japan' 'JE' 'Jersey' 'JO' 'Jordan' 'KZ' 'Kazakhstan' 'KE' 'Kenya' 'KI' 'Kiribati' 'KW' 'Kuwait' 'KG' 'Kyrgyzstan' 'LA' 'Laos' 'LV' 'Latvia' 'LB' 'Lebanon' 'LS' 'Lesotho' 'LR' 'Liberia' 'LY' 'Libya' 'LI' 'Liechtenstein' 'LT' 'Lithuania' 'LU' 'Luxembourg' 'MO' 'Macao' 'MK' 'Macedonia' 'MG' 'Madagascar' 'MW' 'Malawi' 'MY' 'Malaysia' 'MV' 'Maldives' 'ML' 'Mali' 'MT' 'Malta' 'MH' 'Marshall Islands' 'MQ' 'Martinique' 'MR' 'Mauritania' 'MU' 'Mauritius' 'YT' 'Mayotte' 'MX' 'Mexico' 'FM' 'Micronesia' 'MD' 'Moldova' 'MC' 'Monaco' 'MN' 'Mongolia' 'ME' 'Montenegro' 'MS' 'Montserrat' 'MA' 'Morocco' 'MZ' 'Mozambique' 'MM' 'Myanmar' 'NA' 'Namibia' 'NR' 'Nauru' 'NP' 'Nepal' 'NL' 'Netherlands' 'AN' 'Netherlands Antilles' 'NC' 'New Caledonia' 'NZ' 'New Zealand' 'NI' 'Nicaragua' 'NE' 'Niger'

Supplementary File 1: Continued

#	Category	Name data element	Format	Type
13	Demographics	bin_country	String	Dropdown
14		bin_gender	Numeric	Radio
15		bin_sureness	Numeric	*not used*
16		bin_physician	String	Text
17		bin_center	String	Text
18		bin_center_pid	String	Text
19	ARM diagnosis	bin_fistula_krickenbeck	Numeric	Dropdown
20		bin_fistula_krickenbeck_freetext	String	Text
21	Family history	bin_family_biological_father	Numeric	Dropdown
22		bin_family_biological_mother	Numeric	Dropdown
23		bin_family_grandfather_paternal	Numeric	Dropdown
24		bin_family_grandmother_paternal	Numeric	Dropdown

	Value Labels
	'NG' 'Nigeria' 'NU' 'Niue' 'NF' 'Norfolk Island' 'MP' 'Northern Mariana Islands' 'KP' 'North Korea' 'NO' 'Norway' 'OM' 'Oman' 'PK' 'Pakistan' 'PW' 'Palau' 'PS' 'Palestinian Territories' 'PA' 'Panama' 'PG' 'Papua New Guinea' 'PY' 'Paraguay' 'PE' 'Peru' 'PH' 'Philippines' 'PN' 'Pitcairn' 'PL' 'Poland' 'PT' 'Portugal' 'PR' 'Puerto Rico' 'QA' 'Qatar' 'RE' 'Reunion' 'RO' 'Romania' 'RU' 'Russia' 'RW' 'Rwanda' 'SH' 'Saint Helena' 'KN' 'Saint Kitts and Nevis' 'LC' 'Saint Lucia' 'PM' 'Saint Pierre and Miquelon' 'VC' 'Saint Vincent and the Grenadines' 'WS' 'Samoa' 'SM' 'San Marino' 'ST' 'SÃ£o TomÃ© and PrÃncipe' 'SA' 'Saudi Arabia' 'SN' 'Senegal' 'RS' 'Serbia' 'CS' 'Serbia and Montenegro' 'SC' 'Seychelles' 'SL' 'Sierra Leone' 'SG' 'Singapore' 'SK' 'Slovakia' 'SI' 'Slovenia' 'SB' 'Solomon Islands' 'SO' 'Somalia' 'ZA' 'South Africa' 'GS' 'South Georgia and the South Sandwich Islands' 'KR' 'South Korea' 'ES' 'Spain' 'LK' 'Sri Lanka' 'SD' 'Sudan' 'SR' 'Suriname' 'SJ' 'Svalbard and Jan Mayen' 'SZ' 'Swaziland' 'SE' 'Sweden' 'CH' 'Switzerland' 'SY' 'Syria' 'TW' 'Taiwan' 'TJ' 'Tajikistan' 'TZ' 'Tanzania' 'TH' 'Thailand' 'TL' 'Timor-Leste' 'TG' 'Togo' 'TK' 'Tokelau' 'TO' 'Tonga' 'TT' 'Trinidad and Tobago' 'TN' 'Tunisia' 'TR' 'Turkey' 'TM' 'Turkmenistan' 'TC' 'Turks and Caicos Islands' 'TV' 'Tuvalu' 'UG' 'Uganda' 'UA' 'Ukraine' 'AE' 'United Arab Emirates' 'GB' 'United Kingdom' 'US' 'United States' 'UM' 'United States minor outlying islands' 'UY' 'Uruguay' 'UZ' 'Uzbekistan' 'VU' 'Vanuatu' 'VA' 'Vatican City' 'VE' 'Venezuela' 'VN' 'Vietnam' 'VG' 'Virgin Islands, British' 'VI' 'Virgin Islands, U.S.' 'WF' 'Wallis and Futuna' 'EH' 'Western Sahara' 'YE' 'Yemen' 'ZM' 'Zambia' 'ZW' 'Zimbabwe'.
	'1' 'Male' '2' 'Female' '0' 'Unknown'.
	'0' 'Unknown' '1' 'Perineal (cutaneous)' '2' 'Rectourethral Fistula unspecified (only Male)' '3' 'Rectobulbar Fistula (only Male)' '4' 'Rectoprostate Fistula (only Male)' '5' 'Rectovesicular Fistula / Bladderneck' '6' 'Vestibular Fistula (only Female)' '7' 'Cloaca, unspecified Common Channel (only Female)' '8' 'Cloaca, ≤ 3cm Common Channel (only Female)' '9' 'Cloaca, > 3cm Common Channel (only Female)' '10' 'Anal Atresia without Fistula' '11' 'Anal Stenosis' '12' 'Rare Type: Anterior Ectopia Syndrome / Ventrally Dystopic Anus' '13' 'Rare Type: Sinus Urogenitalis (only Female)' '14' 'Rare Type: Cloacal Exstrophy' '15' 'Rare Type: Rectal Atresia' '16' 'Rare Type: Rectal Stenosis' '17' 'Rare Type: Recto-Vaginal Fistula' '18' 'Rare Type: H-Fistula' '19' 'Rare Type: Pouch Colon' '20' 'Rare Type: Other, see Freetext'.
	freetext
	0' 'Unknown' '1' 'Normal' '2' 'Anorectal Malformations' '3' 'Other Gastrointestinal Malformations' '4' 'Urogenital Malformations' '5' 'Skeletal Malformations' '8' 'Other Problem' '9' 'More than one Problem'.
	0' 'Unknown' '1' 'Normal' '2' 'Anorectal Malformations' '3' 'Other Gastrointestinal Malformations' '4' 'Urogenital Malformations' '5' 'Skeletal Malformations' '8' 'Other Problem' '9' 'More than one Problem'.
	0' 'Unknown' '1' 'Normal' '2' 'Anorectal Malformations' '3' 'Other Gastrointestinal Malformations' '4' 'Urogenital Malformations' '5' 'Skeletal Malformations' '8' 'Other Problem' '9' 'More than one Problem'.
	0' 'Unknown' '1' 'Normal' '2' 'Anorectal Malformations' '3' 'Other Gastrointestinal Malformations' '4' 'Urogenital Malformations' '5' 'Skeletal Malformations' '8' 'Other Problem' '9' 'More than one Problem'.

Supplementary File 1: Continued

#	Category	Name data element	Format	Type
25	Family history	bin_family_grandfather_maternal	Numeric	Dropdown
26		bin_family_grandmother_maternal	Numeric	Dropdown
27		bin_family_sibling1	Numeric	Dropdown
28		bin_family_sibling2	Numeric	Dropdown
29		bin_family_sibling3	Numeric	Dropdown
30		bin_family_history_freetext	String	Text
31	Genetic testing and biosamples	bin_genetic_studies	Numeric	Dropdown
32		bin_genetic_abnormality	Numeric	Dropdown
33		bin_genetic_abnormality_freetext	String	Text
34		bin_genetic_dna_sample	Numeric	Dropdown
35		bin_genetic_dna_storage	String	Text
36	Associated anomalies	bin_skeletal_abnormality_upper_limb	Numeric	Radio
37		bin_skeletal_abnormality_lower_limb	Numeric	Radio
38		bin_skeletal_abnormality_costal	Numeric	Radio
39		bin_skeletal_abnormality_vertebra	Numeric	Radio
40		bin_skeletal_abnormality_sacrum	Numeric	Radio
41		bin_skeletal_abnormality_coccyx	Numeric	Radio
42		bin_skeletal_abnormality_freetext	String	Text
43		bin_skeletal_imaging_sacral_ratio	Numeric	Radio
44		bin_skeletal_imaging_sacral_ratio_value	String	Text
45		bin_skeletal_imaging_sacral_ratio_date	String	Date
46		bin_skeletal_imaging_sacral_ratio_method	String	Text

Value Labels
0' 'Unknown' '1' 'Normal' '2' 'Anorectal Malformations' '3' 'Other Gastrointestinal Malformations' '4' 'Urogenital Malformations' '5' 'Skeletal Malformations' '8' 'Other Problem' '9' 'More than one Problem'.
0' 'Unknown' '1' 'Normal' '2' 'Anorectal Malformations' '3' 'Other Gastrointestinal Malformations' '4' 'Urogenital Malformations' '5' 'Skeletal Malformations' '8' 'Other Problem' '9' 'More than one Problem'.
0' 'Unknown' '1' 'Normal' '2' 'Anorectal Malformations' '3' 'Other Gastrointestinal Malformations' '4' 'Urogenital Malformations' '5' 'Skeletal Malformations' '8' 'Other Problem' '9' 'More than one Problem'.
0' 'Unknown' '1' 'Normal' '2' 'Anorectal Malformations' '3' 'Other Gastrointestinal Malformations' '4' 'Urogenital Malformations' '5' 'Skeletal Malformations' '8' 'Other Problem' '9' 'More than one Problem'.
0' 'Unknown' '1' 'Normal' '2' 'Anorectal Malformations' '3' 'Other Gastrointestinal Malformations' '4' 'Urogenital Malformations' '5' 'Skeletal Malformations' '8' 'Other Problem' '9' 'More than one Problem'.
freetext
0' 'Not performed' '1' 'Checked normal' '2' 'Abnormal, specify'.
0' 'Not diagnosed' '1' 'Cat Eye Syndrome' '2' 'Currarino Syndrome' '10' 'Currarino or HLXB9 Mutation' '9' 'Down Syndrome / Trisomie 21' '3' 'Townes-Brocks Syndrome' '4' 'Pallister-Hall Syndrome' '5' 'Multiple Congenital Anomalies (MCA)' '6' 'VATER Association' '7' 'VACTERL Association' '8' 'Other genetic Abnormality, see Freetext'.
freetext
0' 'Not existent' '1' 'EDTA Blood of Index Person' '2' 'EDTA Blood of Trio: Index Person and Biological Parents' '3' 'Saliva of Index Person' '4' 'Saliva of Trio: Index Person and Biological Parents' '5' 'Incomplete Trio: Index Person and Biological Parents'.
freetext
2' 'Abnormal' '1' 'Normal' '0' 'Unknown'
2' 'Abnormal' '1' 'Normal' '0' 'Unknown'
2' 'Abnormal' '1' 'Normal' '0' 'Unknown'
2' 'Abnormal' '1' 'Normal' '0' 'Unknown'
2' 'Abnormal' '1' 'Normal' '3' 'Hemisacrum' '0' 'Unknown'.
2' 'Absent' '1' 'Present' '0' 'Unknown'
freetext
1' Abnormal '2' Normal '3' Not Taken
freetext

Supplementary File 1: Continued

#	Category	Name data element	Format	Type
47		bin_skeletal_imaging_mri	Numeric	Radio
48		bin_skeletal_imaging_xray	Numeric	Radio
49		bin_skeletal_imaging_sonography	Numeric	Radio
50		bin_skeletal_imaging_further_specification	String	Text
51		bin_renal_abnormality	Numeric	Radio
52		bin_renal_abnormality_specification	Numeric	Checkbox
53		bin_renal_abnormality_freetext	String	Text
54		bin_bladder_abnormality	Numeric	Radio
55		bin_bladder_abnormality_freetext	String	Text
56		bin_vesicoureteral_reflux	Numeric	Dropdown
57		bin_genital_abnormality	Numeric	Radio
58		bin_genital_abnormality_specification	String	Checkbox
59	Associated anomalies	bin_genital_abnormality_freetext	String	Text
60		bin_esophageal_agenesis_tracheo_fistula	Numeric	Dropdown
61		bin_other_gastrointestinal_abnormality	Numeric	Radio
62		bin_other_gastrointestinal_abnormality_freetext	String	Text
63		bin_spinal_canal_chord_abnormality	Numeric	Radio
64		bin_spinal_canal_chord_abnormality_specification	String	Dropdown
65		bin_spinal_canal_chord_abnormality_freetext	String	Text
66		bin_limb_abnormality_freetext	String	*not used*
67		bin_brain_abnormality	Numeric	Dropdown
68		bin_brain_abnormality_freetext	String	Text
69		bin_cardiac_abnormality	Numeric	Radio
70		bin_cardiac_abnormality_specification	Numeric	Checkbox
71		bin_cardiac_abnormality_freetext	String	Text

Value Labels
2' 'Pictures Available' '1' 'Done' '3' 'Not Done' '0' 'Unknown'
2' 'Pictures Available' '1' 'Done' '3' 'Not Done' '0' 'Unknown'
2' 'Pictures Available' '1' 'Done' '3' 'Not Done' '0' 'Unknown'
freetext
'1' 'Abnormal' '2' 'Normal' '3' 'Not checked' '0' 'Unknown'.
'1' 'Normal' '2' 'Single Kidney' '3' 'Dysplastic Kidney' '4' 'Hydronephrosis' '5' 'Ectopic Kidney' '6' 'Horseshoe Kidney' '7' 'Double System' '8' 'Other, see Freetext'.
freetext
'3' 'Abnormal' '1' 'Normal' '2' 'Neurogenic' '4' 'Not checked' '0' 'Unknown'.
freetext
'0' 'Not checked for Vesicoureteral Reflux' '1' 'No Vesicoureteral Reflux' '2' 'Grade I' '3' 'Grade II' '4' 'Grade III' '5' 'Grade IV' '6' 'Grade V'.
'1' 'Abnormal' '2' 'Normal' '3' 'Not checked' '0' 'Unknown'.
1' 'Vaginal Agenesis' OR 'Undescended Testes', '2' 'Vaginal Duplication / Septum' OR Undescended Testes Left', '3' 'Bicornuate Uterus / Uterus Duplex' OR 'Undescended Testes Right', '4' 'Mullerian Remnants / Uterus Atresia' OR 'Hypospadias', '5' 'Hydrocolpos' OR 'Bifid Scrotum', '6' 'Other, see Freetext' OR 'Penoscrotal Transposition, '7' 'Other, see Freetext'
freetext
'0' 'Unknown' '1' 'Normal' '2' 'Vogt 1' '3' 'Vogt 2, Gross A' '4' 'Vogt 3a, Gross B' '5' 'Vogt 3b, Gross C' '7' 'Vogt 3c, Gross D' '8' 'Gross E/H' '9' 'Unclear Classification, Other'.
'2' 'Abnormal' '1' 'Normal' '3' 'Not checked' '0' 'Unknown'.
freetext
2' 'Abnormal' '1' 'Normal' '3' 'Not checked' '0' 'Unknown'
' '-' '1' 'Normal' '2' 'Thickened Filum' '3' 'Tethered Cord' '4' 'Intra Spinal Mass' '5' 'Extra Spinal Mass Extension' '6' 'Syrinx' '7' 'Meningocele' '8' 'Presacral Mass' '9' 'Other, see Freetext'.
freetext
'0' 'Unknown' '1' 'Normal' '2' 'Structural Defect / Abnormal, see Freetext' '3' 'Functional Defect / Mental Retardation, see Freetext' '4' 'Other, see Freetext'.
freetext
'2' 'Abnormal' '1' 'Normal' '3' 'Not checked' '0' 'Unknown'
'1' 'Normal' '2' 'Ventricular Septal Defect' '3' 'Atrial Septal Defect' '4' 'Patent Ductus Arteriosus' '5' 'Fallot Tetralogy' '6' 'Coarctation of the Aorta' '7' 'Other, see Freetext'.
freetext

Supplementary File 1: Continued

#	Category	Name data element	Format	Type
72	Associated anomalies	bin_throat_lung_thorax_abnormality	Numeric	Radio
73		bin_throat_lung_thorax_abnormality_freetext	String	Text
74		bin_ear_abnormality	Numeric	Radio
75		bin_ear_abnormality_freetext	String	Text
76		bin_eye_abnormality	Numeric	Radio
77		bin_eye_abnormality_freetext	String	Text
78		bin_facial_dysmorphic_features	Numeric	Radio
79		bin_facial_dysmorphic_features_freetext	String	Text
80		bin_vascular_malformations_hemangioma	Numeric	Radio
81		bin_vascular_malformations_ hemangioma_freetext	String	Text
82		bin_dermatologic_abnormality	Numeric	Radio
83		bin_dermatologic_abnormality_freetext	String	Text
84		bin_further_abnormality	Numeric	Radio
85		bin_further_abnormality_freetext	String	Text
86	Surgery and complications	bin_surgical_procedures_enterostomy	Numeric	Radio
87		bin_surgical_procedures_enterostomy_form	Numeric	Dropdown
88		bin_surgical_procedures_section_bowel_opened	Numeric	Dropdown
89		bin_surgical_procedures_ enterostomy_complications	Numeric	Checkbox
90		bin_surgical_procedures_enterostomy_freetext	String	Text
91		bin_surgical_procedures_enterostomy_closure	Numeric	Checkbox
92		bin_surgical_procedures_ enterostomy_closure_date	String	Date
93		bin_surgical_procedures_stoma_ closure_complications	Numeric	Checkbox
94		bin_surgical_procedures_stoma_ closure_complications_freetext	String	Text
95		bin_surgical_procedures_reconstruction_ostomy	Numeric	Radio
96		bin_surgical_procedures_ reconstruction_ostomy_date	String	Date

Value Labels
2' 'Abnormal' '1' 'Normal' '3' 'Not checked' '0' 'Unknown'.
freetext
2' 'Abnormal' '1' 'Normal' '3' 'Not checked' '0' 'Unknown'.
freetext
2' 'Abnormal' '1' 'Normal' '3' 'Not checked' '0' 'Unknown'.
freetext
2' 'Abnormal' '1' 'Normal' '3' 'Not checked' '0' 'Unknown'.
freetext
2' 'Abnormal' '1' 'Normal' '3' 'Not checked' '0' 'Unknown'.
freetext
2' 'Abnormal' '1' 'Normal' '3' 'Not checked' '0' 'Unknown'.
freetext
2' 'Abnormal' '1' 'Normal' '3' 'Not checked' '0' 'Unknown'.
freetext
2' 'Yes' '1' 'No' '0' 'Unknown'
0' 'Unknown' '1' 'Loop-Ostomy' '2' 'Divided or Diverting Ostomy'.
0' 'Unknown' '1' 'Ileum' '2' 'Ascending Colon' '3' 'Transverse Colon' '4' 'Descending Colon' '5' 'Sigmoid Colon' '7' 'Descending / Sigmoid Junction' '6' 'Others, see Freetext'.
'1' 'No Complication' '2' 'Woundinfection' '3' 'Stenosis' '4' 'Prolaps' '5' 'Others, see Freetext'.
freetext
'1' 'Yes'.
'0' 'Unknown' '1' 'No Complications' '2' 'Woundinfection' '3' 'Leakage' '4' 'Other, see Freetext'.
freetext
'2' 'Yes' '1' 'No' '0' 'Unknown'.

3

Supplementary File 1: Continued

#	Category	Name data element	Format	Type
97	Surgery and complications	bin_surgical_procedures_reconstruction_ostomy_specification	Numeric	Dropdown
98		bin_surgical_procedures_reconstruction_ostomy_freetext	String	Text
99		bin_surgical_procedures_reconstruction_ostomy_electrostimu	String	*not used*
100		bin_surgical_procedures_reconstruction_ostomy_laparoscopy	Numeric	Radio
101		bin_surgical_procedures_reconstruction_ostomy_laparotomy	Numeric	Radio
102		bin_complications_by_reconstructive_surgery	Numeric	Radio
103		bin_surgical_procedures_reconst_surgery_complications	Numeric	Checkbox
104		bin_surgical_procedures_reconst_surgery_complications_freetext	String	Text
105		bin_surgical_procedures_reconst_surgery_redo_date	String	Date
106	Completion check	bin_status	Numeric	Radio
107		bin_status_further_info	String	Text
108	One-year follow-up	bin_follow_up_1_constipation	Numeric	Radio
109		bin_follow_up_1_constipation_treatment	Numeric	Checkbox
110		bin_follow_up_1_defecations_frequency	String	Text
111		bin_follow_up_1_consistency_faeces	Numeric	Radio
112		bin_follow_up_1_diaper_rash	Numeric	Radio
113		bin_follow_up_1_dilated_rectosigmoid	Numeric	Radio
114		bin_follow_up_1_ultrasound	Numeric	Radio
115		bin_follow_up_1_anal_mucosa_prolapse	Numeric	Radio
116		bin_follow_up_1_neoanus_diameter	String	Text
117		bin_follow_up_1_dilatation_therapy_neoanus	Numeric	Radio
118		bin_follow_up_1_pain_during_dilatations	Numeric	Radio
119		bin_follow_up_1_further_comments	String	Text

	Value Labels
	0' '-' '1' 'Cutback' '2' 'Anoplasty' '3' 'Mini-PSARP' '4' 'PSARP' '5' 'ASARP' '6' 'LAARP' '7' 'PSARVUP' '8' 'PSARVUP including TUM' '9' 'No Reconstruction' '10' 'Other, see Freetext'.
	freetext
	'2' 'Yes' '1' 'No' '0' 'Unknown'.
	'2' 'Yes' '1' 'No' '0' 'Unknown'.
	'2' 'Yes' '1' 'No information obtainable' '3' 'No' '0' 'Unknown'.
	'1' 'Woundinfection' '2' 'Wound Dehiscence' '3' 'Stenosis (< Hegar 10 at Age 6 Months)' '4' 'Recurrent Fistula' '5' 'Lesion Urethra' '6' 'Lesion vas Deferens' '7' 'Redo Reconstruction, see Freetext' '8' 'Other, see Freetext'.
	freetext
	'1' 'Done' '0' 'Not done' '2' 'Please check'.
	freetext
	'1' 'Yes' '0' 'No'.
	'0' 'Diet' '1' 'Stool Softener (such as Polyethylene Glycol)' '2' 'Laxatives' '3' 'Enemas'.
	'0' 'Solid' '1' 'Soft' '2' 'Liquid'.
	'0' 'Never or rarely' '1' 'Frequently' '2' 'Severe'.
	'1' 'Palpable Yes' '0' 'No' '2' 'Unknown'.
	'1' 'Yes' '0' 'No' '2' 'Unknown'.
	'1' 'Yes' '0' 'No' '2' 'Unknown'.
	'0' 'Never' '1' 'Finished' '2' 'Still going on'.
	'0' 'Never' '1' 'Only initially' '2' 'Obvious'.
	freetext

Supplementary File 2: ARM-Net registry user questionnaire

1. What do you think is currently the main purpose of the ARM-Net database?
    a. Surveillance of all ARM patients in participating clinical centres
    b. Scientific research
    c. Improvement of clinical care
    d. Other:
    e. I don't know

2. What do you think should be the main purpose of the ARM-Net database?
    a. Surveillance of all ARM patients in participating clinical centres
    b. Scientific research
    c. Improvement of clinical care
    d. Other:
    e. I don't know

3. Do you think the ARM-Net database should collect patient-reported outcome measures in a new/improved database?
    a. No
    b. Yes

4. Would you be willing to pay a fee to be able to maintain the ARM-Net database?
    a. No
    b. Yes; if so, how much maximum per year?

5. Who registers patients in the ARM-Net database in your centre?
    a. Only me (paediatric surgeon)
    b. Another colleague (paediatric surgeon, but always the same one)
    c. Other colleagues (paediatric surgeons, but different ones)
    d. Another specialist or specialist nurse (nurse practitioner, case manager, research nurse)
    e. Me and (an)other colleague(s)
    f. I don't know

6. How much time does it take for you on average to register one patient in the ARM-net database (without one- and five-years follow-up)?
    a. ≤10 minutes
    b. 11-30 minutes
    c. 31-60 minutes
    d. >60 minutes

7. When do you (plan to) register a patient in the ARM-Net database?
    a. Directly after a consultation/visit
    b. I plan a separate time slot
    c. When I remember to do so

8. How do you remember to enter the 1-year (and 5-year) follow-up data?
    a. I don't; I usually forget
    b. I note it down in the patient's electronic medical file as a reminder
    c. I set a reminder in my own calendar
    d. Someone (e.g., nurse, personal assistant) else reminds me
    e. I don't know

9. Would you want the follow-up to be longer than 5 years? (e.g, 10 years)
    a. No
    b. Yes; if so: how long?

10. Do you ever use the user manual for registering a patient in the ARM-Net database?
    a. No, I did not know there was a manual
    b. No, I know how to register a patient
    c. Yes, only for the first patient
    d. Yes, occasionally
    e. Yes, always

11. Do you find the manual for registering a patient in the ARM-Net database helpful?
    a. No
    b. Yes
    c. Not applicable

12. Which of these items do you think can be removed from the ARM-Net database? (Multiple selection possible)
    a. Family history
    b. DNA sample
    c. Throat/lung/thorax abnormalities
    d. Eye/ear abnormalities
    e. Facial dysmorphic features
    f. Other:

13. Would you be willing to collect more data elements?
    a. No
    b. Yes

14. Which of these items would you like to add? (Multiple selection possible)
    a. Order of birth
    b. Prematurity and birth weight
    c. Kidney function (e.g., eCRF and/or creatinine)
    d. Voiding cystourethrogram
    e. Cystoscopy
    f. Echocardiogram
    g. Cardiac abnormality consequences (e.g., need for cardiological follow-up)
    h. Constipation based on Rome IV criteria for 1-year follow-up
    i. Other:

15. How often do you use the “free text” option to add information?
    a. Never
    b. Rarely
    c. Sometimes
    d. Always

16. After expanding the available answer options for certain items, would you still like to keep the “free text” option, or would you be okay with only an “other” option and ‘losing’ information?
    a. I would like to keep the “free text” option to know the exact information
    b. I am happy to only have the option “other” and take my loss

17. How satisfied are you with the ARM-Net database in general?
    a. Not satisfied
    b. Somewhat satisfied
    c. Satisfied
    d. Very satisfied

18. How difficult or easy do you find it to register patients in the ARM-Net database?
    a. Difficult
    b. Somewhat difficult
    c. Easy
    d. Very easy
        i. *If difficult or somewhat difficult; what problems do you encounter when registering a patient in the ARM-Net database?*

19. On a scale of 1-10, with 1 being useless and 10 being perfect, how would you rate the ARM-Net database?

20. What do you think are the main limitations of the ARM-Net database?

What changes would you like to see?

PART 2

Clinical and surgical characteristics of anorectal malformation patients in Europe and Australia

CHAPTER 4

The European Anorectal Malformation Network (ARM-Net) patient registry: ten-year review of clinical and surgical characteristics

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Abstract

With an estimated European prevalence of 1 in 2500-5000 live births, anorectal malformation (ARM) is a rare condition. Collaborative collection of data via patient registries is paramount to rare disease research. The Anorectal Malformation Network (ARM-Net) registry was established in 2010 to bring these scarce and scattered data together. We aimed to describe the clinical and surgical characteristics of the included patients.

The ARM-Net registry collects data on ARM type according to Krickenbeck classification, diagnostics and associated anomalies, surgical details and complications, and one-year follow-up functional outcomes. Data from all patients, included until March 1st 2023, were analysed.

Thirty-four centres included a total of 2619 patients (50% male, median age at reconstructive surgery 4 months (IQR 2-7)). The most common ARM types were perineal fistula for both sexes (42%), vestibular fistula in females (32%), and rectobulbar (17%) and rectoprostatic fistula (15%) in males. Associated anomalies were predominantly skeletal (47%), cardiac (39%), and renal (29%). A stoma was created in 45% of patients. Reconstructive surgery, mostly mini- or classic PSARP (74%), was performed in 92% of patients. Complications occurred in 26%, and 4% required redo surgery. Patients with associated anomalies were more likely to undergo reconstruction at a later age (>3 months) than patients without. One year after surgery, 88% of patients had undergone anal dilatations, and 55% suffered from constipation.

The ARM-Net registry is the largest multicentre ARM cohort. The joint efforts of multiple centres facilitate the understanding of ARM patient characteristics and treatment strategies, ultimately to improve clinical care.

Background

Anorectal malformations (ARM) are a group of rectal and anal birth defects with a European prevalence of about 1 in 2500 to 5000 live births [1-4]. These rare and complex conditions require highly specialized reconstructive surgery in early life, often with a temporary defunctioning stoma [5-7]. ARM are associated with other organ anomalies in 58-78% of patients, therefore all ARM newborns should be screened for associated anomalies [2, 5, 8-11]. The introduction of posterior sagittal anorectoplasty has improved the management of ARM in recent decades [12]. Nevertheless, problems with bowel function can remain throughout adulthood and compromise quality of life [13-20].

With the rarity of ARM, specialized centres see five to 20 new patients each year [21] and knowledge on epidemiology, demographics, treatment strategies, and outcomes is scattered. In 2010, the Anorectal Malformation Network (ARM-Net) Consortium, a group of European paediatric surgeons, patient advocacy groups, geneticists, epidemiologists, and psychologists, established a patient registry [22]. The ARM-Net registry represents the collaboration amongst multiple paediatric surgical centres with a wide geographical coverage [22-36]. Since its inception, more than 2600 patients have been registered. The aim of this study is to describe the clinical and surgical characteristics of ARM patients in the registry.

Methods

Objectives

The primary objective of this retrospective cohort study was to describe patients treated within the ARM-Net Consortium in terms of demographics, diagnostics, clinical characteristics including associated anomalies, surgical details including type of reconstruction, stoma placement, complications, and functional outcomes one year after reconstructive surgery. Secondary objectives were to investigate the relations between associated anomalies and ARM types, and timing of reconstructive surgery.

Subjects and data collection

ARM patients under 18 years of age treated in one of the ARM-Net Consortium and registered in the ARM-Net registry until 1st March 2023 were included. Each centre has a lead paediatric surgeon that is responsible for patient registration

and data collection at their respective centre. Patient data are deidentified and pseudonymized before collection. Surgeons can only reidentify their own patients with personal code-breaking documentation. Data on demographics, ARM type according to Krickenbeck classification [33, 37], diagnostic screening and associated anomalies, surgical details and complications, and one-year follow-up functional outcomes are collected. Records with more than 25% missing data for closed-ended items were excluded from our analyses.

Renal, bladder, cardiac, tracheo-oesophageal, genital, skeletal, vertebral, sacral, spinal cord, and brain associated anomalies, but also other (minor) anomalies, could be registered. Data on genetic studies were collected, including the presence of a syndrome or association. Surgical information included dates and types of stoma and anorectal reconstruction, and postoperative complications (e.g., infection, wound dehiscence, urethral injury, stenosis, recurrent fistula, or insufficient reconstruction requiring redo surgery). Data on short-term colorectal outcome one year after reconstruction was collected, including constipation and treatment, faecal consistency and frequency, anal dilatations, and late complications including perianal dermatitis and rectal mucosal prolapse, assessed at the surgeons' discretion. Surgeons were at liberty to provide additional information in the free text sections.

Statistical analyses

Descriptive statistics were performed for patient demographics, ARM phenotype, clinical characteristics including associated anomalies, surgical details including complications, and functional outcomes one year after reconstruction. Patients with reconstruction within one year of March 1st, 2023, were excluded from the follow-up analyses. To calculate patients' age at time of surgery, date of birth and surgery used the 15th of the month, due to availability of month and year only. Mother's approximate age at time of patient's birth was calculated using birth year of mother and patient.

Logistic regression modelling estimated odds ratios (OR) and 95% confidence intervals (CI) for associations between accompanying anomalies and ARM phenotypes, using perineal fistula as reference. Associations between anomalies and median age at time of reconstruction were examined using Mann-Whitney U-tests, and using chi-squared tests when age was categorized into older or younger than 3 months. All statistical tests were considered significant at a p-value of <0.05.

Data was exported from the ARM-Net registry online database, cleaned with OpenRefine (v.3.4.1; 437dc4d, Google Inc. and contributors) and further cleaned and analysed in SPSS Statistics (v.29.0.0.0; 241, IBM Corporation, Armonk, United States).

Results

There were 2627 patients included in the ARM-Net registry. Eight records with more than 25% missing data were excluded, resulting in a total of 2619 patients included for analysis. Patients were registered through 34 different European centres (**Figure 1**). Patient sex distribution was equal, and the most common ARM phenotype was perineal fistula for both sexes (41.5%), followed by vestibular fistula (31.8%) and cloaca (8.8%) in females, and rectobulbar (16.8%) and rectoprostatic fistula (15.0%) in males (**Table 1**). Patients were born to mothers with a median age of 32 years old (IQR 28-36).

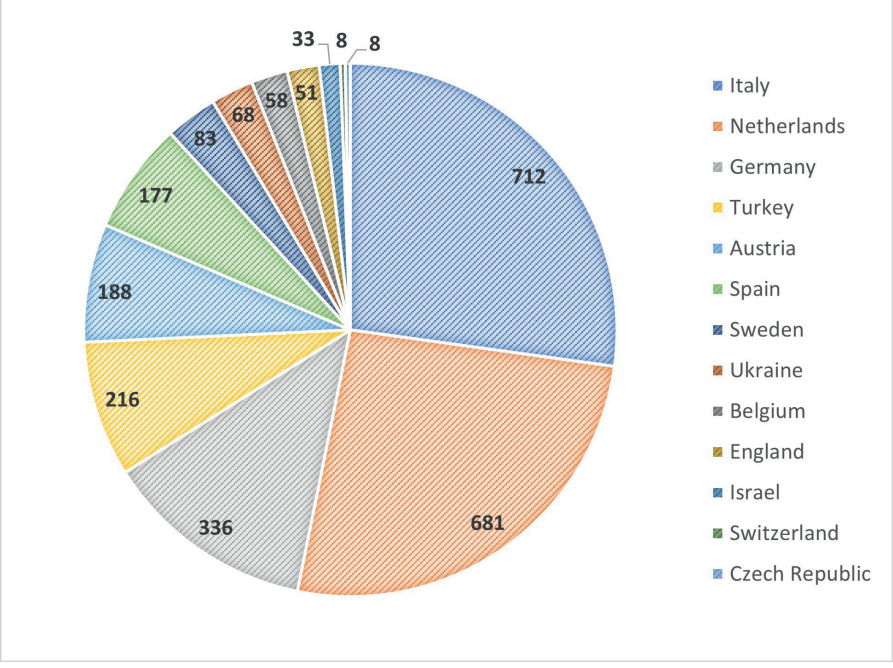

Figure 1: ARM patients in the ARM-Net registry per country (N)

Associated congenital anomalies

A minority of patients (11.4%) had a confirmed genetic diagnosis at time of analysis, and 31.7% of ARMs were isolated, without any associated anomalies. Frequency of associated anomalies are presented in **Supplementary Table 1**.

Significant associations between ARM phenotypes and other anomalies were found (**Table 2)**. Patients with vestibular fistula, rectourethral fistula (any type), recto-bladder neck fistula, cloaca, no fistula, or the group rare and other types were each more likely to have any associated anomalies compared to patients with perineal fistula. The same was true for skeletal, renal, bladder, and genital anomalies separately. Patients with vestibular, rectourethral, or recto-bladder neck fistula were more likely to have cardiac, spinal, or tracheo-oesophageal anomalies than perineal fistula patients. There was no increased risk for cardiac anomalies in patients with cloaca or the group rare and other types, nor for spinal anomalies in patients with no fistula, compared to perineal fistula patients. Patients with anal stenosis were not more likely to have any associated anomalies than patients with perineal fistula. Patients with no fistula had a twofold increased risk for brain anomalies compared to perineal fistula patients, but this was not associated with Down syndrome (p=0.469). Furthermore, there was no association between complex ARM types and any genetic abnormality (p=0.123).

Table 1: ARM patient characteristics of the ARM-Net registry

	N (%*)
Sex ratio (M:F)	1314 (50.4): 1292 (49.6)
Twins	101 (3.9)
Mother's age at childbirth in years (median, IQR)	32 (28-36)
Krickenbeck classification	
Perineal fistula	1086 (41.5)
Vestibular fistula (only female)	415 (15.8)
Rectobulbar fistula (only male)	222 (8.5)
Rectoprostatic fistula (only male)	198 (7.6)
Recto-bladder neck fistula (only male)	66 (2.5)
Rectourethral fistula unspecified (only male)	51 (1.9)
Anal atresia without fistula	162 (6.2)
Anal stenosis	53 (2.0)
Cloaca (only female)	113 (4.3)
<3cm common channel	*65 (2.5)*
>3cm common channel	*29 (1.1)*
unspecified common channel	*19 (0.7)*
Rare types:	
Ventrally dystopic anus	13 (0.5)
Rectal stenosis	17 (0.6)
Rectal atresia	16 (0.6)
Cloacal exstrophy	18 (0.7)
Rectovaginal fistula (only female)	18 (0.7)
H-type fistula	12 (0.5)
Pouch colon	7 (0.3)
Other	50 (1.9)
Unknown	102 (3.9)
Genetic diagnosis confirmed†	**298 (11.4)**
Down Syndrome	65 (2.5)
Cat Eye Syndrome	21 (0.8)
Townes-Brocks Syndrome	15 (0.6)
Currarino Syndrome or *HLXB9* mutation	14 (0.5)
VACTERL Association‡	11 (0.4)
Pallister-Hall Syndrome	4 (0.2)
Other (including chromosomal aberrations)	168 (6.4)

Abbreviations: IQR, interquartile range* Of total known data, excluding unknown or missing data.† All other patients have no confirmed genetic diagnosis or results are pending at time of analysis.‡ This diagnosis was provided by the paediatric surgeon, not by checking the combination of anomalies for the VACTERL association entered [11]

Table 2: Congenital anomalies associated with ARM Krickenbeck phenotypes

Associated anomalies	Krickenbeck type	N (%*)	OR	CI
Any anomaly Sex ratio (M [%]: F [%])* 949 (53.2): 835 (46.8)	Perineal fistula	586 (54.0)	*ref*	*ref*
	Vestibular fistula	314 (75.7)	2.7	2.1-3.4
	Rectourethral fistula	398 (84.5)	4.7	3.5-6.1
	Recto-bladder neck fistula	60 (90.9)	8.5	3.7-19.9
	Cloaca	111 (98.2)	47.4	11.6-192.7
	Anal stenosis	28 (52.8)	1.0	0.6-1.7
	No fistula	130 (80.2)	3.5	2.3-5.2
	Rare and other types	108 (71.5)	2.1	1.5-3.1
Skeletal anomalies Sex ratio (M [%]: F [%])* 471 (52.3): 430 (47.7)	Perineal fistula	259 (32.8)	*ref*	*ref*
	Vestibular fistula	161 (53.5)	2.4	1.8-3.1
	Rectourethral fistula	222 (60.2)	3.1	2.4-4.0
	Recto-bladder neck fistula	43 (81.1)	8.8	4.4-17.8
	Cloaca	64 (67.4)	4.2	2.7-6.7
	Anal stenosis	14 (37.8)	1.3	0.6-2.5
	No fistula	55 (47.8)	1.9	1.3-2.8
	Rare and other types	58 (53.7)	2.4	1.6-3.6
Spinal anomalies Sex ratio (M [%]: F [%])* 244 (52.8): 218 (47.2)	Perineal fistula	91 (10.4)	*ref*	*ref*
	Vestibular fistula	98 (27.8)	3.3	2.4-4.6
	Rectourethral fistula	130 (34.4)	4.5	3.3-6.1
	Recto-bladder neck fistula	26 (51.0)	8.9	5.0-16.1
	Cloaca	45 (47.4)	7.7	4.9-12.2
	Anal stenosis	7 (18.4)	1.9	0.8-4.5
	No fistula	14 (11.3)	1.1	0.6-2.0
	Rare and other types	36 (30.5)	3.8	2.4-5.9
Cardiac anomalies Sex ratio (M [%]: F [%])* 432 (50.9): 416 (49.1)	Perineal fistula	265 (29.1)	*ref*	*ref*
	Vestibular fistula	188 (50.9)	2.5	2.0-3.3
	Rectourethral fistula	178 (45.1)	2.0	1.6-2.6
	Recto-bladder neck fistula	23 (42.6)	1.8	1.0-3.2
	Cloaca	33 (35.1)	1.3	0.9-2.1
	Anal stenosis	10 (26.3)	0.9	0.4-1.8
	No fistula	89 (59.7)	3.6	2.5-5.2
	Rare and other types	35 (31.5)	1.1	0.7-1.7
Renal anomalies Sex ratio (M [%]: F [%])* 391 (57.5): 289 (42.5)	Perineal fistula	186 (19.0)	*ref*	*ref*
	Vestibular fistula	102 (27.2)	1.6	1.2-2.1
	Rectourethral fistula	174 (40.7)	2.9	2.3-3.8
	Recto-bladder neck fistula	36 (63.2)	7.3	4.2-12.8
	Cloaca	66 (61.7)	6.9	4.5-10.5
	Anal stenosis	6 (13.6)	0.7	0.3-1.6
	No fistula	40 (26.7)	1.6	1.0-2.3
	Rare and other types	42 (33.1)	2.1	1.4-3.2

Table 2: Continued

Associated anomalies	Krickenbeck type	N (%*)	OR	CI
Bladder anomalies Sex ratio (M [%]: F [%])* 152 (58.7): 107 (41.3)	Perineal fistula	40 (4.2)	*ref*	*ref*
	Vestibular fistula	32 (9.0)	2.3	1.4-3.7
	Rectourethral fistula	67 (16.0)	4.3	2.9-6.5
	Recto-bladder neck fistula	28 (50.9)	23.6	12.8-43.8
	Cloaca	35 (34.4)	11.9	7.1-20.0
	Anal stenosis	2 (5.0)	1.2	0.3-5.2
	No fistula	12 (8.8)	2.2	1.1-4.3
	Rare and other types	32 (25.4)	7.8	4.7-12.9
Genital anomalies Sex ratio (M [%]: F [%])* 323 (61.5): 202 (38.5)	Perineal fistula	103 (10.4)	*ref*	*ref*
	Vestibular fistula	45 (11.9)	1.2	0.8-1.7
	Rectourethral fistula	149 (32.9)	4.3	3.2-5.6
	Recto-bladder neck fistula	32 (53.3)	9.9	5.7-17.1
	Cloaca	80 (80.0)	34.6	20.4-58.9
	Anal stenosis	6 (13.0)	1.3	0.5-3.1
	No fistula	31 (20.0)	2.2	1.4-3.4
	Rare and other types	59 (41.5)	6.2	4.2-9.1
Tracheo-oesophageal anomalies Sex ratio (M [%]: F [%])* 99 (56.9): 75 (43.1)	Perineal fistula	29 (2.9)	*ref*	*ref*
	Vestibular fistula	39 (10.2)	3.7	2.3-6.1
	Rectourethral fistula	67 (15.4)	6.0	3.8-9.5
	Recto-bladder neck fistula	5 (8.3)	3.0	1.1-8.1
	Cloaca	15 (13.5)	5.2	2.7-10.0
	Anal stenosis	0 (0.0)	N/A	N/A
	No fistula	8 (5.4)	1.9	0.9-4.2
	Rare and other types	5 (3.6)	1.3	0.5-3.3
Brain anomalies Sex ratio (M [%]: F [%])* 98 (53.6): 85 (46.4)	Perineal fistula	59 (9.8)	*ref*	*ref*
	Vestibular fistula	37 (13.9)	1.5	1.0-2.3
	Rectourethral fistula	39 (13.0)	1.4	0.9-2.1
	Recto-bladder neck fistula	5 (14.7)	1.6	0.6-4.3
	Cloaca	8 (10.1)	1.0	0.5-2.3
	Anal stenosis	3 (10.7)	1.1	0.3-3.8
	No fistula	19 (18.4)	2.1	1.2-3.7
	Rare and other types	9 (10.8)	1.1	0.5-2.4

Abbreviations: N/A, not applicable.

* Of total known data, excluding not checked, unknown or missing data per variable.

Table 3: Surgical characteristics of the ARM patients in the ARM-Net registry

	N (%)
Sex ratio (M:F)	1314 (50.4): 1292 (49.6)
Stoma placement*	1125 (44.5)
Type	
Divided	825 (73.3)
Loop	248 (22.0)
Unknown	52 (4.6)
Bowel section	
Descending/sigmoid colon junction	903 (80.3)
Transverse colon	90 (8.0)
Ileum	16 (1.4)
Sigmoid colon	12 (1.1)
Ascending colon	5 (0.4)
Descending colon	4 (0.4)
Other	16 (1.4)
Unknown	79 (7.0)
Complications stoma placement*	242 (25.0)
Stoma closed*	942 (83.7)
Complications stoma closure*	101 (12.3)
Reconstructive surgery performed*	2278 (91.8)
Age at reconstructive surgery in months (median, IQR)*	4 (2-7)
Type	
PSARP	1247 (54.7)
Mini-PSARP	435 (19.1)
ASARP	197 (8.6)
Anoplasty	114 (5.0)
Cutback	49 (2.2)
LAARP	73 (3.2)
PSARV(U)P	60 (2.6)
TUM	43 (1.9)
Other	41 (1.8)
Unknown	19 (0.8)
Complications reconstructive surgery*	542 (25.5)
Late complications*	379 (24.9)
Redo reconstructive surgery*	93 (4.4)

Abbreviations: PSARP, posterior sagittal anorectoplasty; ASARP, anterior sagittal anorectoplasty; LAARP, laparoscopic anterior anorectoplasty; PSARV(U)P, posterior sagittal anorectovagino(urethro)plasty; TUM, total urogenital mobilization.* Of total known data, excluding not checked, unknown or missing data per variable.

Reconstructive surgery and stoma

Of all patients, 44.5% had a stoma. The majority of patients with no fistula, rectourethral fistula (bulbar, prostatic, or unspecified type), cloaca, or recto-bladder neck fistula received a stoma (78.8%, 96.6%, 97.3%, and 98.5%, respectively), whilst 9.5%, 12.0%, and 34.0% of perineal fistula, anal stenosis, or vestibular fistula patients, respectively, did. Of patients that underwent reconstruction, 45.0% received a stoma, and of those without a reconstruction or with unknown data, 29.9% did. Most were divided stomas (73.3%) and placed at the descending / sigmoid colon junction (80.3%). Stoma formation complication rate was 25.0%, including stenosis, wound infection or dehiscence, stomal prolapse, or retraction. Stomas were closed in 83.7% of patients, with complications after closure in 12.3%, including wound infection, anastomotic leakage, adhesions, or incisional hernia. Of the patients whose stoma was not closed (n=183), 21 patients died, 10 had an end stoma, eight were lost to follow-up, three were awaiting reconstruction, and one patient had closure delayed due to prioritization of other issues. The reasons for not closing the stoma could not be deduced from free text entries for the remaining patients.

Of all 2619 patients, 2278 had undergone reconstructive surgery. Information on whether a reconstruction had been performed was unknown for 5.2% of all patients (due to secondary referrals or missing data), and the remaining 7.8% of patients did not undergo reconstructive surgery. Of the patients that did not undergo reconstruction, 30 (14.8%) patients had died before surgery. Of the remaining 173 patients, most had a perineal fistula (64.7%), followed by anal stenosis (8.7%), and ventrally displaced anus (5.2%). Only 16.8% of them had a stoma. From deduction of free text of these 173 patients showed that for 62 patients a reconstruction was not indicated, due to anal dilatation management only or a perineal fistula sufficiently surrounded by sphincter musculature [24]. Ten patients were awaiting surgery, four had a definitive colostomy, three were treated for other issues with priority, and three patients refused surgery. For the remainder of patients (91; 52.6%), the reason to refrain from reconstruction remains elusive.

Of patients with available data (n=2481), 91.8% underwent reconstructive surgery (**Table 3**). Perineal fistulas were mostly corrected by mini-posterior sagittal anorectoplasty (PSARP) (40.3%), PSARP (33.5%), or anterior sagittal anorectoplasty (ASARP; 11.4%), and vestibular fistulas mostly through PSARP (71.9%) or ASARP (19.2%). Anal stenosis was mostly corrected by

anoplasty (37.8%), PSARP (21.6%) or mini-PSARP (21.6%), and rectourethral fistulas (any type), no fistula, and recto-bladder neck fistulas through PSARP (88.1%, 80.7%, and 63.5% respectively). Cloaca's were most often reconstructed by PSARV(U)P (42.9%) or total urogenital mobilization (39.8%). Complications after reconstruction occurred in 25.5% of patients, including wound infections, dehiscence, stenosis, urethral injury, and recurrent fistula. Late complications of frequent or severe perianal dermatitis or rectal mucosal prolapse occurred in 13.8% and 12.3%, respectively. Redo surgery was required in 4.4% of patients.

Median age at time of reconstructive surgery was 4 months (IQR 2-7). Patients with skeletal, spinal, cardiac, renal, bladder, genital, or tracheo-oesophageal anomalies were older at time of surgery than patients without (4 (IQR 2-7) vs. 3 (IQR 1-5) months, $p<0.001$). When categorizing age into younger or older than 3 months, the patients with anomalies (43.5%) more often had undergone reconstruction later than 3 months of age than patients without anomalies (57.9%; $p<0.001$). While skeletal, spinal, renal, bladder, and genital anomalies separately were associated with older age at the time of surgery, cardiac anomalies were not. However, when excluding PDA and patent foramen ovale (PFO, mentioned in free text) from cardiac anomalies, the same relation was found ($p=0.023$).

Functional outcomes one year after anorectal reconstruction

Functional outcomes data at one-year follow-up was available in 60% to 70% varying per outcome measure (**Table 4**). Of these patients, 55.4% suffered from constipation. Treatment for constipation included stool softeners (54.8%), diet (32.4%), laxatives (23.9%), or enemas (23.4%). Faecal consistency was soft for most patients (67.8%), and median frequency was twice per 24 hours (IQR 1-2). Most patients (88.3%) underwent anal dilatations and 41.9% experienced pain during dilatations.

Table 4: Functional outcomes in ARM patients one year after anorectal reconstruction

	Data available N (%)	N (%)*
Constipation	1795 (70.1)	994 (55.4)
Sex ratio (M:F)	876 (48.8): 915 (51.0)	
Constipation treatments		
Stool softener		539 (54.8)
Diet		319 (32.4)
Laxatives		235 (23.9)
Enemas		230 (23.4)
Consistency of feces	1711 (66.9)	
Soft		1160 (67.8)
Solid		483 (28.2)
Liquid		68 (4.0)
Defecation frequency per 24 hours (median, IQR)	1563 (61.1)	2 (1-2)
Dilatations	1743 (68.1)	1539 (88.3)
Sex ratio (M:F)	856 (49.2): 883 (50.8)	
Pain during dilatations		645 (41.9)

* Of total known data, excluding not checked, unknown or missing data per variable.

Discussion

This study describes the clinical and surgical characteristics of patients in the ARM-Net over a ten year period. In accordance with existing literature, most patients had a perineal fistula, followed by vestibular fistula in females and rectobulbar and rectoprostatic fistula in males, [5]. The majority of patients underwent reconstructive surgery and subsequent anal dilatations. Just over half of the patients suffered from constipation one year after reconstructive surgery. Patients frequently had associated anomalies, which were mostly skeletal, cardiac, or renal.

Skeletal (including vertebral), cardiac, and renal anomalies were the three most common associated anomalies in the present report, in concordance with the existing literature [5, 9, 10, 38]. Contrary to our findings, some studies [9, 10, 38, 39] found that genitourinary anomalies were the most frequent, however, this may be due to the inclusion of VUR under genitourinary anomalies, where it is a separate entity in the present study. Remarkably in this cohort, only about a third were screened for VUR,

of which subsequently a third was diagnosed with VUR, emphasizing the potential importance of systematic screening [40]. Incidences of skeletal and vertebral anomalies were within the ranges found in the literature [5, 9, 10, 38], although some studies included spinal cord anomalies, such as tethered cord, in this category. The incidence of tethered cord in our study (8.2%) is similar to one study [10], but lower than others (15-60%) [9, 38, 41, 42]. These discrepancies likely stem from a wide variation amongst centres in defining and diagnosing tethered cord [25]. Although cardiac anomalies are among the three most common anomalies associated with ARM, the frequency in our study (39%) is higher compared to the 10-25% in the literature [9, 10, 38]. However, when excluding hemodynamically insignificant conditions, such as PDA, PFO or spontaneously closed VSD, incidence decreases to 28.9%, close to the aforementioned upper limit.

Different ARM types were significantly associated with accompanying anomalies. Vestibular fistulas, rectourethral fistulas, recto-bladder neck fistulas, cloaca's, no fistulas, and the group of rare and other types were more likely associated with other anomalies than perineal fistulas. Patients with cloaca were most likely to have associated anomalies, but it should be noted that confidence intervals were wide, due to low prevalence of this ARM type. These results show that for patients with common as well as rarer ARM types, thorough diagnostic screening for associated anomalies is warranted. This study showed that associated anomalies may influence timing of reconstructive surgery, as patients with associated anomalies are older at reconstruction than patients without. This probably relates to prioritization of treatment for associated anomalies.

The majority of patients underwent reconstructive surgery, where those patients that did not had either died, had an ARM type without indication for reconstruction, or were managed through dilatations only. Most reconstructed patients underwent a PSARP, which should be considered the standard operative approach [6, 12, 43]. To prevent strictures, a common postoperative complication, most patients underwent subsequent anal dilatations, as described by Peña [12]. Although most centres have adopted the dilatation protocol in their postoperative regimens, several studies have found that dilatations do not lower stricture rates [44, 45]. With over 40% of the patients in this study experiencing pain, protocolized anal dilatations in postoperative management should be reconsidered.

More than half of the patients experienced constipation one year after reconstruction, in accordance with the previous literature [13, 46, 47]. Unfortunately, constipation continues to affect ARM patients beyond childhood into adulthood and may compromise quality of life [17, 47].

This study has several limitations. Data quality, including completeness and comparability, poses challenges in registry data, and should be evaluated before analysing data [48, 49]. A recent quality assessment of the ARM-Net registry found error-prone, yet with appropriate cleaning, valuable data [50]. Although substantial data cleaning was required, most results in this study stem from closed-ended items, minimizing missing data and interpretation variations. The 60-day window of variability in patient's age at time of reconstruction, due to the manner that dates of birth and surgery are calculated is another limitation. Therefore, only median age was reported, which should even out this variability. The data found that several patients did not have their stoma closed or did not undergo reconstruction, this may be explained by incomplete registration by surgeons. Therefore, one of the recommendations for an improved ARM-Net registry is to implement automatic reminders to complete or update data entry [50]. Another limitation is that the current registry only collects stoma closure dates, omitting placement date or indication. Although some ARM phenotypes may require a temporary diverting stoma, management of postoperative complications might also be a stoma indication. The lack of a uniform and validated scoring systems for outcome assessment at 1-year follow-up introduces heterogeneity between the participating centres, and highlights the importance of standardization.

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Supplementary Table 1: Associated congenital anomalies of other organ systems in ARM patients

	N (%)*
Sex ratio (M:F)	1314 (50.4): 1292 (49.6)
Any associated anomaly	1788 (68.3)
Skeletal anomalies	904 (47.3)
Sacrum	473 (21.2)
Coccyx (absent)	395 (21.4)
Vertebrae	382 (17.2)
Costae	182 (8.3)
Lower limbs	175 (7.4)
Upper limbs	136 (5.7)
Spinal cord anomalies	465 (22.4)
Tethered cord	167 (8.2)
Thickened filum/filum lipoma	118 (5.7)
Syrinx	49 (2.4)
(Myelo)meningocele	20 (1.0)
Intraspinal mass	13 (0.6)
Presacral mass	12 (0.6)
Extraspinal mass	3 (0.1)
Other	89 (4.3)
Caudal regression syndrome†	32 (1.5)
Cardiac anomalies	848 (39.0)
Atrial septal defect	477 (21.9)
Ventricular septal defect	253 (11.6)
Patent ductus arteriosus	172 (7.9)
Tetralogy of Fallot	47 (2.2)
Coarctation of the aorta	31 (1.4)
Other	231 (10.6)
Pulmonary stenosis†	43 (2.0)
Persistent left vena cava superior†	41 (1.9)
Bicuspid/stenotic/insufficient aortic valve†	17 (0.8)
Right descending aorta†	14 (0.6)
Partial/total anomalous pulmonary venous return†	12 (0.6)
Tricuspid valve insufficiency†	11 (0.5)
Pulmonary hypertension†	11 (0.5)
Dextrocardia†	10 (0.5)
Double outlet right ventricle†	10 (0.5)
Right ventricular hypertrophy†	7 (0.3)

Supplementary Table 1: Continued

	N (%)*
Tracheo-oesophageal anomalies	174 (7.4)
Oesophageal agenesis (Vogt 1)	11 (0.5)
Oesophageal atresia without fistula (Gross A / Vogt 2)	7 (0.3)
Oesophageal atresia with proximal fistula (Gross B, Vogt 3A)	13 (0.6)
Oesophageal atresia with distal fistula (Gross C / Vogt 3B)	129 (5.5)
Oesophageal atresia with dual fistulas (Gross D / Vogt 3C)	3 (0.1)
Tracheo-oesophageal fistula without atresia (H-type fistula / Gross E)	4 (0.2)
Unclear classification	7 (0.3)
Renal anomalies	680 (29.2)
Hydronephrosis	270 (11.6)
Solitary kidney	149 (6.4)
Dysplastic kidney	121 (5.2)
Ectopic kidney	57 (2.4)
Duplex collecting system	70 (3.0)
Horseshoe kidney	68 (2.9)
Other	155 (6.7)
Vesicoureteral reflux ‡	281 (35.0)
Grade I	44 (5.5)
Grade II	82 (10.2)
Grade III	80 (10.0)
Grade IV	54 (6.7)
Grade V	21 (2.6)
Bladder anomalies	259 (11.6)
Trabeculations/neurogenic bladder†	78 (3.5)
Bladder exstrophy†	14 (0.6)
Urethral valves†	10 (0.4)
Urethral stenosis†	9 (0.4)
Small bladder volume†	8 (0.4)
Vesicostomy†	8 (0.4)
Genital anomalies	525 (22.0)
Female	202 (17.7)
Bicornuate/duplex uterus	72 (6.3)
Vaginal duplication/septum	65 (5.7)
Hydrocolpos	29 (2.5)
Vaginal agenesis	25 (2.2)
Uterine atresia / mullerian remnants	10 (0.9)
Other	78 (6.8)
Imperforate hymen†	8 (0.7)
Urogenital sinus†	8 (0.7)

Supplementary Table 1: Continued

	N (%)*
Male	321 (26.0)
Cryptorchidism	142 (11.5)
Both	67 (5.4)
Left	44 (3.6)
Right	31 (2.5)
Hypospadias	123 (9.9)
Bifid scrotum	83 (6.7)
Penoscrotal transposition	33 (2.7)
Other	82 (6.6)
Penile hypoplasia†	18 (1.5)
Brain anomalies	183 (12.0)
Structural defect	102 (6.7)
Functional defect	33 (2.2)
Other	48 (3.2)

** Of total known data, excluding not checked, unknown or missing data per anomaly.*
† Anomalies specified in accompanying free text and mentioned at least five times.
‡ Of all patients checked for vesicoureteral reflux (n=804; 30.7% of all patients).

CHAPTER 5

Complications after surgery for anorectal malformations: an ARM-Net Consortium registry study

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Submitted.

Abstract

Post-operative complications in ARM-surgery vary widely, with data predominantly derived from single centre, retrospective studies with limited patient numbers. Whether factors such as ARM-type, presence of associated congenital anomalies, a prior enterostomy, or type of reconstructive surgery influence the incidence of complications remains elusive. This study investigated the incidence and types of complications following surgical interventions for ARM, primarily post-reconstruction. Patient- and treatment-related risk factors were analysed.

This multicentre cohort study was performed using the ARM-Net registry with prospectively collected data from 34 centres. Complications after enterostomy formation, reconstruction, and enterostomy closure of all patients who underwent reconstructive surgery before the age of 5 year were included. Patients with more than 25% of missing data, with unknown sex or ARM type, and patients with unknown age at reconstruction were excluded. Multivariable analyses were performed to detect independent risk factors for complication development.

A total of 2 043 patients were eligible for analyses. Complications after enterostomy formation and closure were 25% and 12%, respectively. Post-reconstructive complications occurred in 25% of patients, with wound complications comprising half of the complications. In a multivariable analysis, recto-bladder neck fistula, any associated anomalies, and LAARP procedure were identified as independent risk factors for post-reconstructive complications. By contrast, anoplasty and mini-PSARP reduced risk of complications. A prior enterostomy was generally not found to protect against post-reconstructive complications.

Post-reconstructive complications in ARM patients are common, and patient- and treatment-related characteristics like complex ARM-types, any associated anomaly, and different surgical reconstructive techniques affect the postoperative outcome. These results aid counselling, clinical decision-making and may guide the operative planning of ARM-types that are amenable to several different surgical approaches.

Introduction

Anorectal malformations (ARM) are rare congenital malformations of the gastrointestinal tract with an incidence ranging from 2 to 6 per 10.000 births worldwide [1]. ARM complexity varies widely, with additional associated birth defects present up to 70% of patients [2-4].

Although reconstructive surgical techniques have improved in the last decades [5,6], the functionality of the affected structures is often impaired, causing constipation, faecal incontinence, sexual and reproductive dysfunction, as well as urinary tract dysfunction, which may reduce quality of life [7,8]. Similarly, post-surgical complications may also contribute to impaired functionality. Colostomy-related complications occur in 23-68% after formation, and 13-29% after closure [9-12]. Post-reconstructive complications are reported to occur in approximately 5-40%, including wound infection (7-24%), wound dehiscence (2-43%), anal stenosis (5-38%), rectal mucosal prolapse (3-27%), and recurrent fistula (1-16%) [13-20]. These widely varying numbers, however, are predominantly based on single-centre, retrospective studies on small number of patients over a wide range of time. Whether other factors such as type of ARM, presence of associated congenital anomalies, a prior enterostomy, and type of reconstructive surgery affect the incidence of complications remains elusive. The aim of this study was therefore to investigate the incidence and types of post-surgical complications, and determine patient- and treatment-related risk factors using the largest European ARM-registry currently available.

Methods

Study design and population

The study was conducted as a multicentre cohort study of 34 participating centres in 13 European countries, with data from the ARM-Net Consortium patient registry. This registry prospectively collects pseudonymized data on all consecutive ARM patients treated at the involved paediatric surgical centres [21].

All registered patients who underwent reconstructive surgery at one of the participating centres before the age of 5 year were included. Exclusion criteria were: (I) patients with more than 25% of missing data, (II) patients

with unknown sex or ARM type, or contradictory combinations, and (III) patients with missing data for age at the time of reconstruction.

The primary objective of this study was an assessment of post-reconstructive complications. The secondary objective was an evaluation of complications after enterostomy formation and closure. Conduction and reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [22].

Data collection

Available data include demographic data, ARM type [23], associated congenital anomalies, surgical procedures, and postoperative complications [24]. The registry particularly contains closed-ended single- or multiple-choice questions, with free text possibilities for elaboration or clarification [21].

Complications

Complications were recorded after enterostomy formation, after anorectal reconstruction, and after enterostomy closure. Data regarding the moment of complications occurrence was not available, so all registered complications were eligible for analysis. Based on predefined answer options and additional free text responses, we defined four complication-groups: wound complications (infection and dehiscence), anal stenosis, requirement for redo-surgery, and other complications. Each complication was recorded as an individual event. Distinguishing minor and major complications was based on the Clavien-Madadi classification specific to paediatric surgery [25].

Potential risk factors

Patient-related characteristics included sex, ARM type, associated congenital anomalies, and approximate age at time of reconstruction (<3 months and ≥3 months). Associated congenital anomalies included at least one of any skeletal, renal, genital, spinal, cardiac, and tracheo-oesophageal anomalies. Patent ductus arteriosus and patent foramen ovale were excluded from cardiac anomalies, as these are usually physiological, depending on the timing of diagnostic procedures.

Treatment-related characteristics included type of reconstruction and enterostomy formation. Details concerning the type, location, and complications after enterostomy formation and closure were available. Reconstructive surgery was performed by standard or ‘mini’ posterior sagittal anorectoplasty (PSARP),

anterior sagittal anorectoplasty (ASARP), cutback and anoplasty, laparoscopic assisted anorectoplasty (LAARP), posterior sagittal anorectovagino(urethro) plasty (PSARV(U)P), and 'other type of surgery'. Definition of standard- versus mini-PSARP was up to the discretion of the surgeon.

Statistical analyses

Patient characteristics sex, ARM type, age at reconstruction, associated congenital anomalies, and surgical details including enterostomy formation, type of reconstruction, and complications were analysed with descriptive statistics. Frequencies are presented as percentages.

The associations between potential risk factors and post-reconstructive complications were analysed using univariable and multivariable logistic regression modelling to estimate odds ratios (OR) and 95% confidence intervals (CI). Factors considered in the multivariable model were the patient's sex, ARM type (rectoperineal fistula as reference), associated congenital anomalies (any anomaly: yes/no), enterostomy formation (yes/no), age at time of surgery (<3 and ≥3 months), and type of reconstructive surgery (PSARP as reference).

Subanalyses were also performed to estimate associations between potential risk factors and (I) any major post-reconstructive complication, (II) wound complications, and (III) stenosis.

Surgical approaches for rectoperineal and rectovestibular fistulas, such as ASARP or PSARP, were up to the surgeon's preference. To aid surgeons in their future decision-making, additional analyses were performed to investigate associations between reconstructive surgical approach and complications, separately for different ARM types. Multivariable logistic regression models were used, including the variables sex, enterostomy, associated congenital anomalies, and age at surgery. The same was done for enterostomy formation in ARM types where an enterostomy is opened at the surgeon´s discretion and not as a standard procedure (e.g. rectoperineal fistula, rectovestibular fistula, rectal stenosis).

Finally, potential risk factors were investigated for enterostomy-related complications after formation and/or closure (if applicable). Associations were estimated using univariable and multivariable logistic regression modelling including ARM type (rectoperineal fistula as reference), patient's sex, associated congenital anomalies, bowel section (descending/sigmoid

junction as reference), and enterostomy type (divided type as reference). Separate analyses were also performed for patients with a rectoperineal and rectovestibular fistula with an enterostomy.

All statistical analyses were conducted in SPSS Statistics (v.29.0.0.0; 241, IBM Corporation, Armonk, United States) and considered significance at a p-value of <0.05.

Results

The registry contained 2627 patients on March 1st, 2023. A total of 2043 patients were eligible after exclusion of patients according to the exclusion criteria.

Clinical and surgical characteristics

Most patients had a rectoperineal fistula (43%), followed by a rectobulbar fistula in males (10%), and a rectovestibular fistula in females (17%) (**Table 1**). Associated congenital anomalies were frequent (65%), the most common being skeletal anomalies (47%). Of all patients, 8% had a tethered cord, which was 38% of patients with a spinal cord anomaly. Less than half of the patients (44%) received an enterostomy, mostly a divided type (76%) in the descending colon/sigmoid junction (88%). A type of PSARP was most often performed (75%), and 54% of patients underwent surgery at or beyond 3 months of age.

Post-reconstructive and enterostomy-related complications

A post-reconstructive was registered in 503 patients (25%) (**Table 2**), of which half were wound complications. Redo reconstruction was performed in 75 patients, accounting for 15% of patients with complications, and an overall redo-rate of 4%. Patients with less complex ARM-types including rectoperineal fistula, rectovestibular fistula, and anal stenosis had the least complications, most commonly wound complications, while in complex ARM-types, such as recto-bladder neck and cloacal malformation, most complications, primarily stenosis, were recorded (**Table 3**). Concerning the surgical approach, cutback, anoplasty, and mini-PSARP resulted in least complications, whereas PSARV(U)P and LAARP had the highest complication rate (**Table 3**). The complication rate after enterostomy formation was higher (25%) than after closure (12%), most frequently infection.

Table 1: Demographic, clinical, and surgical characteristics of 2043 ARM patients included in the ARM-Net registry who underwent reconstructive surgery

	N (%*)
Male sex	1063 (52.0)
ARM type	
Rectoperineal fistula (M/F)	876 (436/440) (42.9)
Rectovestibular fistula	348 (17.0)
Rectourethral fistula	412 (20.2)
Bulbar type	*202 (9.9)*
Prostatic type	*170 (8.3)*
Unspecified	*40 (2.0)*
Recto-bladder neck fistula	53 (2.6)
Anal atresia without fistula	136 (6.7)
Anal stenosis	34 (1.7)
Cloacal malformation	88 (4.3)
<3cm common channel	*56 (2.7)*
>3cm common channel	*23 (1.1)*
Unspecified length	*9 (0.4)*
Rare and other types	96 (4.7)
At least one associated congenital anomaly†	1324 (65.0)
Vertebral anomaly	300 (16.5)
Sacral anomaly	380 (21.0)
Absent coccyx	322 (21.6)
Spinal cord anomaly	375 (22.3)
Cardiac anomaly	502 (28.8)
Tracheo-oesophageal anomaly	136 (7.1)
Renal anomaly	630 (34.1)
Genital anomaly	395 (20.4)
Limb anomaly	204 (10.5)
Enterostomy	897 (43.9)
Enterostomy closed	839 (93.5)
Age at reconstructive surgery	
<3 months	945 (46.3)
≥3 months	1098 (53.7)
Type of reconstructive surgery	
PSARP	1110 (54.5)
Mini-PSARP	409 (20.1)
ASARP	181 (8.9)
Anoplasty	100 (4.9)

Table 1: Continued

	N (%*)
Cutback	45 (2.2)
LAARP	71 (3.5)
PSARV(U)P	51 (2.5)
PSARVUP with TUM	38 (1.9)
Other	33 (1.6)

Abbreviations: ARM, anorectal malformation; PSARP, posterior sagittal anorectoplasty; ASARP, anterior sagittal anorectoplasty; LAARP, laparoscopic assisted anorectoplasty; PSARV(U)P posterior sagittal anorectovagino(urethro)plasty; TUM, total urogenital mobilization. Of total known data, excluding missing data per variable.†Congenital vertebral, sacral, coccygeal, spinal, cardiac, tracheo-oesophageal, renal, genital, or limb anomalies.*

Clinical and surgical factors associated with post-reconstructive complications

Patients with rectourethral fistula, recto-bladder neck fistula, cloacal malformation, and the patient-group with rare and other ARM-types showed an increased risk for post-reconstructive complications compared to patients with rectoperineal fistula in univariable analyses (**Table 4**). The same was true for patients with associated congenital anomalies, ≥3 months of age at time of surgery, an enterostomy, and a LAARP procedure compared to a PSARP. By contrast, a cutback, anoplasty, or mini-PSARP demonstrated a reduced risk. However, in a multivariable analysis, only a recto-bladder neck fistula, any associated congenital anomalies, and a LAARP procedure remained as independent risk factors for post-reconstructive complications. Anoplasty and mini-PSARP remained associated with reduced risks. Sex, age at surgery, and enterostomy were not associated with the occurrence of complications.

Analyses were performed concerning enterostomy formation for those ARM-types that are amenable to both primary repair, as well as a defunctioning enterostomy prior to reconstruction. Post-reconstructive complication rates for patients with and without enterostomy did not differ in rectoperineal and rectovestibular fistula patients. Patients with anal atresia without fistula however, showed a significantly lower post-reconstructive complication rate when a defunctioning enterostomy was present (18%), compared to patients treated with a primary repair (39%), even after adjustment for sex, associated congenital anomalies, and reconstruction type (OR 0.2, CI 0.1-0.7). The most prevalent complication after primary repair was a wound complication.

Table 2: Post-reconstructive and enterostomy-related complications in 2043 ARM patients included in the ARM-Net registry

	N (%)
At least one complication after reconstructive surgery	503 (24.6)*
Wound complications	257 (12.6)*
Stenosis	96 (4.7)*
Others	191 (9.3)*
Urethral lesion	17 (0.8)*
Recurrent fistula	15 (0.7)*
Mucosal prolapse #	57 (2.8)*
Bladder/urinary tract issues #	28 (1.4)*
Vaginal lesions #	17 (0.8)*
Small bowel obstruction #	9 (0.4)*
Megarectum #	6 (0.3)*
Redo reconstruction	75 (3.7)*
At least one complication after enterostomy formation	202 (25.3)†
Wound infection	52 (6.5)†
Stenosis	38 (4.8)†
Prolapse	32 (4.0)†
Other	123 (15.4)†
Misplaced/inverted loops #	29 (3.6)†
Dehiscence #	24 (3.0)†
Retraction #	10 (1.3)†
Dermatitis #	8 (1.0)†
Adhesions #	5 (0.6)†
At least one complication after enterostomy closure	92 (12.0)‡
Wound infection	28 (3.7)‡
Leakage	15 (2.0)‡
Other	61 (8.0)‡
Adhesions/obstruction #	13 (1.7)‡
Excoriation #	6 (0.8)‡
Other infection #	6 (0.8)‡
Parastomal hernia #	5 (0. 6)‡

** Out of 2043 patients# Complications mentioned in accompanying free text at least 5 times.*
† Out of 797 patients with an enterostomy and without missing data on complications
‡ Out of 764 patients whose enterostomy was closed and without missing data on complications

Table 3: Types of post-reconstructive complications by clinical and surgical characteristics in 2043 ARM patients included in the ARM-Net registry

	Total	At least one complication	Wound	Stenosis	Other	Redo
	N	N (%)	N (%*)	N (%*)	N (%*)	N (%*)
ARM type						
Rectoperineal fistula	876	173 (19.7)	122 (13.9)	26 (3.0)	40 (4.6)	19 (2.2)
Rectovestibular fistula	348	83 (23.9)	52 (14.9)	12 (3.4)	24 (6.9)	9 (2.6)
Rectourethral fistula	412	119 (28.3)	40 (9.7)	25 (6.1)	61 (14.8)	22 (5.3)
Recto-bladder neck fistula	53	27 (50.9)	5 (9.4)	12 (22.6)	14 (26.4)	8 (15.1)
Cloacal malformation	88	33 (37.5)	10 (11.4)	5 (5.7)	18 (20.5)	8 (9.1)
Anal stenosis	34	4 (11.8)	1 (2.9)	1 (2.9)	3 (8.8)	1 (2.9)
Anal atresia without fistula	136	31 (22.8)	13 (9.6)	8 (5.9)	16 (11.8)	5 (3.7)
Rare and other types	96	33 (34.4)	14 (14.6)	7 (7.3)	15 (15.6)	3 (3.1)
Male sex	1063	267 (25.1)	113 (10.6)	60 (5.6)	118 (11.1)	46 (4.3)
Female sex	980	236 (24.1)	144 (14.7)	36 (3.7)	73 (7.4)	29 (3.0)
No associated anomalies†	714	135 (18.9)	80 (11.2)	25 (3.5)	30 (4.2)	22 (3.1)
At least one associated anomaly†	1324	368 (27.8)	177 (13.4)	71 (5.4)	161 (12.2)	53 (4.0)
Age at surgery						
<3 months	945	202 (21.4)	123 (13.0)	30 (3.2)	63 (6.7)	23 (2.4)
≥3 months	1098	301 (27.4)	134 (12.2)	66 (6.0)	128 (11.7)	52 (4.7)
No enterostomy	1132	233 (20.6)	157 (13.9)	32 (2.8)	60 (5.3)	23 (2.0)
Enterostomy	897	269 (30.0)	100 (11.1)	63 (7.0)	131 (14.6)	52 (5.8)
Reconstructive surgery type						
PSARP	1110	290 (26.1)	144 (13.0)	57 (5.1)	110 (9.9)	42 (3.8)
Cutback	45	5 (11.1)	1 (2.2)	1 (2.2)	1 (2.2)	2 (4.4)
Anoplasty	100	11 (11.0)	7 (7.0)	2 (2.0)	3 (3.0)	3 (3.0)
mini-PSARP	409	64 (15.6)	42 (10.3)	7 (1.7)	17 (4.2)	2 (0.5)
ASARP	181	55 (30.5)	43 (23.8)	10 (5.5)	10 (5.5)	13 (7.2)
LAARP	71	35 (49.3)	7 (9.9)	11 (15.5)	24 (33.8)	7 (9.9)
PSARV(U)P	51	19 (37.3)	4 (7.8)	2 (3.9)	14 (27.5)	2 (3.9)
PSARVUP/TUM	38	11 (28.9)	4 (10.5)	4 (10.5)	3 (7.9)	2 (5.3)
Other	33	12 (36.4)	4 (12.1)	2 (6.1)	9 (27.3)	2 (6.1)
Total	2043	503 (24.6)	257 (12.6)	96 (4.7)	191 (9.3)	75 (3.7)

*Abbreviations: ARM, anorectal malformation; PSARP, posterior sagittal anorectoplasty; ASARP, anterior sagittal anorectoplasty; LAARP, laparoscopic assisted anorectoplasty; PSARV(U)P posterior sagittal anorectovagino(urethro)plasty; TUM, total urogenital mobilization. * Of total known data, excluding missing data per variable. †Congenital vertebral, sacral, coccygeal, spinal, cardiac, tracheo-oesophageal, renal, genital, or limb anomalies.*

Table 4: Clinical and surgical factors associated with post-reconstructive complications in 2043 ARM patients included in the ARM-Net registry

	Crude		**Adjusted**	
	OR	**(95% CI)**	**OR**	**(95% CI)**
ARM type				
Rectoperineal fistula	*ref*		*ref*	
Rectovestibular fistula	1.27	(0.95-1.71)	0.88	(0.61-1.26)
Rectourethral fistula	1.73	(1.25-2.38)	0.94	(0.61-1.44)
Recto-bladder neck fistula	4.42	(2.45-7.96)	**2.03**	**(1.01-4.06)**
Cloacal malformation	2.33	(1.43-3.81)	2.27	(0.95-5.39)
Anal stenosis	0.54	(0.19-1.56)	0.71	(0.24-2.11)
Anal atresia without fistula	1.20	(0.78-1.85)	0.80	(0.48-1.33)
Rare and other types	2.13	(1.35-3.35)	1.57	(0.90-2.71)
Male sex	*ref*		*ref*	
Female sex	0.95	(0.77-1.16)	0.98	(0.72-1.33)
No associated anomalies*	*ref*		*ref*	
At least one associated anomaly*	1.65	(1.32-2.06)	**1.36**	**(1.07-1.72)**
Age at surgery				
<3 months	*ref*		*ref*	
≥3 months	1.39	(1.13-1.70)	1.07	(0.85-1.35)
No enterostomy	*ref*		*ref*	
Enterostomy	1.65	(1.35-2.02)	1.10	(0.79-1.54)
Reconstructive surgery type				
PSARP	*ref*		*ref*	
Cutback	0.35	(0.14-0.90)	0.43	(0.16-1.14)
Anoplasty	0.35	(0.18-0.66)	**0.40**	**(0.20-0.79)**
mini-PSARP	0.53	(0.39-0.71)	**0.61**	**(0.43-0.87)**
ASARP	1.23	(0.88-1.74)	1.36	(0.94-1.98)
LAARP	2.75	(1.69-4.46)	**2.05**	**(1.21-3.46)**
PSARV(U)P	1.68	(0.94-3.01)	0.75	(0.31-1.78)
PSARVUP/TUM	1.15	(0.56-2.35)	0.45	(0.16-1.29)
Other	1.62	(0.79-3.33)	1.15	(0.51-2.63)

*Abbreviations: ARM, anorectal malformation; CI, confidene interval; OR, odds ratio; ref, reference; PSARP, posterior sagittal anorectoplasty; ASARP, anterior sagittal anorectoplasty; LAARP, laparoscopic assisted anorectoplasty; PSARV(U)P posterior sagittal anorectovagino(urethro)plasty; TUM, total urogenital mobilization. * Congenital vertebral, sacral, coccygeal, spinal, cardiac, tracheo-oesophageal, renal, genital, or limb anomalies.*

Table 5: Associations between post-reconstructive complications and reconstructive surgery type per ARM type, and the rates of wound complications and stenosis

	Total N*	Complications N (%)	Adjusted†		Wound N (%)	Stenosis N (%)
			OR	(95% CI)		
Rectoperineal fistula	871	171 (19.6)			121 (13.9)	26 (3.0)
PSARP	290	68 (23.4)	*ref*		45 (15.5)	12 (4.1)
Cutback	41	5 (12.2)	0.47	(0.17-1.25)	1 (2.4)	1 (2.4)
Anoplasty	78	7 (9.0)	**0.32**	**(0.14-0.73)**	4 (5.1)	1 (1.3)
mini-PSARP	363	57 (15.7)	**0.63**	**(0.42-0.94)**	39 (10.7)	7 (1.9)
ASARP	99	34 (34.3)	**1.73**	**(1.05-2.88)**	32 (32.3)	5 (5.1)
Rectovestibular fistula	343	82 (23.9)			52 (15.2)	12 (3.5)
PSARP	251	60 (23.9)	*ref*		40 (15.9)	7 (2.8)
mini-PSARP	21	4 (19.0)	0.87	(0.28-2.75)	2 (9.5)	0
ASARP	71	18 (25.4)	1.20	(0.64-2.27)	10 (14.1)	5 (7.0)
Rectourethral fistula	406	118 (29.1)			39 (8.4)	25 (6.2)
PSARP	362	98 (27.1)	*ref*		34 (9.4)	20 (5.5)
LAARP	**44**	**20 (45.5)**	**2.19**	**(1.15-4.18)**	5 (11.4)	5 (11.4)
Rectobulbar fistula	201	46 (22.9)			20 (10.0)	8 (4.0)
PSARP	194	44 (22.7)	*ref*		19 (9.8)	7 (3.6)
LAARP	5	2 (40.0)	2.06	(0.33-12.85)	1 (20.0)	1 (20.0)
Rectoprostatic fistula	168	62 (36.9)			16 (9.5)	10 (6.0)
PSARP	129	44 (34.1)	*ref*		12 (9.3)	6 (4.7)
LAARP	39	18 (46.2)	1.73	(0.81-3.70)	4 (10.3)	4 (10.3)
Recto-bladder neck fistula	51	26 (51.0)			5 (9.8)	12 (23.5)
PSARP	32	17 (53.1)	*ref*		4 (12.5)	8 (25.0)
LAARP	19	9 (47.4)	0.76	(0.23-2.48)	1 (5.3)	4 (21.1)

Abbreviations: ref, reference; PSARP, posterior sagittal anorectoplasty; ASARP, anterior sagittal anorectoplasty; LAARP, laparoscopic assisted anorectoplasty; PSARV(U)P posterior sagittal anorectovagino(urethro)plasty; TUM, total urogenital mobilization. Excluding missing data for type of reconstruction † Adjusted for sex, enterostomy, associated congenital anomalies, and age at surgery (<3 and ≥3 months)*

Focusing on reconstructive surgical approach for each ARM-type, we found a reduced post-reconstructive risk for complications after anoplasty (9%) and mini-PSARP (16%) in patients with a rectoperineal fistula, but a higher risk when an ASARP (34%) was performed, compared to PSARP (23%) (**Table 5)**. For rectourethral fistula (bulbar/prostatic), LAARP was associated with a significantly higher risk for post-reconstructive complications compared to PSARP (OR 2.2, CI 1.2-4.2; 46% vs. 27%).

After complication classification according to the Clavien-Madadi classification [25], most complications were documented as major (**Supplementary File, Table A**). A higher risk for major complications was found for cloacal malformation, and the group of rare and other ARM-types (**Supplementary File, Table B**). Enterostomy formation and ASARP or LAARP procedures were also associated with an increased risk for major post-reconstructive complications. Mini-PSARP had the lowest risk for major complications (5%).

Clinical and surgical factors associated with enterostomy-related complications

Patients with an enterostomy in the descending colon/sigmoid junction had the lowest risk of complications after enterostomy formation. The most prevalent type of complication differed between loop (prolapse) and divided enterostomy (wound complications). In patients with a rectoperineal or rectovestibular fistula, a divided enterostomy type had higher complication rates (23%) after formation than a loop enterostomy (5%, OR 14.5, CI 1.7-121.3).

Discussion

This ARM-Net registry study in 2043 ARM patients demonstrated that 25% of patients developed at least one post-reconstructive complication, half of which were wound complications. Patient-related characteristics such as certain complex ARM-types (recto-bladder neck, cloacal malformation, and rare and other types) as well as any associated congenital anomaly were associated with an increased risk of post-reconstructive complications. Concerning surgical approach, cutback, anoplasty, and mini-PSARP were associated with the lowest complication rates compared to PSARP, whereas LAARP procedures had the highest. A prior enterostomy generally did not reduce the risk of post-reconstructive complications. Enterostomy-related complications were common.

Patient-related factors that have been determined to affect post-reconstructive complications were complex ARM-types, regardless of surgical approach. An impressive 51% of patients with a recto-bladder neck fistula experienced at least one post-reconstructive complication, mostly a stenosis. While literature on recto-bladder neck fistulas primarily focuses on the poor functional outcome [26], there is a paucity of evidence concerning post-reconstructive complications. One report documented no post-reconstructive stenosis [14] in a small study population, while in another series the post-reconstruction stenosis rate was 15%, primarily after laparoscopic dissection [20]. The latter report concluded that their 50% anal stricture rate after LAARP was caused due to advancement of the rectum through an insufficiently wide pull-through tunnel and perineal incision, resulting not only in an anocutaneous anastomotic stricture, but stenosis along the anal canal itself as well [20]. Furthermore, we speculate that mobilizing the high rectal pouch from the bladder neck level to the skin will leave an anocutaneous anastomosis solely reliant on intramural blood supply over a significant distance, adding to an increased stenosis risk.

The laparoscopic dissection as an adjunct to a posterior approach (LAARP) has been introduced by Georgeson [27] at the turn of the century, and has gained increasing advocation since [28-31]. The functional and cosmetic outcomes appear to be excellent, yet at the consistently reported expense of a considerable rate of rectal prolapse [17, 30-33], and the aforementioned higher stenosis rate [20]. Our study showed an increased risk of stenosis associated with a LAARP procedure compared to PSARP as well, mainly in patients with a recto-urethral fistula.

Wound complications occurred most commonly, followed by stenosis, the latter accounting for around 5% of all patients, which seems to be at the lower limit of the reported stenosis rate of 2.2-38% in recent reports [18-20, 34, 35]. Interestingly, wound complications specifically developed more often in the less complex ARM-types, while stenosis was observed more commonly in more complex types. Many studies have reported on wound complications ranging from 3-43% [13, 16, 18, 35-37], but the distribution between the various ARM-types is variable, and not necessarily highest in complex types [13]. Our results support this, showing the lowest risk of wound complications in the rectourethral and recto-bladder neck fistula group. A convincing explanation is not easily available, but it can be speculated that development of wound complications may be more related

to peri-operative management, including bowel preparation, antibiotic regimes, wound care, and time of feeding [38], and further research into these relations is warranted. Furthermore, less bacterial contamination due to a present diverting enterostomy might also limit these complications. Although the protective role of a prior enterostomy in this regard cannot be dismissed, our study could not substantiate this claim. While incidentally complex ARM are repaired primarily [35], the vast majority of complex ARM-patients receive an enterostomy prior to reconstruction. The protective effect of an enterostomy has been asserted in selected studies [13,37], while other studies have failed to endorse that statement [38], or have reported contrary results [39]. More importantly, whether an enterostomy protects against post-reconstructive complications can only be ascertained in ARM-types that can be treated with or without an enterostomy, such as rectoperineal and rectovestibular fistulas. In these malformations, reports on the different approaches show variable results [40-42]. Our study showed no difference in post-reconstructive complications in these ARM types, regardless of a defunctioning enterostomy. So when opting for an enterostomy in these less complex ARM types, the additional enterostomy-related complications [43,44] need to be considered.

Not only ARM-types, but treatment-related characteristics such as the surgical approach were shown to have an effect on complication development as well. We determined the complication rates of different techniques in those ARM-types that are typically subject to different approaches. The focus has been on either the sagittal approaches (e.g., ASARP vs PSARP), or the adjunct of an abdominal dissection in reconstruction (e.g., PSARP alone vs LAARP), as detailed earlier. In patients with a rectoperineal fistula, the cutback, anoplasty, and mini-PSARP showed fewer complications compared to the PSARP. ASARP, on the contrary, appeared to be associated with a higher risk of complications. Although cutback and anoplasty have been performed for many decades, since the introduction of the posterior sagittal approach by DeVries and Peña in the early 80's [5], the PSARP technique has been popularized for all ARM-types including the rectoperineal and rectovestibular fistulas. Nevertheless, recent data continue to support the potential advantages of limited surgical dissections as the cutback or anoplasty [45, 46], with favourable long-term functional outcome [47, 48]. Our data add to this support. The ASARP procedure as an alternative to the posterior approach has been adopted, and advocated by some [49, 50], with mixed results concerning

complications [51]. There are no accounts in current literature of higher complication rates in ASARP compared to PSARP in rectoperineal fistulas, but possibly a publication bias is present stressing the advantages of the less adopted ASARP approach by those that have become enthusiasts.

The majority of documented complications in our study were classified as major [25]. This is remarkable, especially in the light of wound complications and stenosis comprising up to 70% of the described complications. Especially wound dehiscence and infections are generally considered to be benign, and therefore considered minor complications. One should bear in mind, however, that any intervention or evaluation in this paediatric patient group will almost certainly be conducted under anaesthesia, like correction of small mucosal prolapses or repetitive dilatations, leading to a major complication by definition.

Enterostomy-related complications were determined to be 25% in our study, in line with what is reported in literature [11, 12, 44]. Although the type of enterostomy did not significantly impact overall postoperative recovery, in patients not typically receiving an enterostomy, a divided enterostomy seemed to have significantly more complications than a loop enterostomy. As a divided enterostomy has been the preferred type for years [44], recently more favourable reports have been published concerning loop colostomies [52, 53], and adoption of this technique has increased. Based on our results, when opting for an enterostomy, the loop enterostomy seems the preferred approach. Different review papers however show loop enterostomies primarily in the transverse colon to give rise to a higher incidence of prolapse [11, 54]. The preferred location for a loop colostomy is therefore the descending colon/sigmoid junction. This actually holds true for any type of enterostomy, as our study showed an increased risk of complications after formation at any different location.

Even though this study is the largest to date addressing post-reconstructive and enterostomy-related complications in ARM-patients, limitations need to be addressed. A definition of complication, nor of a specific time frame (i.e. within 30 days of surgery), was provided in the registry. Data checking and monitoring amongst centres is still under development, so underreporting of complications is possible.

The framework of the registry does not allow us to delineate certain elements, leaving them up for interpretation. One issue is the date of

enterostomy formation, which is not documented in the registry. Although enterostomies could be fashioned during or after reconstruction to prevent or treat complications, enterostomies were interpreted as being fashioned prior to reconstruction as a standard three-staged procedure based on earlier data from our own consortium [55]. In addition, the distinction between PSARP and mini-PSARP has not been defined, and determination has been left to the discretion of the individual surgeon providing surgical care. This may introduce bias, although one may in general be inclined to define a surgical procedure as mini-PSARP instead of PSARP, migrating certain PSARP procedures into the mini-PSARP group, mitigating the detected impact on complication occurrence, rather than overstating it. Furthermore, a 'redo' can be selected when registering post-reconstructive complications in the registry, and would refer to a formal redo reconstruction to correct an insufficient initial reconstruction. However, as reporting of details or indications are not obligatory, the actual reintervention cannot be ascertained, and may be as little as mucosal trimming or partial anoplasty for a stenosis. Redo as a formal reconstructive operation is therefore most probably less prevalent than the mentioned frequency in this study of 4%. Finally, data cleaning was extensive due to the enthusiastic usage of the free text commentary option, and the structure of the registry [21]. A cautious interpretation of the contradictory predefined answers compared to free text explanations urged us not irregularly to dismiss answers provided, and change them into unknown. Thereby the power of reliability was given priority over the power of size.

Regardless, based on the analysed number of patients this study delivers a valuable and comprehensive overview of the post-reconstructive and enterostomy-related complications in a large European cohort of ARM-patients. This is of special importance since complications after ARM-reconstructions have negative implications on patients' suffering, families' lives, health care burden, and not the least on economic issues for both families and health care systems.

In conclusion, our study bears significance for various reasons. It clearly demonstrates from the largest ARM registry currently available, that complications after reconstructive surgery in ARM patients are common, and that certain patient- and treatment-related characteristics including complex ARM-types, any associated anomaly, and different surgical reconstructive techniques affect the postoperative outcome. These results

may trigger clinical decision-making, and are usable in patient counselling. Moreover, having identified risk factors, our results can guide operative planning of ARM-types that may be corrected through several different approaches. Finally, our results contribute to the growing body of literature on ARM, which is needed to advance our understanding of this complex condition, and ultimately improve patient outcomes.

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Supplementary Files

Supplementary File Table A: Clavien-Madadi classification of post-reconstructive complications per ARM type

	Post-reconstructive complications (N [%])			
ARM type	**None**	**Minor**	**Major**	**Unknown**
Rectoperineal fistula	703 (80.3)	53 (6.1)	68 (7.8)	52 (5.9)
Rectovestibular fistula	265 (76.1)	29 (8.3)	31 (8.9)	23 (6.6)
Rectourethral fistula	293 (71.1)	20 (4.9)	66 (16.0)	33 (8.0)
Recto-bladder neck fistula	26 (49.1)	1 (1.9)	17 (32.1)	9 (17.0)
Cloacal malformation	55 (62.5)	3 (3.4)	21 (23.9)	9 (10.2)
Anal stenosis	30 (88.2)	0	2 (5.9)	2 (5.9)
Anal atresia without fistula	105 (77.2)	7 (5.1)	16 (11.8)	8 (5.9)
Rare and other types	63 (65.6)	3 (3.1)	20 (20.8)	10 (10.4)
Total	1540 (75.4)	116 (5.7)	241 (11.8)	146 (7.1)

Abbreviation: ARM, anorectal malformation.

Supplementary File Table B: Clinical and surgical factors associated with major post-reconstructive complications vs. no complications in 1781 ARM patients included in the ARM-Net registry

	Total	Complications	Crude		Adjusted	
	N*	N (%)	OR	(95% CI)	OR	(95% CI)
ARM type						
Rectoperineal fistula	771	68 (8.8)	*ref*		*ref*	
Rectovestibular fistula	296	31 (10.5)	1.21	(0.77-1.89)	0.73	(0.43-1.25)
Rectourethral fistula	359	66 (18.4)	*2.33*	(1.62-3.36)	1.08	(0.60-1.96)
Recto-bladder neck fistula	43	17 (39.5)	6.76	(3.49-13.08)	2.31	(0.98-5.48)
Cloacal malformation	76	21 (27.6)	3.95	(2.25-6.92)	**3.37**	**(1.17-9.75)**
Anal stenosis	32	2 (6.3)	0.69	(0.16-2.95)	0.74	(0.17-3.30)
Anal atresia without fistula	121	16 (13.2)	1.58	(0.88-2.82)	0.89	(0.44-1.79)
Rare and other types	83	20 (24.1)	3.28	(1.87-5.75)	**2.08**	**(1.04-4.18)**
Male sex	932	136 (14.6)	*ref*		*ref*	
Female sex	849	105 (12.4)	0.83	(0.63-1.09)	1.05	(0.67-1.64)
No associated anomalies†	641	62 (9.7)	*ref*		*ref*	
At least one associated anomaly†	1135	179 (15.8)	1.75	(1.29-2.38)	1.33	(0.97-1.82)
Age at surgery						
<3 months	822	79 (9.6)	*ref*		*ref*	
≥3 months	959	162 (16.9)	1.91	(1.44-2.55)	1.24	(0.90-1.71)
No enterostomy	986	87 (8.8)	*ref*		*ref*	
Enterostomy	782	154 (19.7)	2.53	(1.91-3.36)	**1.70**	**(1.07-2.70)**
Reconstructive surgery type						
PSARP	949	129 (13.6)	*ref*		*ref*	
Cutback	45	5 (11.1)	0.80	(0.31-2.05)	1.33	(0.48-3.69)
Anoplasty	97	8 (8.2)	0.57	(0.27-1.21)	0.86	(0.38-1.96)
mini-PSARP	362	17 (4.7)	0.31	(0.19-0.53)	**0.50**	**(0.27-0.91)**
ASARP	158	32 (20.3)	1.61	(1.05-2.48)	**2.37**	**(1.44-3.91)**
LAARP	61	25 (41.0)	4.41	(2.57-7.60)	**2.66**	**(1.46-4.83)**
PSARV(U)P	42	10 (23.8)	1.99	(0.95-4.14)	0.52	(0.18-1.56)
PSARVUP/TUM	34	7 (20.6)	1.65	(0.70-3.86)	0.38	(0.11-1.31)
Other	28	7 (25.0)	2.12	(0.88-5.08)	1.24	(0.45-3.43)

Abbreviations: ARM, anorectal malformation; CI, confidene interval; OR, odds ratio; ref, reference; PSARP, posterior sagittal anorectoplasty; ASARP, anterior sagittal anorectoplasty; LAARP, laparoscopic assisted anorectoplasty; PSARV(U)P posterior sagittal anorectovagino(urethro)plasty; TUM, total urogenital mobilization. Excluding patients that have complications classified as minor or unknown, excluding missing data per variable.†Congenital vertebral, sacral, coccygeal, spinal, cardiac, tracheo-oesophageal, renal, genital, or limb anomalies.*

CHAPTER 6

Anorectal malformation patients in Australia and Europe: different location, same problem?

A retrospective comparative registry-based study

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Abstract

Anorectal malformations (ARM) encompass a spectrum of rare congenital defects of the rectum and anus, requiring specialized reconstructive surgery. To improve epidemiological and clinical research in rare diseases such as ARM, collaborative efforts and patient registries are key.

This retrospective study pools clinical data over a 30-year period from two ARM patient registries (The Royal Children's Hospital (RCH) in Melbourne, Australia, and the ARM-Network Consortium in Europe). It aims to draw comparisons on demographics, management, and outcomes between ARM patients in Australia and Europe.

A total of 2947 ARM patients were included in the analyses. The RCH cohort had more complex ARM types (including rectal atresia and recto-vaginal fistula) and more associated anomalies, specifically skeletal, cardiac, and/or trachea-oesophageal, than ARM-Net patients. Other patient characteristics were similar. Treatments clearly differed between the groups. European surgeons favoured the PSARP approach for both less complex and more complex ARM types, where Australian surgeons opted more often for cutback surgery in less complex, and laparoscopic assistance in more complex types. Complications were differently distributed, with less complications after LAARP and more after PSARP at RCH, compared to ARM-Net. While RCH patients more often required a redo, ARM-Net patients more commonly underwent anal dilatations.

Anorectal malformation patients in Australia and Europe had minor differences in disease characteristics, and both operative and medical approaches differed. Joint efforts such as the present study emphasize the importance of collaboration to elucidate areas of improvement where surgeons may learn from each other across the world, ultimately improving patient outcomes.

Background

Anorectal malformations (ARM) encompass a spectrum of rare congenital defects where the development of the rectum and anus is affected, requiring specialized reconstructive surgery and often a temporary defunctioning stoma [1]. Postoperatively, patients regularly undergo anal dilatations and eventual closure of the stoma [2]. Anorectal malformations are often associated with a range of congenital defects affecting one or multiple other organ systems, such as vertebral, cardiac, tracheo-oesophageal, renal, spinal cord, or limb anomalies [3]. Despite technical advances, the combination of associated anomalies, impaired bowel functioning, and the physical, sexual, and psychosocial consequences of these morbidities continue to affect patients throughout their lives [4-7].

Anorectal malformations have an estimated prevalence of one in 2500 to 5000 live births [8, 9], and most specialized centres treat less than twenty new cases per year [10]. With the rarity of this disease, clinical data are scattered, and research focused upon patient and disease characteristics, treatment strategies, and short- and long-term outcomes is challenging. To improve epidemiological and clinical research in rare diseases, collaborative efforts through pooling of data in registries are essential [11]. Patient registries are organized systems that observationally collect data to evaluate specified outcomes for a population defined by a particular disease [12]. In the spirit of collaboration to improve our understanding of the demographics, treatments and outcomes of ARM, this study combines clinical data from two ARM patient registries.

The Royal Children's Hospital (RCH) in Melbourne, Australia, maintains a prospective ARM and Hirschsprung disease patient registry, collecting clinical, surgical, and functional outcome data. The RCH Colorectal Database has registered over 500 ARM patients and represents the largest ARM cohort in the Pacific region. The ARM Network (ARM-Net) registry, the largest multicentre ARM registry internationally, with over 2600 patients included, was founded by the European ARM-Net Consortium [13, 14]. The registry collects data on patient demographics, associated anomalies, surgical details, and functional outcomes. With over 3000 patients combined, the aim of this study was to describe the clinical and surgical characteristics of the largest ARM population to date, and to compare demographics, management, and outcomes between Australia and Europe.

Methods

Objectives

The primary objective of this study was to describe and compare the ARM patients included in the two registries in terms of patient characteristics, surgical details and complications, and post-operative treatments. The secondary objective was to describe the distribution of patient and treatment characteristics of all ARM patients over time.

Subjects and data collection

The subjects were paediatric (<18 years old) patients diagnosed with ARM and registered in the RCH Colorectal Database or ARM-Net registry.

Anorectal malformations patients born from 1985 onwards that were managed in the RCH Department of Paediatric Surgery were prospectively included in the RCH Colorectal Database. Informed consent was collected through an opt-out procedure and ethics approval was sought by the RCH Human Research Ethics Committee.

Patients managed at one of the 34 centres of the ARM-Net Consortium born before 2010 were included in ARM-Net registry retrospectively at time of the registry inception, and new patients born from 2010 onwards were added prospectively [13]. In accordance with local ethical requirements in each centre, only deidentified data were collected and stored.

Data on patient, diagnostic and surgical characteristics, and bowel management were collected. Patient and disease characteristics included sex, year of birth, ARM type according to the Krickenbeck classification [15], genetic diagnosis, associated skeletal, spinal, renal, cardiac, genital, and tracheo-oesophageal anomalies. Surgical characteristics included enterostomy formation, closure, and enterostomy-related complications. Furthermore, reconstructive surgery type, age at time of reconstructive surgery, complications, and redo operations were registered. Post-operative treatments included anal dilatations and bowel management such as constipation regimens including stool softeners or laxatives (e.g. macrogol, polyethylene glycol, lactulose, psyllium fibers, senna, bisacodyl), enemas (phosphate, sorbitol), or rectal/transanal irrigations (e.g. peristeen tubes). These datapoints were collected one year after reconstructive surgery in the ARM-Net registry, and no timeframe was specified for RCH Colorectal Database.

Duplicate entries, patients with missing or unknown sex or ARM type, or with conflicting sex and ARM type (e.g. male with vestibular fistula), and patients with more than 25% of missing data for closed-ended items were excluded.

Ethical approval for the present study was sought and approved from the RCH Human Research and Ethics Committee (HREC/93070/RCHM-2023).

Statistical analyses

Descriptive statistics were performed presenting frequencies with percentages and medians with interquartile ranges (IQR; 25-75 percentile). Age at reconstructive surgery was further categorised into < 3 months or ≥ 3 months. Both laparoscopic-assisted anorectoplasty (LAARP) and posterior sagittal anorectoplasty (PSARP) with laparoscopy were considered LAARP, because although the original procedure by Georgeson [16] was with a small skin incision and a 'blinded' pull through, the majority of patients were treated with a laparoscopic dissection and limited posterior sagittal procedure. Analyses comparing characteristics between RCH and ARM-Net patients were conducted using chi-squared or Fishers exact tests for association and Mann-Whitney-U tests, as appropriate depending on the type of variables and numbers included. When further investigating the difference in incidences of associated anomalies and enterostomy formation between the two cohorts, a logistic regression model estimating odds ratios (OR) and 95% confidence intervals (CI) was conducted to adjust for potential confounders ARM type and associated anomalies, respectively. Distribution of the disease and treatment characteristics across a 30-year period of the combined RCH and ARM-Net cohorts of patients born between 1993 and 2022 were analysed, and changes over time were tested for significance using logistic regression models, adjusting for registry (RCH or ARM-Net) as confounding variable. For this analysis, birthyear was categorised into four groups: 1993-2007, 2008-2012, 2013-2017, and 2018-2022. Statistical tests were considered significant at a p-value below 0.05 and performed in IBM SPSS Statistics (v.29).

Results

There were 528 patients registered in the RCH Colorectal Database up until 1st March 2023. Duplicate entries (n=8), patients without ARM (n=37;

e.g. anteriorly displaced anus, sacrococcygeal teratoma), with unknown/missing ARM type (n=21), and with >25% of missing data (n=6) were excluded, resulting in 456 (86%) RCH patients eligible for analyses. Of the 2627 patients registered in the ARM-Net registry until 1st March 2023, patients without ARM (n=13), patients with missing/unknown ARM type (n=102), with unknown sex (n=6), conflicting ARM type and sex (n=7), and with >25% of missing data (n=8) were excluded, leaving 2491 (95%) ARM-Net patients. Together, 2947 ARM patients from Australia and Europe were included in the analyses.

Compared to the ARM-Net patients, the RCH cohort was older (**Table 1**). The distribution of ARM types was approximately similar, but there were significantly less perineal fistula and ARM without fistula patients in the RCH registry, and more anal stenosis and rare types, such as rectal atresia, recto-vaginal fistula, and cloacal exstrophy, when compared with the European cohort. RCH perineal fistula patients were significantly more often male (58%; p=0.005), where in ARM-Net there were more females (53%) with this ARM type. More RCH patients had at least one associated anomaly (78% vs 67%), specifically skeletal, cardiac or tracheo-oesophageal anomalies. The incidences of renal and genital anomalies, including distribution across sexes, was similar between the registries. When adjusted for ARM type, RCH patients were still more likely to have associated anomalies than ARM-Net patients (OR 1.8, CI 1.4-2.3).

Table 1: Patient and disease characteristics of 2947 Australian and European ARM patients compared.

	RCH (n=456)	**ARM-Net (n=2491)**	
	N (%*)	**N (%*)**	**p-value†**
Male sex	249 (54.6)	1248 (50.1)	0.077
Year of birth (median, range)	2012 (1985-2022)	2015 (1992-2023)	**<0.001**
ARM type			
Perineal fistula (M/F)	168 (98/70) (36.8)	1080 (505/575) (43.4)	**0.010**
Vestibular fistula	75 (16.4)	413 (16.6)	0.944
Rectourethral fistula	84 (18.4)	470 (18.9)	0.822
Prostatic type	49 (10.7)	198 (7.9)	**0.048**
Bulbar type	31 (6.8)	221 (8.9)	0.145
Unspecified	4 (0.9)	51 (2.0)	0.090
Anal stenosis (M/F)	35 (24/11) (7.7)	53 (30/23) (2.1)	**<0.001**

Table 1: Continued

	RCH (n=456)	ARM-Net (n=2491)	
	N (%*)	**N (%*)**	**p-value†**
Cloaca	17 (3.7)	113 (4.5)	0.440
<3cm common channel	5 (1.1)	65 (2.6)	0.051
>3cm common channel	5 (1.1)	29 (1.2)	0.901
unspecified common channel	7 (1.5)	19 (0.8)	0.107
Recto-bladder neck fistula	15 (3.3)	62 (2.5)	0.325
ARM without fistula (M/F)	11 (7/4) (2.4)	162 (126/36) (6.5)	**<0.001**
Rare and other types	51 (11.2)	138 (5.5)	**<0.001**
Rectal atresia (M/F)	23 (17/6) (5.0)	16 (9/7) (0.6)	**<0.001**
Recto-vaginal fistula	12 (2.6)	18 (0.7)	**<0.001**
Cloacal exstrophy	8 (1.8)	18 (0.7)	**0.050**
H-type fistula (M/F)	3 (0/3) (0.7)	12 (1/11) (0.5)	0.716
Rectal stenosis (M/F)	1 (0/1) (0.2)	17 (15/2) (0.7)	0.340
Other	4 (0.9)	57 (2.3)	**0.050**
Genetic diagnosis	59 (13.0)	287 (11.5)	0.378
Down syndrome (M/F)	13 (10/3) (22.0)	62 (37/25) (2.5)	**<0.001**
At least one associated anomaly‡	354 (77.6)	1663 (66.8)	**<0.001**
Skeletal anomaly	194 (42.5)	828 (33.2)	**0.001**
Sacral anomaly	73 (16.0)	451 (20.9)	0.116
Absent coccyx	15 (3.3)	382 (21.3)	**<0.001**
Spinal cord anomaly	84 (18.4)	443 (22.1)	0.087
Cardiac anomaly	258 (57.3)	818 (38.8)	**<0.001**
Patent ductus arteriosus	98 (21.8)	165 (7.8)	**<0.001**
Atrial septal defect	85 (18.9)	458 (21.8)	0.174
Ventricular septal defect	61 (13.6)	239 (11.4)	0.190
Tetralogy of Fallot	13 (2.9)	46 (2.2)	0.369
Coarctation of aorta	5 (1.1)	30 (1.4)	0.601
Other	72 (16.0)	221 (10.5)	**<0.001**
Tracheo-oesophageal anomaly	47 (10.3)**	168 (7.3)	**0.031**
Renal anomaly	131 (29.0)	645 (28.8)	0.247
Hydronephrosis	44 (9.7)	256 (11.4)	0.290
Dysplastic/cystic kidney	40 (8.8)	115 (5.1)	**0.002**
Solitary kidney	17 (3.8)	136 (6.1)	0.052
Duplex kidney	9 (2.0)	66 (2.9)	0.258
Horseshoe kidney	6 (1.3)	65 (2.9)	0.056
Ectopic kidney	11 (2.4)	56 (2.5)	0.516

Table 1: Continued

	RCH (n=456)	ARM-Net (n=2491)	
	N (%*)	**N (%*)**	**p-value†**
Other	42 (9.3)	148 (6.6)	**0.043**
Genital anomaly	93 (20.5)	499 (21.6)	0.620
Male	61 (24.7)[1]	304 (25.4)[1]	0.807
Hypospadias	25 (10.2)[1]	120 (10.1)[1]	0.957
Cryptorchidism either side	22 (8.9)[1]	131 (11.0)[1]	0.340
Bifid scrotum	14 (5.7)[1]	77 (6.4)[1]	0.100
Penoscrotal transposition	2 (0.8)[1]	30 (2.5)[1]	0.656
Other	23 (9.3)[1]	81 (6.8)[1]	0.157
Female	32 (15.5)[2]	195 (17.4)[2]	0.504
Bicornuate uterus / uterine didelphys	16 (7.8)[2]	69 (6.2)[2]	0.402
Vaginal septum	9 (4.4)[2]	64 (5.8)[2]	0.424
Hydrocolpos	5 (2.4)[2]	29 (2.6)[2]	0.881
Mullerian remnants / atresia	3 (1.5)[2]	10 (0.9)[2]	0.440
Other	12 (5.8)[2]	74 (6.7)[2]	0.658

*Abbreviations: RCH, Royal Children's Hospital; ARM-Net, Anorectal Malformation Network; ARM, anorectal malformation. * Of total known data, excluding missing data per variable. † Calculated using chi-square tests for association.‡ Any skeletal, spinal, cardiac, renal, bladder, or genital anomaly. ** Out of all 456 patients, due to >80% with 'unknown' answers, which was regarded as 'no'. [1] Out of all males and excluding missing data. [2] Out of all females and excluding missing data.*

Treatment-related approach differed between the two cohorts (**Table 2**). RCH patients more often had an enterostomy than ARM-Net patients (64% vs 44%), and this difference was seen specifically in perineal and vestibular fistula patients (52% vs 16%), even when adjusted for associated anomalies (OR 5.4, CI 4.0-7.3). Less RCH patients (87%) underwent reconstructive surgery than ARM-Net patients (93%). Excluding the patients that died, this difference remained significant (RCH 88% vs ARM-Net 94%). Of the 53 surviving RCH patients that did not undergo reconstruction, the majority had less complex ARM types, which was also the case for surviving, unreconstructed ARM-Net patients. However, the RCH cohort showed significantly more patients with anal stenosis (40% vs 8%), and less perineal fistula (25% vs 68%) than ARM-Net. Indeed, within the RCH cohort, most anal stenosis patients (62%) had no reconstruction and were most frequently treated with anal dilatations alone (56%).

Table 2: Treatment characteristics of 2947 Australian and European ARM patients compared.

	RCH (n=456)	**ARM-Net (n=2491)**	
	N (%*)	**N (%*)**	**p-value†**
Enterostomy	282 (64.1)	1069 (43.8)	**<0.001**
Perineal fistula	66 (41.0)	100 (9.6)	**<0.001**
Vestibular fistula	55 (76.4)	138 (33.9)	**<0.001**
Rectourethral fistula, prostatic type	49 (100.0)	193 (98.0)	0.587
Rectourethral fistula, bulbar type	30 (100.0)	211 (95.5)	0.614
Anal stenosis	5 (14.7)	6 (12.0)	0.751
Cloaca	14 (87.5)	109 (97.3)	0.117
Recto-bladder neck fistula	15 (100.0)	62 (100.0)	-
ARM without fistula	8 (88.9)	126 (78.8)	0.687
Rare and other types	36 (72.0)	75 (55.6)	**0.045**
Enterostomy closed	243 (86.2)	921 (86.2)	0.995
Reconstructive surgery	378 (86.5)	2243 (92.9)	**<0.001**
Age in months at reconstructive surgery (median, IQR)	4.7 (2.0-8.6)	4.0 (2.0-7.0)	**<0.001**
With enterostomy (median, IQR)	5.5 (3.9-9.3)	5.0 (3.0-8.0)	0.089
Without enterostomy (median, IQR)	0.3 (0.1-5.1)	3.0 (0.0-5.0)	0.159
Type of reconstructive surgery per ARM type:			
Perineal fistula	148	934	
PSARP	71 (48.0)	692 (74.1)	**<0.001**
Cutback	65 (43.9)	44 (4.7)	**<0.001**
Anoplasty	4 (2.7)	86 (9.2)	**0.008**
ASARP	0	107 (11.5)	**<0.001**
LAARP	7 (4.7)	0	**<0.001**
Other	1 (0.7)	5 (0.5)	0.831
Vestibular fistula	66	386	
PSARP	55 (83.3)	300 (77.7)	0.305
PSARP + laparotomy	5 (7.6)	1 (0.3)	**<0.001**
Cutback	2 (3.0)	0	**0.021**
Anoplasty	1 (1.5)	0	0.146
ASARP	0	75 (19.4)	**<0.001**
LAARP	3 (4.5)	2 (0.5)	**0.024**
PSARV(U)P	0	6 (1.6)	0.599
Other	0	2 (0.5)	1.000
Rectourethral fistula, prostatic type	48	189	
PSARP	8 (16.7)	125 (66.1)	**<0.001**
PSARP + laparotomy	1 (2.1)	13 (6.9)	0.312
LAARP	39 (81.3)	47 (24.9)	**<0.001**
Other	0	4 (0.5)	0.585
Rectourethral fistula, bulbar type	30	215	

Table 2: Continued

	RCH (n=456)	ARM-Net (n=2491)	
	N (%*)	**N (%*)**	**p-value†**
PSARP	20 (66.7)	200 (93.0)	**<0.001**
PSARP + laparotomy	3 (10.0)	7 (3.3)	0.110
LAARP	7 (23.3)	6 (2.8)	**<0.001**
Other	0	2 (0.5)	1.000
Recto-bladder neck fistula	12	60	
PSARP	2 (16.7)	7 (11.7)	0.639
PSARP + laparotomy	1 (8.3)	21 (35.0)	0.090
ASARP	0	1 (1.7)	1.000
LAARP	9 (75.0)	30 (50.0)	0.113
Other	0	1 (1.7)	1.000
Cloaca	13	98	
PSARP	2 (15.4)	9 (9.2)	0.615
PSARP + laparotomy	0	3 (3.1)	1.000
ASARP	0	1 (1.0)	1.000
LAARP	1 (7.7)	2 (2.0)	0.314
PSARVUP +/- TUM	8 (61.5)	81 (82.7)	0.130
Other	2 (15.4)	2 (2.0)	0.067
Anal stenosis	13	37	
PSARP	3 (23.1)	13 (35.1)	0.508
PSARP + laparotomy	0	3 (8.1)	0.558
Cutback	10 (76.9)	5 (13.5)	**<0.001**
Anoplasty	0	14 (37.8)	**0.010**
Other	0	2 (5.4)	1.000
ARM without fistula	8	145	
PSARP	4 (50.0)	124 (85.5)	**0.025**
PSARP + laparotomy	0	6 (4.1)	1.000
Anoplasty	0	2 (1.4)	1.000
ASARP	0	3 (2.1)	1.000
LAARP	4 (50.0)	8 (5.5)	**0.001**
Other	0	4 (2.8)	1.000
Constipation regimen	103 (22.6)	965 (55.2)	**<0.001**
Laxatives/stool softeners	88 (19.3)	726 (76.0)	**<0.001**
Enemas/irrigation	38 (8.4)	222 (23.2)	**<0.001**

*Abbreviations: RCH, Royal Children's Hospital; ARM-Net, Anorectal Malformation Network; ARM, anorectal malformation; IQR, interquartile range; PSARP, posterior sagittal anorectoplasty; ASARP, anterior sagittal anorectoplasty; LAARP, laparoscopic assisted anorectoplasty; PSARV(U)P posterior sagittal anorectovagino(urethra)plasty; TUM, total urogenital mobilization. * Of total known data, excluding missing data per variable. † Calculated using chi-square tests for association or Mann-Whitney-U test for age at surgery.*

At time of reconstruction, RCH patients were slightly older than ARM-Net patients (4.7 vs 4.0 months, p<0.001), although when categorised into with or without enterostomy, this difference was no longer statistically significant. Within each cohort, patients with an enterostomy were older at reconstruction than patients without. In terms of surgical approach, patients with a perineal fistula were mostly corrected using PSARP at both ARM-Net and RCH (74% vs 48%), although RCH patients also commonly underwent cutback surgery (44%). None of the perineal or vestibular fistula patients at RCH underwent an anterior sagittal anorectoplasty (ASARP), compared with 12% and 19%, respectively, in ARM-Net. Instead, vestibular fistula patients at RCH more commonly underwent PSARP (83%). Recto-prostatic patients were largely reconstructed with LAARP at RCH (81%), where the majority of these types in the ARM-Net cohort were reconstructed by PSARP (66%). Although there were no significant differences in approach for recto-bladder neck fistula, with mostly LAARP at both RCH (75%) and ARM-Net (50%), ARM-Net also commonly showed PSARP with laparotomy (35%). Patients with a recto-bulbar fistula were most often reconstructed with PSARP in both cohorts, but the RCH surgeons still operated 23% with LAARP, which was not seen in the ARM-Net group (3%). Also, for ARM without fistula there was a preference for LAARP at RCH (50%) that was not seen in ARM-Net (6%), where PSARP was preferred (86%). Anal stenosis patients were mostly corrected through cutback at RCH (77%), but ARM-Net patients mostly through anoplasty (38%) or PSARP (35%). Reconstruction types for cloaca patients were similar between the two cohorts, with a posterior sagittal anorectovagino(urethro)plasty (PSARVUP) with or without total urogenital mobilization as the most performed surgery. Postoperatively, significantly fewer patients in the RCH cohort were treated for constipation, compared with the ARM-Net cohort.

Surgical complication rates, both enterostomy-related and post-reconstruction, differed between the cohorts (**Table 3**). RCH patients had half the number of enterostomy-related complications compared to ARM-Net patients, especially in rectourethral fistulas (16% vs 31%). Fewer RCH patients had more than one enterostomy-related complication, and also less stomal stenosis or another enterostomy-related complication, compared to the ARM-Net patients. Post-reconstructively, complication rates between RCH and ARM-Net did not significantly differ (23% vs 25%). However, lower complication rates were seen in RCH patients with perineal fistulas, compared to ARM-Net perineal fistulas (12% vs 20%). The highest

complication rate in ARM-Net perineal fistulas was after ASARP (35%). After excluding these, complication rates after PSARP were similar, but rates after cutback were, although not significantly, lower in RCH than in ARM-Net (7% vs 12%). Interestingly, RCH perineal fistula patients with an enterostomy had higher post-reconstructive complication rates than those without (71% vs 29%, p=0.005). Furthermore, although not statistically significant, vestibular and rectourethral fistula complication rates in the RCH cohort (28% and 35%, respectively) were higher than in ARM-Net (24% and 29%, respectively), and rates in recto-bladder neck fistula were lower (38% vs 53%). When delving into complication rates after surgical techniques, RCH patients had significantly less complications after LAARP (29%) than ARM-Net patients (54%). By contrast, RCH patients had slightly more complications after PSARP than ARM-Net patients, although not statistically significant (28% vs 22%).

Table 3: Enterostomy-related and post-reconstructive complications of 2947 Australian and European ARM patients compared.

	RCH (n=456)	**ARM-Net (n=2491)**	
	N (%*)	**N (%*)**	**p-value†**
At least one enterostomy-related complication	31 (15.4)	310 (30.8)	**<0.001**
Per ARM type:			
Perineal fistula	5 (12.8)	21 (21.6)	0.236
Vestibular fistula	6 (14.0)	28 (21.9)	0.260
Rectourethral fistula	10 (16.4)	135 (31.1)	**0.017**
Recto-bladder neck fistula	2 (18.2)	16 (30.2)	0.714
Cloaca	2 (22.2)	40 (40.0)	0.478
Anal stenosis	0	3 (50.0)	0.464
ARM without fistula	0	42 (34.4)	0.177
Rare and other types	6 (20.7)	25 (35.2)	0.154
More than one enterostomy-related complication	2 (1.0)	31 (3.1)	**<0.001**
Types of complications:			
Prolapse	10 (5.0)	38 (3.8)	0.424
Stenosis	2 (1.0)	42 (4.2)	**0.028**
Other	21 (10.4)	265 (26.3)	**<0.001**
At least one post-reconstructive complication	70 (23.3)	527 (25.3)	0.447
Per ARM type			
Perineal fistula	14 (12.3)	181 (20.4)	**0.039**
Vestibular fistula	18 (28.1)	86 (24.3)	0.514

Table 3: Continued

	RCH (n=456)	ARM-Net (n=2491)	
	N (%*)	**N (%*)**	**p-value†**
Rectourethral fistula	23 (34.8)	124 (29.2)	0.349
Recto-bladder neck fistula	3 (37.5)	30 (52.6)	0.475
Cloaca	5 (55.6)	35 (38.0)	0.477
Anal stenosis	1 (8.3)	4 (11.4)	1.000
ARM without fistula	1 (14.3)	32 (23.2)	1.000
Rare and other types	5 (23.8)	35 (36.1)	0.281
Per reconstruction type			
PSARP	40 (28.4)	319 (22.0)	0.082
PSARP + laparotomy	2 (25.0)	32 (50.8)	0.264
Cutback	5 (6.8)	5 (11.1)	0.502
Anoplasty	0	12 (11.9)	1.000
ASARP	NA	57 (31.1)	NC
LAARP	18 (28.6)	52 (54.2)	**0.001**
PSARV(U)P	2 (40.0)	23 (41.1)	1.000
PSARVUP/TUM	1 (50.0)	12 (28.6)	0.508
Other	1 (33.3)	12 (32.4)	1.000
More than one post-reconstructive complication	10 (3.3)	137 (6.6)	**0.014**
Types of complications:			
Stenosis	21 (7.0)	100 (4.8)	0.108
Wound infection	11 (3.7)	59 (2.8)	0.430
Rectal mucosal prolapse	11 (3.7)[1]	66 (3.2)[2]	0.656
Dehiscence	10 (3.3)	231 (11.1)	**<0.001**
Recurrent fistula	5 (1.7)	16 (0.8)	0.173
Other	19 (6.3)	218 (10.5)	**0.024**
Redo/revision	34 (10.8)	87 (4.2)	**<0.001**

*Abbreviations: RCH, Royal Children's Hospital; ARM-Net, Anorectal Malformation Network; ARM, anorectal malformation; PSARP, posterior sagittal anorectoplasty; ASARP, anterior sagittal anorectoplasty; LAARP, laparoscopic assisted anorectoplasty; PSARV(U)P posterior sagittal anorectovagino(urethra)plasty; TUM, total urogenital mobilization, NA, not applicable; NC, not calculatable. * Of total known data, excluding missing data per variable. † Calculated using chi-square tests for association. [1] One of the given options when registering post-reconstructive complications. [2] Not one of the given options when registering post-reconstructive complications but mentioned in free text.*

Furthermore, significantly less wound dehiscence was seen in the RCH cohort (3% vs 11%), but more RCH patients required a redo operation (11% vs 4%). When only looking at the patients who required a redo operation, most patients had rectourethral fistula in both the RCH and ARM-Net cohorts (32% and 30%, respectively), followed by vestibular (24%) and perineal fistula (18%) at RCH, and perineal (25%) and recto-bladder neck fistula (13%) in ARM-Net. When comparing redo rates between the cohorts in rectourethral fistulas only, RCH showed a significantly higher frequency (17% vs 6%, p=0.004). The difference in redo rates also remained statistically significant for recto-bulbar subtype (18% vs 4%, p=0.027), and a similar trend was found for recto-prostatic type (17% vs 7%, p=0.062). Analysing PSARP and LAARP approaches in the rectourethral fistula group, redo operations at RCH were significantly more frequently after PSARP (33%) than after LAARP (10%), and in ARM-Net, although not statistically significant, more after LAARP (11%) than PSARP (5%).

Across a 30-year period categorised into four groups, the distribution of ARM types and sex was similar, but associated anomalies and treatment characteristics differed (**Table 4**). Patients with at least one associated anomaly became more common, particularly spinal anomalies, with an increase to 24% from 2013 onwards, compared to 15-19% in the preceding years. The detection of cardiac anomalies also became slightly more frequent, from 38% in 1993 to 2007 to over 40% from 2008 onwards. Patients were slightly younger at time of reconstruction in more recent years, especially patients with enterostomies, with median 6 months of age between 1993 and 2007, and 5 months from 2018 onwards. In terms of reconstructive techniques, perineal fistulas were increasingly corrected by PSARP, as the frequency of cutback and ASARP decreased with time. Although not statistically significant, cutback also became less frequent in patients with anal stenosis, with increasing frequency of PSARP and anoplasty. However, where PSARP was most common between 2008 and 2017, anoplasty became the significantly most common surgical approach from 2018 onwards. Lastly, post-reconstructive complications decreased significantly from 32% to 20%. In terms of postoperative treatment, the number of patients on constipation regimens significantly reduced throughout the years.

Table 4: Distribution over a period of 30 years of clinical and surgical characteristics of 2939 ARM patients born between 1993 and 2022.

	Year of birth categorized into four groups				
	1993-2007 N (%*)	**2008-2012 N (%*)**	**2013-2017 N (%*)**	**2018-2022 N (%*)**	**p-value†**
Total	289 (9.9)	801 (27.3)	937 (31.9)	907 (30.9)	-
RCH / ARM-Net	141 / 148 (48.8 / 51.2)	85 / 716 (10.6 / 89.4)	108 / 829 (11.5 / 88.5)	115 / 792 (12.7 / 87.3)	<0.001
Male sex	154 (53.3)	391 (48.8)	464 (49.5)	481 (53.0)	0.310
ARM type:					
Perineal fistula	115 (39.8)	340 (42.2)	382 (40.8)	408 (45.0)	0.289
Vestibular fistula	46 (15.9)	129 (16.1)	163 (17.4)	146 (16.1)	0.903
Rectourethral fistula	52 (18.0)	147 (18.4)	189 (20.2)	164 (18.1)	0.975
Recto-bladder neck fistula	9 (3.1)	25 (3.1)	24 (2.6)	19 (2.1)	0.231
Cloaca	12 (4.2)	36 (4.5)	49 (5.2)	31 (3.4)	0.314
Anal stenosis	20 (6.9)	25 (3.1)	16 (1.7)	27 (3.0)	0.063
ARM without fistula	12 (4.2)	54 (6.7)	52 (5.5)	53 (5.8)	0.694
Rare and other types	23 (8.0)	45 (5.6)	62 (6.6)	59 (6.5)	0.500
Genetic diagnosis	36 (12.5)	107 (13.4)	102 (10.9)	98 (10.8)	0.161
Down syndrome	8 (4.9)	24 (3.3)	20 (2.4)	22 (2.7)	0.357
At least one associated anomaly‡	197 (68.2)	528 (66.2)	652 (70.1)	631 (70.7)	**0.013**
Skeletal	93 (32.7)	273 (35.2)	343 (37.8)	306 (35.3)	0.219
Spinal	42 (15.4)	124 (18.5)	181 (23.5)	178 (24.1)	**<0.001**
Cardiac	93 (37.5)	263 (43.4)	348 (40.4)	369 (44.4)	**0.002**
Renal	63 (24.3)	221 (33.9)	257 (28.3)	219 (25.4)	**0.037**
Genital	64 (23.1)	160 (21.0)	182 (20.6)	184 (22.1)	0.881
Enterostomy	146 (50.9)	360 (45.3)	439 (47.9)	400 (46.0)	0.449
Enterostomy-related complications	30 (22.7)	100 (29.7)	132 (32.2)	76 (23.5)	0.176
Reconstructive surgery	261 (90.9)	713 (90.0)	853 (93.1)	782 (92.7)	0.308
Age in months at reconstruction (median, IQR)	4.8 (1.0-9.0)	4.0 (2.0-7.0)	4.0 (2.0-8.0)	4.0 (2.0-6.0)	**0.007**
With enterostomy	6.0 (3.7-10.0)	5.0 (3.0-8.0)	6.0 (4.0-9.0)	4.7 (3.0-7.6)	**0.005**
Without enterostomy	1.0 (0.0-6.9)	2.0 (0.0-6.0)	2.2 (0.0-5.0)	3.0 (0.1-5.0)	0.522
Type of surgery per ARM type:					
Perineal fistula					
PSARP	52 (48.1)	176 (62.2)	270 (81.3)	264 (74.2)	**<0.001**
Cutback	41 (38.0)	35 (12.4)	13 (3.9)	19 (5.3)	**<0.001**
Anoplasty	7 (6.5)	25 (8.8)	21 (6.3)	36 (10.1)	0.675

Table 4: Continued

	Year of birth categorized into four groups				
	1993-2007 N (%*)	**2008-2012 N (%*)**	**2013-2017 N (%*)**	**2018-2022 N (%*)**	**p-value†**
ASARP	8 (7.4)	47 (16.6)	23 (6.9)	29 (8.1)	**0.001**
LAARP	0	0	2 (0.6)	5 (1.4)	**0.020**
Other	0	0	3 (0.9)	3 (0.9)	0.989
Vestibular fistula					
PSARP	32 (76.2)	99 (78.6)	1252(77.7)	99 (79.8)	0.561
PSARP + laparotomy	0	0	1 (0.6)	5 (4.0)	**0.024**
Cutback	2 (4.8)	0	0	0	0.988
Anoplasty	0	0	1 (0.6)	0	0.608
ASARP	7 (16.7)	25 (19.8)	27 (17.2)	16 (12.9)	0.056
LAARP	0	0	4 (2.5)	1 (0.8)	0.204
PSARV(U)P	0	2 (1.6)	1 (0.6)	3 (2.4)	0.425
Other	1 (2.4)	0	1 (0.6)	0	0.199
Rectourethral fistula					
PSARP	28 (57.1)	111 (77.1)	139 (74.3)	111 (74.5)	0.529
PSARP + laparotomy	6 (12.2)	8 (5.6)	10 (5.3)	6 (4.0)	0.091
LAARP	13 (26.5)	23 (16.0)	37 (19.8)	28 (18.8)	0.646
Other	2 (4.1)	2 (1.4)	1 (0.5)	4 (2.7)	0.793
Recto-bladder neck fistula					
PSARP	1 (14.3)	3 (12.0)	2 (9.1)	3 (16.7)	0.808
PSARP + laparotomy	4 (57.1)	10 (40.0)	3 (13.6)	5 (27.8)	0.067
ASARP	0	0	1 (4.5)	0	0.761
LAARP	2 (28.6)	12 (48.0)	16 (72.7)	9 (50.0)	0.255
Other	0	0	0	1 (5.6)	0.996
Cloaca					
PSARP	1 (9.1)	2 (6.1)	5 (11.4)	2 (9.5)	0.678
PSARP + laparotomy	1 (9.1)	0	1 (2.3)	1 (4.8)	0.924
ASARP	0	0	1 (2.3)	0	0.746
LAARP	1 (9.1)	0	0	2 (9.5)	0.479
PSARVUP +/- TUM	8 (72.7)	29 (87.9)	37 (84.1)	15 (71.4)	0.491
Other	0	2 (6.1)	0	1 (4.8)	0.940
Anal stenosis					
PSARP	0	6 (46.2)	7 (63.6)	3 (17.6)	0.997
PSARP + laparotomy	1 (11.1)	1 (7.7)	1 (9.1)	0	0.088
Cutback	7 (77.8)	5 (38.5)	0	3 (17.6)	0.124

Table 4: Continued

	Year of birth categorized into four groups				
	1993-2007 N (%*)	2008-2012 N (%*)	2013-2017 N (%*)	2018-2022 N (%*)	p-value†
Anoplasty	0	1 (7.7)	2 (18.2)	11 (64.7)	**0.004**
Other	1 (11.1)	0	1 (9.1)	0	0.162
ARM without fistula					
PSARP	5 (55.6)	43 (86.0)	41 (80.4)	38 (90.5)	**0.024**
PSARP + laparotomy	2 (22.2)	1 (2.0)	2 (3.9)	1 (2.4)	0.219
Anoplasty	0	2 (4.0)	0	0	0.239
ASARP	2 (22.2)	1 (2.0)	0	0	**0.018**
LAARP	0	3 (6.0)	7 (13.7)	2 (4.8)	0.490
Other	0	0	1 (2.0)	1 (2.4)	0.294
Post-reconstructive complications	78 (32.2)	181 (26.9)	195 (24.8)	136 (20.2)	**<0.001**
Constipation regimen	128 (46.4)	406 (57.4)	351 (47.1)	180 (38.6)	**<0.001**

*Abbreviations: ARM, anorectal malformation; IQR, interquartile range; PSARP, posterior sagittal anorectoplasty; ASARP, anterior sagittal anorectoplasty; LAARP, laparoscopic assisted anorectoplasty; PSARV(U)P posterior sagittal anorectovagino(urethra)plasty; TUM, total urogenital mobilization. * Of patients within birth year category with known data, excluding missing data per variable.† P-value represents overall effect of time, adjusted for registry (RCH or ARM-Net) as a confounder using logistic regression modelling. ‡ Any skeletal, spinal, cardiac, renal, bladder, or genital anomaly.*

Discussion

The present study compares the patient and treatment characteristics of 2947 ARM patients included in the RCH Colorectal Database and the ARM-Net registry, and the distribution of these characteristics of the combined cohorts over time.

Compared with the ARM-Net cohort, the RCH group showed more complex rare ARM types, possibly because it serves as a specialized paediatric surgical centre to a geographically dispersed area, unlike Europe, where specialized centres exist across all its densely-populated countries. Patients with less complex types might be treated at hospitals in their vicinity, while complex types are referred. This may also explain the older age at surgery and more enterostomies at RCH, as patients from far may have referral delays and an enterostomy allows for more time until reconstruction. Another explanation might be the larger south-east Asian

and subcontinental population in Australia compared with Europe, where more complex ARM types demonstrate a higher prevalence [17-19].

More RCH than ARM-Net patients had one or more associated anomalies, even when adjusted for ARM complexity. This increased incidence is in line with the literature, where 79-93% of Australian patients had associated anomalies, compared with 62% of European patients [20-22]. Interestingly, diagnostic screening practices for associated anomalies does not seem to differ between these regions, with full vertebral, spinal, cardiac, tracheo-oesophageal, renal and limb (VACTERL) screening performed in about 80% of patients [20-22]. By contrast, only 45-68% of patients undergo full screening in the United States [23, 24]. One explanation for the higher incidence of associated anomalies in the RCH cohort might be that Australia has one of the highest rates of artificial reproductive technology use worldwide, which is a maternal risk factor for the development of congenital anomalies [25-27]. More than half of the patients in this study had cardiac anomalies, compared with 19-34% described in the literature [3, 20, 28]. However, these studies only included major cardiac anomalies and not small septal defects or patent ductus arteriosus, conditions that may still resolve spontaneously with age and do not require cardiological follow-up [29]. Nevertheless, these simple defects are included as cardiac anomalies in this report and may explain the high incidences, as an American study that also included these had similar results, with an incidence of up to 58% [30]. Furthermore, more cardiac anomalies were found in the RCH cohort than in the ARM-Net cohort, which may be explained by comparing a single centre with a specific echocardiogram screening protocol (RCH), with varying protocols across multiple different centres (ARM-Net). Another reason could be that the RCH is the main cardiac referral centre for Australia, which firstly, may result in cardiac patients with associated ARM to be referred, and secondly, patients are more likely to undergo full cardiac screening than patients in other centres.

Treatment-related characteristics differed between RCH and ARM-Net patients. Notably, RCH surgeons more frequently opted for a defunctioning enterostomy, especially for perineal and vestibular fistulas even when adjusted for associated anomalies, while a discussion remains in these types specifically [31]. Besides the opportunity to bridge the mentioned referral time, this difference might stem from RCH being a single centre with specific surgical preferences, whereas ARM-Net represents surgeon

preferences from 34 European centres. A recent ARM-Net Consortium study found that an enterostomy did not protect from complications after reconstruction [32]. In fact in this study, RCH perineal fistula patients with an enterostomy had higher post-reconstructive complication rates than those without. Therefore, multiple-staged procedures should be contemplated, as enterostomies may also cause complications [33]. However, fewer RCH than ARM-Net patients had enterostomy-related complications, so other factors such as enterostomy type or bowel segment may also play a role [34, 35]. Another explanation for the lower enterostomy-related complication rates at RCH might be the higher volume of enterostomies performed, as increased surgeon experience is related to better patient outcomes [36, 37].

Surgeons in ARM-Net mostly opted for PSARP for perineal fistula, where RCH surgeons also elected cutback. Contrarily, PSARP was most common surgery for vestibular fistula, where 20% of these patients in ARM-Net also underwent ASARP. Surgical approach for rectourethral fistula and ARM without fistula was mostly PSARP in ARM-Net, where RCH patients frequently underwent LAARP. These geographical variations may be explained by patient and surgeon preferences, differences in surgical training, or surgeons' beliefs [38]. Outcomes after PSARP and LAARP have frequently been investigated, and a meta-analysis found no differences in rates of rectal prolapse, anal stenosis, and bowel functioning [39]. Here too, variation influenced outcomes: ARM-Net's complication rate was significantly higher after LAARP, which might be due to the lower frequency of LAARP procedures within ARM-Net compared to RCH. Interestingly, more RCH patients required redo surgery, specifically after PSARP, contrasting with ARM-Net where redo was more common after LAARP, again potentially reflecting the volume-outcome ratio. However, other perioperative factors, such as mechanical bowel preparation, antibiotic regimens, or time to oral feeding may also play a role [40].

Slightly more patients did not undergo reconstruction at RCH than in ARM-Net, where most of the RCH patients had less complex ARM types such as anal stenosis or perineal fistula. Australian anal stenosis patients were more frequently treated with anal dilatations alone than Europeans. However, European surgeons seemed more conservative in their approach for perineal fistulas, which could have been non-stenotic or minimally displaced, conditions that may be treated conservatively [41].

When exploring the distribution of patient and treatment characteristics over time, several interesting trends could be observed. Firstly, the incidence of documented associated anomalies has increased significantly. It is more likely that this is due to an increase in patients diagnosed, than to an increase in disease prevalence, with the rising attention for standardized diagnostic screening for associated anomalies [20, 22]. Furthermore, popularity of the PSARP reconstructive approach has grown over time, as the interest in the cutback surgery has diminished. However, from 2018 onwards, anoplasty has made a come-back and regained popularity. This may be related to the also notable trend of decreased anal dilatations practices, with Heineke-Mikulicz anoplasty as an alternative to treat post-operative strictures [42]. High rates of complications, such as wound dehiscence, may have forced surgeons to reconsider the more minimally invasive procedures, and to lower parental burden [43]. The trend of fewer patients on constipation regimens may be linked to the lower complication rates over the years, which may be explained by the creation of specialized paediatric surgical centres, as centralization of care is associated with improved patient outcomes [44, 45].

Several limitations are observed in this study. Primarily, the European comparator represents patient and treatment characteristics from 34 centres across 13 countries within the ARM-Net Consortium, while RCH is a single centre in Australia. Secondly, data are extrapolated from patient registries, posing challenges in data quality [46]. Although quality of the ARM-Net registry has been assessed [47], issues of completeness, timeliness, user variability, accuracy, and comparability remain for both registries. Certain RCH data points, such as tracheo-oesophageal anomalies and specific constipation treatments, had over 80% missing data, necessitating extensive cleaning for comparison. Furthermore, discrepancies in defining and identifying surgical complications (e.g. within 30 days), may have arisen due to different data collection methods. Lastly, the cohorts vary in distribution of the patients' birthyears, potentially impacting comparability. However, after excluding patients to align median birthyears, more than 25% of the RCH patients had to be excluded, but analyses did not differ from our current findings. For this reason, we have decided to analyse and present all included patients.

Conclusion

This study presents the collaboration of the RCH and the ARM-Net Consortium, analysing nearly 3000 ARM patients across Australia and Europe, marking the largest ARM cohort study to date. While patients globally shared ARM types and associated anomalies, treatment approaches varied regionally. Australian surgeons favoured cutback surgery in less complex ARM types and laparoscopic assistance in more complex types, whilst European surgeons favoured PSARP for both less complex and complex ARM types. These differences in treatment distributions corresponded with varying postoperative outcomes, underscoring the importance of surgeons specialising in their strengths. This study contributes to the growing understanding of patient, disease, and treatment characteristics of ARM, ultimately aiming to improve patient outcomes. It emphasizes the absence of a singular correct approach in managing rare complex colorectal conditions like ARM, advocating for collaboration to elucidate challenges and share knowledge. Anorectal malformation patients in Australia and Europe may be similar, but their locations are different, and so are their surgeons.

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PART 3

Innovation through collaboration: novel registries for patients with anorectal malformations

CHAPTER 7

The Australia New Zealand Congenital Colorectal Registry (ANZCCoRe): driving innovation through collaboration

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Abstract

Colorectal paediatric surgeons, rare and complex colorectal patients, and data on this patient group are dispersed far and wide in Australia and New Zealand (ANZ). Online databases facilitate sharing and collating of data, and may help to connect physically separated clinicians and researchers. The Australia New Zealand Congenital Colorectal Registry (ANZCCoRe) is an international, multicentre patient registry that aims to improve clinical outcomes, standardise care, and enhance collaborations between centres with expertise in paediatric colorectal conditions across ANZ.

The ANZCCoRe will collect retrospective and prospective clinical data of patients with anorectal malformations (ARM) and/or Hirschsprung disease (HD) through an electronic data capturing platform. Collected data will include demographic characteristics, diagnostics, care pathways, associated anomalies, surgical details and complications, and functional outcomes. The datapoints will be categorised into required core data elements and requested additional data elements. Data will be deidentified and stored on secured servers, meeting ethical and legal requirements. Data quality procedures will exist and feasible application of the findability, accessibility, interoperability, and reusability (FAIR) principles will promote data sharing and reuse with other registries.

Besides gaining a better understanding of the patient and disease characteristics, monitoring care, and evaluating health-related outcomes, the ANZCCoRe provides a source for potential research participants. Lastly, the ANZCCoRe enhances advocacy for patients and families affected by colorectal conditions.

The ANZCCoRe is the first multicentre congenital colorectal patient registry in this geographical region. Its strengths lie in facilitating research, standardisation of care, patient advocacy, and collaboration with paediatric surgical centres across ANZ and beyond.

Background

Australia and New Zealand (ANZ) are both characterised by relatively small populations across large geographical areas. In addition, colorectal paediatric surgeons, rare and complex colorectal patients, and clinical data from this patient group are dispersed far and wide [1]. This breadth of exposure and knowledge results in varying approaches to clinical care and creates challenges when conducting research on this relatively small group of patients. Across a number of continents and countries, large online patient registries have emerged within many health care disciplines to conglomerate patient data and connect clinicians and researchers who are physically separated [2]. Congenital colorectal conditions have been included in some of these databases, such as the European Reference Network (ERN) eUROGEN registry for rare urogenital diseases and complex conditions, and the Anorectal Malformation Network (ARM-Net) registry [3, 4].

Patient registries are organised systems that use observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease or condition [2]. They are powerful tools that may be used to evaluate outcomes when randomised controlled trials are difficult to conduct [2]. This is especially true for rare or complex diseases, where patient data are scarce due to low prevalence. International collaboration and centralisation of data through a registry platform may not only facilitate research but may also allow for exchange of expertise and knowledge, and enhancement of (existing) partnerships. Furthermore, collection of clinical data from centres with variance in practice may provide a rich source to evaluate and standardise care, ultimately aiming to improve health-related outcomes.

Anorectal malformations (ARM) and Hirschsprung disease (HD) are complex congenital colorectal conditions requiring expert surgical intervention and focused, long-term bowel management [5-9]. With a prevalence of 1 in 3000 to 5000 live births, research into these conditions is often hampered by low sample sizes. Therefore, a collaborative effort of multiple paediatric surgical centres to collectively combine data in an online patient registry may be a solution to overcome these challenges. This paper introduces the objectives and design of the Australia New Zealand Congenital Colorectal Registry (ANZCCoRe), a web-based, international, multicentre patient registry collecting retrospective and prospective clinical data of ARM and

HD patients. The registry aims to improve clinical outcomes, standardise care, and enhance collaborations of clinical expertise centres across ANZ. In publishing the ANZCCoRe methodology, the authors also aim to provide an example for other rare disease patient registries in areas where patients as well as healthcare sites (HCSs) are dispersed.

Methods

Purpose and objectives

The purpose of the ANZCCoRe is to centralise clinical data of ARM and HD patients treated in paediatric surgical centres in ANZ. The key objectives of the ANZCCoRe are to:

- Collect clinical data of good quality
- Provide a source for identification and selection of patients for research
- Describe ARM and HD patients and disease characteristics
- Evaluate and improve health-related outcomes
- Monitor, improve, and standardise clinical care
- Create and enhance collaborations between paediatric surgical centres across ANZ
- Enhance advocacy for patients and families affected by ARM and HD

Ethics and data protection

The ANZCCoRe platform and its collected data will be initially based at The Royal Children's Hospital (RCH) in Melbourne, Australia. Ethics approval will be sought from the RCH Human Research Ethics Committee, which complies with the National Statement on Ethical Conduct in Human Research (2007).

Informed consent

The use and disclosure of health information without an individual's consent by organisations for health research for the purpose of research, relevant to the public health, or the management or monitoring of a health service is approved as outlined in the guidelines under Section 95 of the Privacy Act 1988 in force in Australia [10]. Therefore, the ANZCCoRe is not required to request informed consent [11]. However, to promote transparency and patient involvement, and more importantly to provide patients with a sense of security and inclusion in decision-making, eligible patients treated at the participating HCSs will be offered an opt-out option of consenting

to the inclusion of their data in the ANZCCoRe. Patients' caregivers will be provided information about the registry, will be asked whether they have read and understood it, and will be offered to opt out and decline participation. Otherwise, patients' caregivers will consent to the collection of data pertaining to personal details (excluding names and addresses), diagnosis, care pathways including diagnostics and treatments, and outcomes. They will consent to the use and sharing of their deidentified data for research purposes by the ANZCCoRe managers or approved third-party researchers.

Data ownership

The data collected in the ANZCCoRe are ultimately the property of the respective patients. However, the patients' caregivers will have consented to the use and sharing of the patients' data, making the treating HCS the custodians of their data. The data management team of the ANZCCoRe will be the data controller and processor, determining the purposes and the processing of patient data.

Data access

The data management team will be responsible for the protection of the data through security procedures and restricted access to the ANZCCoRe. Only authorised appointed local data managers of participating HCSs will have access to enter and edit data of patients treated in their respective centres. Access to the electronic data capture (EDC) platform is through a personalised username and password, secured with multi-factor authentication. The HCSs will only have access to data of patients treated at their own centre. Only the data management team will have access to all data and may provide requesting research parties, such as a healthcare centre wishing to conduct research with data from the entire registry, with an export of deidentified data after a data access application and data sharing agreement has been approved by the research committee.

Patient privacy

All patient data are deidentified, pseudonymised, and collected through a secure web-based EDC. Data are stored on the secure and private multi-factor protected RCH server. Identifiers will not be entered in the EDC. Participating HCSs are responsible for securely storing code-breaking documents linking ANZCCoRe pseudonymisation numbers to local patient medical record numbers, should they need to reidentify their patients. No one person will be

able to reidentify patients except for the local data manager at the HCS of the respective patients. In the case of data export requests for research purposes by participating HCSs or third-party researchers, only deidentified data will be shared. Should the requesting party want to approach included patients for additional data collection, they will only be permitted to do so if the patient has not opted-out of being contacted for research purposes initially described. The requesting party may submit a wish-to-contact addendum to the data transfer agreement request to the research committee.

Design

Platform

The ANZCCoRe EDC platform is facilitated by the Research Electronic Data Capture (REDCap) tools, hosted at the Australian and New Zealand Association of Paediatric Surgeons (ANZAPS) and allows for centralised collection and management of the data [12, 13]. It is an online web-based platform where data are collected in electronic case report forms (CRFs) or patient-oriented surveys.

Subjects

All eligible patients diagnosed with ARM and/or HD treated at participating HCSs will be included in the ANZCCoRe after informed consent, unless they have opted out. If opting out, their diagnosis and reason, if applicable, will be registered for evaluation of external validity and selection bias of the registry. Patients may choose not to provide a reason for opting out. Patients wishing to retract their data and retrospectively opt out from the ANZCCoRe may decide to do so at any time.

The ARM and/or HD diagnosis may be an isolated presentation or part of a syndrome or association. The diagnosis should be synonymous with preferably the Orphanet Nomenclature and Classification of Rare Diseases (ORPHAcodes) [14], or alternatively International Classification of Diseases (ICD) [15], Systematised Nomenclature Of Medicine Clinical Terms (SNOMED CT) [16], or Online Mendelian Inheritance in Man (OMIM) [17] codes for ARM and HD.

Exclusion criteria include language barriers not manageable with an official translator, patients whose reconstructive surgery has not taken place at one of the participating HCSs, patients who have already been included in the

preexisting RCH Colorectal Database to prevent duplicate registration, and patients whose reconstructive surgery has taken place more than five years ago.

Outcomes

The key clinical objectives may be translated into measurable outcomes, including:

- Diagnostic details (e.g. diagnosis of ARM / HD, associated gene mutations, diagnostic tests confirming the diagnosis);
- Associated anomalies (e.g. findings of diagnostic screening, interventions)
- Surgical details (e.g. stoma placement, reconstructive surgery type, age at surgery)
- Complications (short- and long-term) after reconstructive surgery and related to stoma placement and closure
- Functional outcomes (e.g. constipation, faecal and urinary continence) and patient reported outcomes (general and disease-specific quality of life)
- Care pathway (e.g. referrals, number of visits, structure of care)
- Practice variability amongst the participating HCSs (e.g. waiting time until reconstructive surgery, timing of diagnostic screening)

Data elements

The data elements collected in the ANZCCoRe will be categorised into two sets. Categorisation of data elements into a required set, and an additional, requested set, is recommended to improve efficiency in establishing a registry and promote interoperability with other registries [2]. Therefore, the first set consists of the core data elements (CDEs) that are mandatory to collect to create a basic yet comprehensive overview of the patient (**Table 1**). These data elements include an adaptation of the common data elements for rare disease registration developed by the Joint Research Centre (JRC) of the European Commission [18]. The CDEs cover the patient's details, consent, diagnosis, care pathway, and surgical treatments.

Besides the CDEs, which are required to be entered upon inclusion of a patient in the ANZCCoRe, there are additional data elements (ADEs) that should be collected, if available. These aim to create a more detailed record of the patient and cover diagnostic tests confirming the diagnosis and investigating associated anomalies, presence of associated anomalies, medical and surgical treatment details, postoperative and stoma-related complications, and functional outcomes, as per the complete ANZCCoRe data dictionary (**Supplementary File 1**).

Table 1: Core Data Elements

ANZCCoRe CORE DATA ELEMENTS				
Group	**Element Name**	**Element Label**	**Entry format**	**Answer options (if applicable)**
ID	[pid]	ANZCCoRe ID	Automatic	
	[pid_site]	Site-specific ID	Text	
Patient details	[dob]	Date of birth	Text (date_dmy)	
	[sex]	Sex at birth	Single selection	0, Male 1, Female 2, Undetermined 99, Unknown
	[status]	Status	Single selection	0, Alive 1, Dead 2, Lost to follow-up
	[dod]	Date of death	Text (date_dmy)	
	[cob]	Country of birth	Single selection	*All countries*
Consent	[c_contact]	Consent for contact	Single selection	0, Consented 1, Opted-out
Diagnosis	[diagnosis_c]	Clinical diagnosis	Single selection	1, Anorectal malformation 2, Hirschsprung disease 99, Unknown
	[arm]	Anorectal malformation type	Single selection	*List of ARM types according to Krickenbeck classification*
	[cloaca_length]	Length common channel	Single selection	1, < 3cm 2, > 3cm 99, Unknown
	[arm_oth]	Other type of anorectal malformation	Text	
	[arm_syn]	Is the anorectal malformation isolated or part of a syndrome/association	Single selection	0, Isolated 1, Syndrome/association 2, Not (yet) determined 99, Unknown

Table 1: Continued

ANZCCoRe CORE DATA ELEMENTS				
Group	**Element Name**	**Element Label**	**Entry format**	**Answer options (if applicable)**
Diagnosis	[arm_syn_type]	Syndrome or association	Single selection	*List of associated syndromes and associations*
	[arm_syn_typ_oth]	Other syndrome or association	Text	
	[hd]	Hirschsprung disease type	Single selection	1, Short aganglionic segment 2, Long aganglionic segment 3, Total colonic aganglionosis 4, Total intestinal aganglionosis 77, Other
	[hd_oth]	Other type of Hirschsprung disease	Text	
	[hd_syn]	Is the Hirschsprung disease isolated or part of a syndrome	Single selection	0, Isolated 1, Syndrome/association 2, Not (yet) determined 99, Unknown
	[hd_syn_type]	Syndrome	Single selection	*List of associated syndromes*
	[hd_syn_typ_oth]	Other syndrome or association	Text	
	[diagnosis_p]	Phenotypic diagnosis	Text (OMIM)	
	[age_diag]	Age at diagnosis	Single selection	0, Antenatal 1, At birth 2, Specific date of diagnostic test 3, Undetermined
	[age_diag_date]	Date of diagnosis as specific moment	Text (date_dmy)	
Care pathway	[rov]	Reason first visit for colorectal care	Single selection	0, Care initiated at this healthcare site 1, Referral and transfer of care 2, Surgery 3, Second opinion 77, Other 99, Unknown
	[dov_known]	Date of first visit for colorectal care known?	Single selection	0, No 1, Yes
	[dov]	Date first visit for colorectal care	Text (date_dmy)	

Table 1: Continued

ANZCCoRe CORE DATA ELEMENTS				
Group	**Element Name**	**Element Label**	**Entry format**	**Answer options (if applicable)**
Care pathway	[dept]	Department of care	Single selection	0, Paediatric Surgery 1, Paediatric Urology 2, Paediatrics 3, Paediatric Gastroenterology 77, Other 99, Unknown
Surgery	[stoma]	Stoma	Single selection	0, No 1, Yes 99, Unknown
	[reconstruction]	Reconstructive surgery	Single selection	0, No 1, Yes 99, Unknown
	[reconstruction_type]	Type of reconstructive surgery	Single selection	1, Anoplasty 2, Mini-PSARP 3, Sphincter-sparing PSARP 4, Perineal-sparing PSARP 5, PSARP 6, ASARP 7, LAARP 8, Open repair 9, TUM 10, PSARV(U)P 77, Other 99, Unknown
	[reconstruction_type_oth]	Other type of reconstructive surgery	Text	
	[reconstruction_date_known]	Date of reconstructive surgery known?	Single selection	0, No 1, Yes
	[reconstruction_date]	Date of reconstructive surgery	Text (date_dmy)	

Table 1: Continued

ANZCCoRe CORE DATA ELEMENTS				
Group	**Element Name**	**Element Label**	**Entry format**	**Answer options (if applicable)**
Surgery	[reconstruction_age]	Age at reconstructive surgery (months)	Calculation	
	[pullthrough]	Pull-through procedure	Single selection	0, No 1, Yes 99, Unknown
	[pullthrough_type]	Type of pull-through procedure	Single selection	1, Swenson 2, Duhamel 3, Soave 77, Other 99, Unknown
	[pullthrough_type_oth]	Other type of pull-through procedure	Text	
	[pullthrough_approach]	Approach pull-through procedure	Single selection	1, Transanal only 2, Transanal and laparoscopic assisted 3, Transanal and laparotomy 99, Unknown
	[pullthrough_date_known]	Date of pull-through procedure known?	Single selection	0, No 1, Yes
	[pullthrough_date]	Date of pull-through procedure	Text (date_dmy)	
	[pullthrough_age]	Age at pull-through procedure (months)	Calculation	

Abbreviations: PSARP, posterior sagittal anorectoplasty; ASARP, anterior sagittal anorectoplasty; LAARP, laparoscopic anterior anorectoplasty; TUM, total urogenital mobilization; PSARV(U)P, posterior sagittal anorecto-vagino-(urethro)-plasty.

Additional to the CDEs and ADEs, the ANZCCoRe plans to collect patient-reported data elements (PDEs), aimed to collect non-clinical functional outcome data that are based on what the patient reports. The PDEs are not mandatory, but should be collected when available and cover general and disease-specific quality of life, bladder and bowel functioning, growth and development, psychosocial functioning, accessibility and structure of care, and experience of received healthcare. The PDEs will only be implemented once the ANZCCoRe has been successfully collecting CDEs from recruited patients for at least two years.

Data collection procedures

Data collection for the ANZCCoRe will be divided into retrospective and prospective collection. The appointed local data manager at each participating HCS is responsible for clinical data collection for the patients at their HCS. Data of each HCS will be centrally collected in the ANZCCoRe (**Figure 1**).

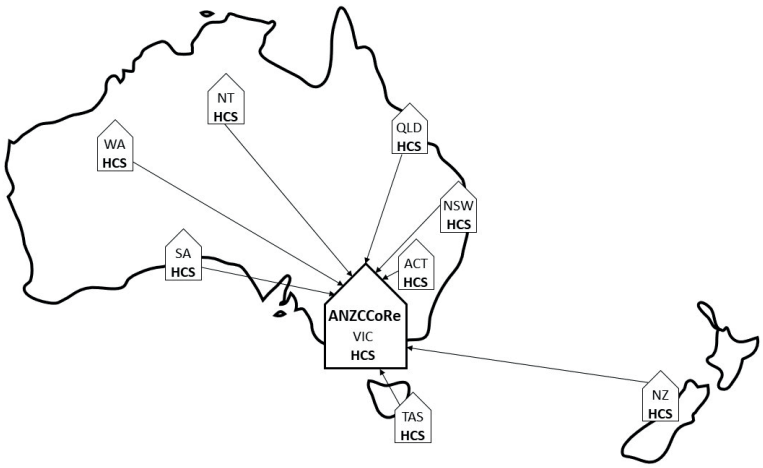

Figure 1: ANZCCoRe central data collection

Abbreviations: HCS, healthcare site; WA, Western Australia; SA, South Australia; NT, Northern Territory; QLD, Queensland; NSW, New South Wales; ACT, Australian Capital Territory; VIC, Victoria; TAS, Tasmania, NZ, New Zealand.

Prospective data collection involves the inclusion of new patients. Each eligible new patient at the HCS, unless opted out, will be prospectively included in the ANZCCoRe. When the patient presents to the HCS for their first consultation, the patient is screened for eligibility. The physician or nurse responsible for the care of the patient informs the patient of

the registry and offers the option to opt out. If not opted out, the patient is recruited. The local data manager extracts the relevant data from the patient's medical file and enters them in standardised CRFs in the EDC, with separate sections for the CDEs and ADEs. The CRFs have specific checkpoints based on the patient's journey in their care pathway. If a patient has not yet undergone surgery, items related to the surgery will be skipped via branching logic and marked as incomplete.

Retrospective collection involves the inclusion of eligible existing patients that have been identified at a follow-up visit in their HCS, do not meet any of the exclusion criteria, and have not opted out to their inclusion. The data manager will conduct a chart review and extract the necessary data to collect in the CRFs.

Data quality

Data quality may be assessed at three different levels. Firstly, before data collection (quality assurance), secondly, during and after data collection (quality control), and lastly, as part of assessment of the registry as a whole (quality assessment) [19]. Quality assurance will be guaranteed by the solid ANZCCoRe governance, identification of key objectives, clear inclusion and exclusion criteria, standardised electronic CRFs, a user-friendly web-based EDC platform, categorised CDE and ADE datasets, patient medical records as a reliable data source, and a dedicated data management team.

Quality control procedures will include prevention of duplicate entries through the EDC system, prevention of input error through standardised logical checks upon data entry (e.g. date of surgery must be after date of birth), error notifications upon blanks and missing data, use of standardised ontology coding language, and automated follow-up entry reminders. Furthermore, data entry of the first 25 patients at each participating HCS will be monitored by the data management team. The data management team will also produce annual data quality reports evaluating the different dimensions of data quality, including completeness, accuracy, timeliness, usefulness, interoperability, accessibility, and data security [20]. This report will also include progress per participating HCS and identifies HCSs that require local site monitoring and/or training. A user manual including instructions and a frequently asked questions (FAQ) document will be made publicly available on the ANZCCoRe website. The data management team will also be available to provide personalised support to HCSs.

Quality assessment of the registry as a whole will be performed by the data management team. After the ANZCCoRe has been collecting data for one year, feedback surveys will be sent out to participating HCSs to inquire about issues and recommendations regarding data entry and the ANZCCoRe's structure and included data elements. These feedback surveys will be repeated annually and published in the quality report. If necessary, the registry will be adapted accordingly.

FAIR principles

In the field of rare disease research, where data are scarce and scattered, the four guiding principles of findability, accessibility, interoperability, and reusability (FAIR) to promote data sharing and reuse are indispensable [19, 21]. The FAIR data principles increase collaboration and attract new partnerships [22]. Therefore, with creating and enhancing collaborations and clinical networks as one of its main aims, the ANZCCoRe's application of the FAIR principles is of great importance.

Findability

To promote findability of the ANZCCoRe and its data, the registry will apply to be a member of the Australian National Alliance of Rare Disease Registries, associated with Rare Voices Australia, the rare disease patient advocacy body, and to be listed in the Genetic Undiagnosed And Rare Disease (GUARD) Collaborative. Furthermore, findability will also be promoted through publication and promotion of the ANZCCoRe registry on the RCH Colorectal and Pelvic Reconstructive Service (CPRS) website. Finally, studies involving ANZCCoRe data will be published in Open Access journals.

Accessibility

The ANZCCoRe is accessible by making the registry's data dictionary, or metadata, publicly available on the ANZCCoRe website. The data management team will also apply for the ANZCCoRe's metadata to be available in the Australian Institute of Health and Welfare's Metadata Online Registry. The procedures for applying for a deidentified ANZCCoRe dataset for research purposes will also be published on the website. Persons who meet explicitly stated conditions, including ethical approval for sensitive data, may have full accessibility to the data from an online location after an authentication and authorisation procedure. As the ANZCCoRe does not (yet) have the informational technology and funding, the data in the registry will not be mapped with semantic modelling.

Interoperability

Interoperability of the ANZCCoRe data with other registries and datasets will be facilitated through the use of standardised ontologies for defining the diagnosis. As the ANZCCoRe does not (yet) have the informational technology and funding, the other data elements in the registry will not be defined with standardised language. The ANZCCoRe will, however, collect data elements that are synonymous with the JRC Common Data Elements and the ERN eUROGEN registry Clinical Practice Snapshot data elements for ARM [18, 23]. Furthermore, the data will be formatted as an exportable Comma-Separated Values (CSV) file.

Reusability

The ANZCCoRe will be made reusable by the public availability of its metadata and the standardised CRFs used for data collection. The data collected in ANZCCoRe may be reusable through mutual agreement between the ANZCCoRe and a requesting research party. The mutual agreements will be reviewed and signed by the research party's legal representatives, the RCH Human Research Ethics Committee, the ANZCCoRe Steering Committee, and the research party, and if applicable, the relevant participating HCSs.

Application of the FAIR principles is not without its challenges, and the ANZCCoRe does not (yet) have the facilities to comply with the principles to their optimal extent, such as the use of semantic modelling or standardised ontologies for all data elements. Nevertheless, a feasible application of the FAIR principles will ensure that the ANZCCoRe data may contribute to open science.

Governance

Stakeholders and funding

The key stakeholders of the ANZCCoRe include ARM and HD HCSs, ARM and HD patients and their caregivers, ARM and HD patient advocacy groups, ARM and HD treating clinician groups, affiliated academic and research institutions, and researchers in the field of ARM and HD research. The ANZCCoRe will initially be funded by a grant from The Royal Children's Hospital Foundation for its design and implementation. Additional funding sources will be sought to provide ongoing maintenance and quality assurance procedures.

Registry team

The ANZCCoRe will be governed by the registry team comprising the Steering Committee, the Data Management Team, the Privacy and Ethics Officer, and the Research Committee. Each team will carry their own tasks and responsibilities.

The Steering Committee will lead the registry and will include clinical experts in the field of ARM and HD, research coordinators, patient advocacy group representatives, registry developers and managers. It will be responsible for coordinating and managing the components of the registry, including management of the other ANZCCoRe teams, budget and funding, communication with participating HCSs, strategic decisions, and ongoing oversight of the implementation and management process. The Data Management Team will be responsible for anything pertaining to the data collection process, including modifications to datasets, case report forms, data capturing structure, and access to and security of the EDC platform. They will also be responsible for data quality procedures. The Privacy and Ethics Officer will be responsible for the ANZCCoRe to be compliant with any legal, regulatory, and ethical requirements to manage data ownership, data protection, and patient privacy. The Research Committee will consider all research and data sharing applications by participating HCSs, affiliated research institutes, and independent research requesting to conduct with research with the ANZCCoRe data.

The clinical experts participating in the Steering Committee will be paediatric surgeons, with a representative for each Australian state and New Zealand. Each participating Australian and New Zealand HCS appoints a local data manager responsible for ANZCCoRe data input of the patients treated at their centre. The complete ANZCCoRe team conducts annual meetings to discuss the implementation and operation of the registry, such as data quality and completeness, and any research-related matter, such as data sharing applications and scientific publications pertaining to data of the registry.

Discussion

The ANZCCoRe aims to be a multifaceted colorectal registry serving a multitude of purposes. The collected data from different surgical centres across multiple countries may add to the epidemiological understanding of patient and disease characteristics, and aids to describe and evaluate the

various practices of care. The differences and similarities in clinical care, combined with the positive and negative functional outcomes, may help to improve care, and conceivably, standardise best practice. Ultimately, the goal is to improve health-related outcomes and quality of life in complex colorectal patients.

The data collected in the ANZCCoRe alone may not suffice to answer more specific research questions and therefore, the ANZCCoRe aims to provide a repository of potential participants that may be recruited for other research projects. This way the ANZCCoRe facilitates research without the time-consuming process of identification and selection of patients.

Furthermore, the ANZCCoRe embodies collaborations and connections. The registry cannot exist without the joint effort of clinical expertise across ANZ, nor without the participation of patients' families who consent to the use and sharing of their data. The formation of these clinical networks across surgical centres facilitates the exchange of expertise and skills, and may improve transfer of care. Additionally, the ANZCCoRe enhances and promotes advocacy for complex colorectal patients and their families through associations with Rare Voices Australia and the GUARD Collaborative. By publishing reliable information on its website, the ANZCCoRe also hopes to stimulate awareness and remove the stigma around these impactful conditions.

The objectives and design of the ANZCCoRe are developed with the intent to be compatible and interoperable with other colorectal or rare disease registries, to facilitate linkage of multiple registries, and facilitate overarching research access [24]. Furthermore, the methods published in this report are also intended to inspire and provide a template for others interested in setting up a rare disease patient registry in similar geographical or financial circumstances.

The ANZCCoRe in turn has taken inspiration from other successful registries and recognised the challenges they face. A recent review has created an overview of the main elements of design, data quality, and challenges for rare disease registries [25]. The ARM-Net registry, one of the largest ARM registries with over 2600 patients, is a joint venture of a voluntary group of European paediatric surgeons, epidemiologists, geneticists, and patient advocacy groups [26]. It has recently undergone a thorough quality

assessment, emphasising the challenges of data handling of open-ended items, completeness and sustainability, and long-term maintenance [27]. For this reason, the ANZCCoRe will limit the number of open-ended items and categorise the data elements in the CDE set of required items and the ADE set requested when available. Furthermore, the ANZCCoRe will have quality monitoring procedures in place, including periodical user feedback sessions to improve its structure and datasets.

The ANZCCoRe is not without limitations. Firstly, securing funding for long-term maintenance remains a challenge. Some other registries, like the registry for inherited retinal dystrophies in Portugal (IRD-PT), the German acromegaly registry, and the TuberOus SCclerosis registry to increase disease Awareness (TOSCA) benefit from funding through pharmaceutical companies [28-30]. Registries with industry funding frequently have policies in place to ensure long-term sustainability and are therefore more likely to be of high quality [31]. Other registries may tackle this issue by seeking funding from authoritative bodies, such as the European Union supporting ERN registries, including the ERN eUROGEN and rare kidney disease (ERKReg) registries [3, 32]. Acknowledging the lack of long-term funding, the ANZCCoRe is in the early phase of development, and opportunities are currently being sought for continuous funding after implementation. Furthermore, the ARM-Net registry has proven that, although not without obstacles and without intending this for the ANZCCoRe, voluntary efforts of dedicated people can also be successful.

Another limitation is the restricted information that is collected in the registry. Although the additional dataset adds valuable data, there is always more information that could and should be collected in an ideal situation. Nonetheless, ideal data collection is rarely synonymous with feasibility. Paediatric surgeons responsible for data entry often have a heavy workload, and patient registration may not be a priority. For this reason, we have carefully selected which information is most important and required for the core dataset, recognising that this might result in incomplete or missing data in the additional datasets. Lastly, another limitation is that a multicentre registry likely introduces bias, such as inter- and intra-user variability, where paediatric surgeons might have different interpretations of information in medical files. The ARM-Net registry has shown that this is an issue that should be considered when conducting analyses with the collected data [27, 33]. Selection bias should also be considered in

statistical analyses and conclusions, since patients may refuse to consent to participation in the registry. Therefore, the registry population may differ from the entire congenital colorectal patient population.

Conclusion

The ANZCCoRe is a multicentre colorectal paediatric patient registry that aims to describe patient and disease characteristics, monitor and standardise care, improve health-related outcomes, facilitate research, and advocate for patients and families affected by complex colorectal conditions across ANZ. In publishing its methodology and challenges, the authors hope to set an example and inspire other rare disease patient registry initiatives.

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Supplementary File 1: ANZCCoRe data dictionary

Variable Name	Core /Additional	Required	Variable Type	Variable Label
pid	Core	Automatic	text	ANZCCoRe ID
pid_site	Core	Yes	text	Site-specific ID
dob	Core	Yes	date_dmy	Date of birth
sex	Core	Yes	radio	Sex at birth
status	Core	Yes	radio	Status
dod	Core	Branching	date_dmy	Date of death
cob	Core	Yes	dropdown	Country of birth
c_contact	Core	Yes	radio	Consent for contact
diagnosis_c	Core	Yes	radio	Clinical diagnosis
arm	Core	Yes	radio	Anorectal malformation type
cloaca_length	Core	Branching	radio	Length common channel
arm_oth	Core	Yes	text	Other type of anorectal malformation
arm_syn	Core	Yes	radio	Is the anorectal malformation isolated or part of a syndrome/ association
arm_syn_type	Core	Yes	radio	Syndrome or association

Value Labels	Branching Logic	Logic checks
0, Male | 1, Female | 3, Undetermined | 99, Unknown		
0, Alive | 1, Dead | 2, Lost to follow-up		
	[status] = '1'	
All countries listed		
0, Consented | 1, Opted-out		
99, Unknown | 1, Anorectal malformation | 2, Hirschsprung disease		
1, Perineal fistula | 2, Rectourethral fistula, bulbar type | 3, Rectourethral fistula, prostatic type | 4, Rectovesical/recto-bladder neck fistula | 5, Rectovestibular fistula | 6, Cloaca | 7, No fistula | 8, Anal stenosis | 9, Pouch colon | 10, Rectal atresia/stenosis | 11, Rectovaginal fistula | 12, H-type fistula | 77, Other	[diagnosis_c] = '1'	
1, < 3cm | 2, > 3cm | 99, Unknown	[arm] = '6'	
	[arm] = '77'	
0, Isolated | 1, Syndrome/association | 2, Not (yet) determined | 99, Unknown	[diagnosis_c] = '1'	
1, Al-Awadi/Raas-Rothschild syndrome | 2, Cat eye syndrome | 3, CHARGE syndrome | 4, Currarino syndrome | 5, Down syndrome (trisomy 21) | 6, Fanconi anemia, complementation group O | 7, FG-syndrome / Opitz-Kaveggia syndrome | 8, Fraser syndrome | 9, Goldenhar syndrome / craniofacial microsomia | Heterotaxy, visceral, 1, X-linked | 10, Jacobsen syndrome | 11, Johanson-Blizzard syndrome | 12, Kabuki syndrome | 13, Caudal regression syndrome | 14, Klippel-Feil syndrome | 15, Mayer-Rokitansky-Küster-Hauser syndrome type 2 (MURCS) | 16, McKusick-Kaufman syndrome / hydrometrocolpos syndrome | 17, Manitoba Oculotrichoanal (MOTA) syndrome | 18, Omphalocele-exstrophy-imperforate anus-spinal defects (OEIS) complex | 19, Pallister-Hall syndrome | 20, Pallister-Killian syndrome | 21, ROCA (retardation of growth and development, ocular ptosis, cardiac defect, and anal atresia) syndrome | 22, Saldino-Noonan syndrome | 23, Townes-Brocks syndrome 24, Ulnar-mammary / Schinzel syndrome | 25, VACTERL association | 26, Velocardiofacial syndrome (deletion 22q11.21) | 77, Other | 99, Unknown	[arm_syn] = '1'	

Supplementary File 1: Continued

Variable Name	Core /Additional	Required	Variable Type	Variable Label
arm_syn_typ_oth	Core	Yes	text	Other syndrome or association
hd	Core	Yes	radio	Hirschsprung disease type
hd_oth	Core	Yes	text	Other type of Hirschsprung disease
hd_syn	Core	Yes	radio	Is the Hirschsprung disease isolated or part of a syndrome
hd_syn_type	Core	Yes	radio	Syndrome
hd_syn_typ_oth	Core	Yes	text	Other syndrome or association
diagnosis_p	Core	Yes	text	Phenotypic diagnosis
age_diag	Core	Yes	radio	Age at diagnosis
age_diag_date	Core	Branching	date_dmy	
rov	Core	Yes	radio	Reason first visit for colorectal care
dov_known	Core	Yes	radio	Date of first visit for colorectal care known?
dov	Core	Yes	date_dmy	Date first visit for colorectal care
dept	Core	Yes	radio	Department of care
stoma	Core	Yes	radio	Stoma
reconstruction	Core	Yes	radio	Reconstructive surgery
reconstruction_type	Core	Yes	radio	Type of reconstructive surgery

Value Labels	Branching Logic	Logic checks
BIOPORTAL:OMIM	[arm_syn_type] = '77'	
1, Short aganglionic segment | 2, Long aganglionic segment | 3, Total colonic aganglionosis | 4, Total intestinal aganglionosis | 77, Other	[diagnosis_c] = '2'	
	[hd] = '77'	
0, Isolated | 1, Syndrome | 2, Not (yet) determined | 99, Unknown	[diagnosis_c] = '2'	
1, Aarskog sydrome | 2, Bardet-Biedl syndrome | 3, BRESHECK syndrome | 4, Cartilage-Hair hypoplasia | 5, Congenital central hypoventilation syndrome | 6, Down syndrome (trisomy 21) | 7, Fryns syndrome | 8, Goldberg-Shprintzen syndrome | 9, Goldenhar syndrome | 10, Kauffman-McKusick syndrome | 11, L1 syndrome | 12, Lesch-Nyhan syndrome | 13, Mowat-Wilson syndrome | 14, Multiple endocrine neoplasia (MEN) type 2 (A or B) | 15, Neurofibromatosis 1 | 16, Pallister-Hall syndrome | 17, Pitt-Hopkins syndrome | 18, Riley-Day syndrome (familial dysautonomia) | 19, Rubinstein-Taybi syndrome | 20, Smith-Lemli-Optiz syndrome | 21, Toriello-Carey syndrome | 22, Waardenburg syndrome type 4 (Waardenburg-Shah syndrome) | 77, Other | 99, Unknown	[hd_syn] = '1'	
BIOPORTAL:OMIM	[hd_syn_type] = '77'	
BIOPORTAL:HP	[diagnosis_c] = '99'	
0, Antenatal | 1, At birth | 2, Specific date of diagnostic test | 3, Undetermined		
	[age_diag] = '2'	Must be after [dob]
0, Care initiated at this healthcare site | 1, Referral and transfer of care | 2, Surgery | 3, Second opinion | 77, Other | 99, Unknown		
0, No | 1, Yes		
	[dov_known]='1'	
0, Paediatric Surgery | 1, Paediatric Urology | 2, Paediatrics | 3, Paediatric Gastroenterology | 77, Other | 99, Unknown		
0, No | 1, Yes | 99, Unknown		
0, No | 1, Yes | 99, Unknown	[diagnosis_c] = '1'	
1, Anoplasty | 2, Mini-PSARP | 3, Sphincter-sparing PSARP | 4, Perineal-sparing PSARP | 5, PSARP | 6, ASARP | 7, LAARP | 8, Open repair | 9, TUM | 10, PSARV(U)P | 77, Other | 99, Unknown	[reconstruction] = '1'	

Supplementary File 1: Continued

Variable Name	Core /Additional	Required	Variable Type	Variable Label
reconstruction_ type_oth	Core	Yes	text	Other type of reconstructive surgery
reconstruction_ date_known	Core	Yes	radio	Date of reconstructive surgery known?
reconstruction_date	Core	Yes	date_dmy	Date of reconstructive surgery
reconstruction_age	Core	Automatic	calc	Age at reconstructive surgery (months)
pullthrough	Core	Yes	radio	Pull-through procedure
pullthrough_type	Core	Yes	radio	Type of pull-through procedure
pullthrough_ type_oth	Core	Yes	text	Other type of pull-through procedure
pullthrough_ approach	Core	Yes	radio	Approach pull-through procedure
pullthrough_ date_known	Core	Yes	radio	Date of pull-through procedure known?
pullthrough_date	Core	Yes	date_dmy	Date of pull-through procedure
pullthrough_age	Core	Automatic	calc	Age at pull-through procedure (months)
hd_transitionzone_ long	Additional	No	radio	Transition zone long-segment
hd_transitionzone_ total	Additional	No	radio	Transition zone total aganglionosis
enterocolitis	Additional	No	radio	Enterocolitis episode(s)
enterocolitis_timing	Additional	No	checkbox	Before or after pull-through
enterocolitis_ firstdate	Additional	No	date_dmy	Date first episode of enterocolitis
enterocolitis_ lastdate	Additional	No	date_dmy	Date last episode of enterocolitis
enterocolitis_ episodes	Additional	No	radio	How many episodes of enterocolitis after pull-through procedure
diag_renalus	Additional	No	radio	Renal ultrasound
diag_renalus_date	Additional	No	date_dmy	Date of first renal ultrasound
diag_vcug	Additional	No	radio	Voiding cystourethrogram
diag_vcugs_date	Additional	No	date_dmy	Date of first VCUG
diag_cysto	Additional	No	radio	Cysto(vagino)scopy
diag_cysto_date	Additional	No	date_dmy	Date of cysto(vagino)scopy
diag_uds	Additional	No	radio	Urodynamic studies
diag_uds_date	Additional	No	date_dmy	Date urodynamic studies
diag_xray	Additional	No	radio	X-ray spine/sacrum

Value Labels	Branching Logic	Logic checks
	[reconstruction_type] = '77'	
0, No | 1, Yes	[reconstruction]='1'	
	[reconstruction] = '1' and [reconstruction_date_known]='1'	
rounddown(datediff([dob],[reconstruction_date], "M", "dmy"),2)	[reconstruction]='1' and [reconstruction_date_known]='1'	
0, No | 1, Yes | 99, Unknown	[diagnosis_c] = '2'	
1, Swenson | 2, Duhamel | 3, Soave | 77, Other | 99, Unknown	[pullthrough]='1'	
	[pullthrough_type]='77'	
1, Transanal only | 2, Transanal and laparoscopic assisted | 3, Transanal and laparotomy | 99, Unknown	[pullthrough]='1'	
0, No | 1, Yes	[pullthrough]='1'	
	[pullthrough_date_known]='1'	
rounddown(datediff([dob],[pullthrough_date], "M", "dmy"),2)	[pullthrough]='1' and [pullthrough_date_known]='1'	
1, Splenic flexure | 2, Transverse colon | 3, Ascending colon | 99, Unknown	[diagnosis_c]='2' and [hd]='2'	
1, Total colon | 2, Total colon and small intestine | 99, Unknown	[diagnosis_c]='2' and [hd]='3'	
0, No | 1, Yes | 99, Unknown	[diagnosis_c]='2'	
1, Before pull-through | 2, After pull-through | 99, Unknown	[enterocolitis]='1'	
	[enterocolitis_timing(1)] = '1' or [enterocolitis_timing(2)] = '1'	
	[enterocolitis_timing(1)] = '1' or [enterocolitis_timing(2)] = '1'	
1, 1-3 times | 2, 4-7 times | 3, >7 times | 99, Unknown	[enterocolitis_timing(2)] = '1'	
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='1'	
	[diag_renalus] = '1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='1'	
	[diag_vcug] = '1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='1'	
	[diag_cysto] = '1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='1'	
	[diag_uds]='1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='1'	

Supplementary File 1: Continued

Variable Name	Core /Additional	Required	Variable Type	Variable Label
diag_xray_date	Additional	No	date_dmy	Date of first X-ray of spine/sacrum
diag_mri	Additional	No	radio	MRI spine/sacrum
diag_mri_date	Additional	No	date_dmy	Date of first MRI spine/sacrum
diag_spinalus	Additional	No	radio	Spinal ultrasound
diag_spinalus_date	Additional	No	date_dmy	Date of first spinal ultrasound
diag_cardiacus	Additional	No	radio	Cardiac ultrasound
diag_cardiacus_date	Additional	No	date_dmy	Date of first cardiac ultrasound
diag_rsbiopsy	Additional	No	radio	Rectal suction biopsy
diag_rsbiopsy_date	Additional	No	date_dmy	Date of first rectal suction biopsy
diag_osbiopsy	Additional	No	radio	Open strip / full thickness biopsy
diag_osbiopsy_date	Additional	No	date_dmy	Date of first open strip biopsy
manometry	Additional	No	radio	Anorectal manometry
manomatry_date	Additional	No	date_dmy	Date first anorectal manometry
contrastenema	Additional	No	radio	Contrast enema
contrastenema_date	Additional	No	date_dmy	Date first contrast enema
colostogram	Additional	No	radio	Colostogram
colostogram_date	Additional	No	date_dmy	Date first colostogram
anom_spine	Additional	No	checkbox	Spinal anomalies
anom_spine_oth	Additional	No	text	Other spinal anomaly
anom_spine_vert	Additional	No	checkbox	Vertebral anomalies
anom_spine_ vert_oth	Additional	No	text	Other vertebral anomaly
anom_spine_spine	Additional	No	checkbox	Spinal anomalies
anom_spine_ spine_oth	Additional	No	text	Other spinal anomaly
anom_spine_cord	Additional	No	checkbox	Cord malformations

Value Labels	Branching Logic	Logic checks
	[diag_xray] = '1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='1'	
	[diag_mri] = '1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='1'	
	[diag_spinalus] = '1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='1'	
	[diag_cardiacus] = '1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='2'	
	[diag_rsbiopsy] = '1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='2'	
	[diag_osbiopsy] = '1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown	[diagnosis_c]='2'	
	[manometry]='1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown		
	[contrastenema]='1'	Must be after [dob]
0, No or not yet | 1, Yes | 99, Unknown		
	[colostogram]='1'	Must be after [dob]
0, None | 1, Vertebral malformations (e.g., hemivertebrae, butterfly vertebrae, supernumerary vertebrae, fusion of vertebrae) | 2, Spinal malformations (e.g., scoliosis, kyphosis, lordosis, absence or fusion of spine) | 3, Cord malformations (e.g., tethered cord, thickened filum / lipoma of terminal filum, syrinx, spinal dysraphism / spina bifida) | 77, Other | 99, Unknown	[diagnosis_c]='1'	
	[anom_spine(77)] = '1'	
1, Hemivertebrae | 2, Butterfly vertebrae | 3, Supernumerary vertebrae | 4, Fusion of vertebrae | 77, Other | 99, Unknown	[anom_spine(1)] = '1'	
	[anom_spine_vert(77)] = '1'	
1, Scoliosis | 2, Kyphosis | 3, Lordosis | 4, Absence or fusion of spine | 77, Other | 99, Unknown	[anom_spine(2)] = '1'	
	[anom_spine_spine(77)] = '1'	
1, Tethered cord | 2, Thickened filum / lipoma of terminal filum | 3, Syrinx | 4, Spinal dysraphism / spina bifida | 77, Other | 99, Unknown	[anom_spine(3)] = '1'	

Supplementary File 1: Continued

Variable Name	Core /Additional	Required	Variable Type	Variable Label
anom_spine_ cord_oth	Additional	No	text	Other cord anomaly
anom_sacr	Additional	No	checkbox	Sacral anomalies
anom_sacr_oth	Additional	No	text	Other sacral anomaly
anom_cardia	Additional	No	checkbox	Cardiac anomalies
anom_cardia_oth	Additional	No	text	Other cardiac anomaly
anom_trach	Additional	No	checkbox	Tracheo-oesophageal anomalies
anom_trach_oth	Additional	No	text	Other tracheo-oesophageal anomaly
anom_uro	Additional	No	checkbox	Urological anomalies
anom_uro_oth	Additional	No	text	Other urological anomaly
anom_vur	Additional	No	radio	Vesicoureteral reflux
anom_vur_side	Additional	No	checkbox	Affected side
anom_vur_grade_l	Additional	No	checkbox	Grade of vesicoureteral reflux left side
anom_vur_grade_r	Additional	No	checkbox	Grade of vesicoureteral reflux right side
anom_genit_m	Additional	No	checkbox	Genital anomalies
anom_genit_m_oth	Additional	No	text	Other genital anomaly

Value Labels	Branching Logic	Logic checks
	[anom_spine_cord(77)] = '1'	
0, None | 1, Coccygeal hypoplasia / agenesis | 2, Hemisacrum | 3, Sacral hypoplasia / partial sacral agenesis | 4, Complete sacral agenesis / non-existence of sacral vertebrae | 5, Fused sacral vertebrae | 6, Presacral mass | 77, Other | 99, Unknown	[diagnosis_c]='1'	
	[anom_sacr(77)] = '1'	
0, None | 1, Persistent ductus arteriosus | 2, Patent foramen ovale | 3, Atrial septal defect | 4, Ventricular septal defect | 5, Pulmonary hypertension | 6, Bilateral superior vena cava | 7, Tetralogy of Fallot | 8, Transposition of great vessels | 9, Heart valve disease | 10, Hypoplastic left heart syndrome | 77, Other | 99, Unknown		
	[anom_cardia(77)] = '1'	
0, None | 1, Oesophageal agenesis (Vogt 1) | 2, Oesophageal atresia without tracheoesophageal fistula (pure atresia; Gross A / Vogt 2) | 3, Oesophageal atresia with proximal tracheoesophageal fistula (Gross B, Vogt 3A) | 4, Oesophageal atresia with distal tracheoesophageal fistula (Gross C / Vogt 3B) | 5, Oesophageal atresia with dual tracheoesophageal fistulas (Gross D / Vogt 3C) | 6, Tracheoesophageal fistula without atresia (H-type fistula / Gross E) | 7, Tracheomalacia | 77, Other | 99, Unknown	[diagnosis_c]='1'	
	[anom_trach(77)] = '1'	
0, None | 1, Hydronephrosis | 2, Renal dysplasia/ hypoplasia | 3, Solitary kidney | 4, Horseshoe kidney | 5, Ectopic kidney | 6, Polycystic kidney | 7, Duplicated collecting system | 8, Ectopic ureter | 9, Ureter stenosis | 10, Posterior urethral valves | 11, Neurogenic bladder | 12, Urethral stricture | 13, Cystocele | 14, Meatal stenosis | 77, Other | 99, Unknown		
	[anom_uro(77)] = '1'	
0, No | 1, Yes | 99, Unknown		
1, Left | 2, Right | 99, Unknown	[anom_vur] = '1'	
1, Grade I | 2, Grade II | 3, Grade III | 4, Grade IV | 5, Grade V | 99, Unknown	[anom_vur_side(1)] = '1'	
1, Grade I | 2, Grade II | 3, Grade III | 4, Grade IV | 5, Grade V | 99, Unknown	[anom_vur_side(2)] = '1'	
0, None | 1, Cryptorchidism / undescended testis | 2, Hypospadias | 3, Epispadias | 4, Bifid scrotum | 5, Penoscrotal transposition | 6, Ambiguous genitalia | 7, Penile hypoplasia | 77, Other | 99, Unknown	[sex] = '0'	
	[anom_genit_m(77)] = '1'	

Supplementary File 1: Continued

Variable Name	Core /Additional	Required	Variable Type	Variable Label
anom_genit_f	Additional	No	checkbox	Genital anomalies
anom_genit_f_oth	Additional	No	text	Other genital anomaly
anom_limb	Additional	No	checkbox	Limb anomalies
anom_limb_oth	Additional	No	text	Other limb anomaly
anom_face	Additional	No	checkbox	Craniofacial anomalies
anom_face_oth	Additional	No	text	Other craniofacial anomaly
stoma_type	Additional	No	radio	Type of stoma
stoma_type_oth	Additional	No	text	Other type of stoma
stoma_date_known	Additional	No	radio	Date of stoma placement known?
stoma_date	Additional	No	date_dmy	Date of stoma placement
stoma_comp	Additional	No	checkbox	Complications of stoma formation
stoma_comp_oth	Additional	No	text	Other complication of stoma formation
stoma_close	Additional	No	radio	Stoma closed?
stoma_close_ date_known	Additional	No	radio	Date of stoma closure known?
stoma_close_date	Additional	No	date_dmy	Date of stoma closure
stoma_close_comp	Additional	No	checkbox	Complications of stoma closure
stoma_close_ comp_oth	Additional	No	text	Other complication of stoma closure
stoma2	Additional	No	radio	Secondary stoma
stoma2_type	Additional	No	radio	Type of stoma
stoma2_type_oth	Additional	No	text	Other type of stoma
stoma2_date_known	Additional	No	radio	Date of second stoma placement known?
stoma2_date	Additional	No	date_dmy	Date of placement second stoma

Value Labels	Branching Logic	Logic checks
0, None | 1, Vaginal septum | 2, Vaginal atresia | 3, Mullerian remnants / vagina agenesis | 4, Bicornuate uterus | 5, Ambiguous genitalia | 77, Other | 99, Unknown	[sex] = '1'	
	[anom_genit_f(77)] = '1'	
0, None | 1, Accessory thumbs | 2, Congenital absence of hand(s)/finger(s)/thumb(s) | 3, Radial dysplasia / club hand | 4, Club foot | 5, Polydactyly or syndactyly | 6, Congenital dysplasia of the hip | 77, Other | 99, Unknown	[diagnosis_c]='1'	
	[anom_limb(77)] = '1'	
0, None | 1, Cleft lip | 2, Cleft palate | 3, Hearing impairment | 4, Microtia / anotia | 5, Choanal stenosis / atresia | 6, Vision impairment | 77, Other | 99, Unknown		
	[anom_face(77)] = '1'	
1, Colostomy | 2, Ileostomy | 3, Cecostomy | 77, Other | 99, Unknown	[stoma] = '1'	
	[stoma_type] = '77'	
0, No | 1, Yes	[stoma]='1'	
	[stoma_date_known]='1'	Must be after [dob]
0, No complications | 1, Wound infection | 2, Wound dehiscence | 3, High output | 4, Stoma prolapse | 5, Leakage | 6, Stenosis | 7, Parastomal hernia | 77, Other | 99, Unknown	[stoma] = '1'	
	[stoma_comp(77)] = '1'	
0, No | 1, Yes | 99, Unknown	[stoma] = '1'	
0, No | 1, Yes	[stoma_close]='1'	
	[stoma_close_date_known] = '1'	Must be after [stoma_date]
0, No complications | 1, Wound infection | 2, Wound dehiscence | 3, Anastomotic leak | 4, Anastomotic stenosis | 5, Adhesive obstruction | 77, Other | 99, Unknown	[stoma_close] = '1'	
	[stoma_close_comp(77)] = '1'	
0, No | 1, Yes | 99, Unknown	[stoma] = '1'	
1, Colostomy | 2, Ileostomy | 3, Cecostomy | 77, Other | 99, Unknown	[stoma2] = '1'	
	[stoma2_type] = '77'	
0, No | 1, Yes	[stoma2]='1'	
	[stoma2_date_known] = '1'	Must be after [stoma_date]

Supplementary File 1: Continued

Variable Name	Core /Additional	Required	Variable Type	Variable Label
stoma2_comp	Additional	No	checkbox	Complications of stoma formation
stoma2_comp_oth	Additional	No	text	Other complication of stoma formation
stoma2_close	Additional	No	radio	Stoma closed?
stoma2_close_date_known	Additional	No	radio	Date of second stoma closure known?
stoma2_close_date	Additional	No	date_dmy	Date of closure second stoma
stoma2_close_comp	Additional	No	checkbox	Complications of stoma closure
stoma2_close_comp_oth	Additional	No	text	Other complication of stoma closure
mace	Additional	No	radio	Appendicostomy (Malone or MACE)
reconstruction_comp	Additional	No	checkbox	Complications of reconstructive surgery
reconstruction_comp_oth	Additional	No	text	Other complication of reconstructive surgery
reconstruction_comp_class1	Additional	No	radio	Classification of complication
reconstruction_comp_class2	Additional	No	radio	Classification of complication
reconstruction_comp_class3	Additional	No	radio	Classification of complication
reconstruction_comp_class4	Additional	No	radio	Classification of complication
reconstruction_comp_class5	Additional	No	radio	Classification of complication
reconstruction_comp_class6	Additional	No	radio	Classification of complication

Value Labels	Branching Logic	Logic checks
0, No complications | 1, Wound infection | 2, Wound dehiscence | 3, High output | 4, Stoma prolapse | 5, Leakage | 6, Stenosis | 7, Parastomal hernia | 77, Other | 99, Unknown	[stoma2] = '1'	
	[stoma2_comp(77)] = '1'	
0, No | 1, Yes | 99, Unknown	[stoma2] = '1'	
0, No | 1, Yes	[stoma2_close]='1'	
	[stoma2_close_date_known] = '1'	Must be after [stoma_date]
0, No complications | 1, Wound infection | 2, Wound dehiscence | 3, Anastomotic leak | 4, Anastomotic stenosis | 5, Adhesive obstruction | 77, Other | 99, Unknown	[stoma2_close] = '1'	
	[stoma2_close_comp(77)] = '1'	
0, No | 1, Yes | 99, Unknown		
0, No complications | 1, Wound infection | 2, Wound dehiscence | 3, Rectal / mucosal prolapse | 4, Recurrent recto-urogenital fistula | 5, Mislocated rectum / anus | 6, Anal stricture / stenosis | 7, Remnant of original fistula | 8, Insufficient initial reconstruction requiring redo reconstructive surgery* | 9, Neurogenic bladder or urinary retention | 77, Other | 99, Unknown	[diagnosis_c]='1' AND [reconstruction]='1'	
	[reconstruction_comp(77)] = '1'	
1, No need for pharmacological, surgical, endoscopic, or radiological interventions, besides symptomatic treatment (antiemetics, analgesics, diuretics, electrolytes). | 2, Requiring pharmacological treatment such as antibiotics, blood transfusions, or total parenteral nutrition. | 3, Requiring surgical, endoscopic, or radiologic intervention. | 4, Life-threatening requiring intensive care management. | 5, Patient died.	[reconstruction_comp(1)] = '1'	
Clavien-Dindo options previously listed	[reconstruction_comp(2)] = '1'	
Clavien-Dindo options previously listed	[reconstruction_comp(3)] = '1'	
Clavien-Dindo options previously listed	[reconstruction_comp(4)] = '1'	
Clavien-Dindo options previously listed	[reconstruction_comp(5)] = '1'	
Clavien-Dindo options previously listed	[reconstruction_comp(6)] = '1'	

Supplementary File 1: Continued

Variable Name	Core /Additional	Required	Variable Type	Variable Label
reconstruction_ comp_class7	Additional	No	radio	Classification of complication
redo_reconstruction	Additional	No	checkbox	Type of redo reconstructive surgery
redo_ reconstruction_oth	Additional	No	text	Other type of redo reconstruction
redo_ reconstruction_date	Additional	No	date_dmy	Date of redo reconstructive surgery
reconstruction_ comp_class9	Additional	No	radio	Classification of complication
reconstruction_ comp_class77	Additional	No	radio	Classification of complication
pullthrough_comp	Additional	No	checkbox	Complications pull-through procedure
pullthrough_ comp_oth	Additional	No	text	Other complication of pull-through procedure
pullthrough_ comp_class1	Additional	No	radio	Classification of complication
pullthrough_ comp_class2	Additional	No	radio	Classification of complication
pullthrough_ comp_class3	Additional	No	radio	Classification of complication
pullthrough_ comp_class4	Additional	No	radio	Classification of complication
pullthrough_ comp_class5	Additional	No	radio	Classification of complication
pullthrough_ comp_class6	Additional	No	radio	Classification of complication
pullthrough_ comp_class7	Additional	No	radio	Classification of complication
redo_pullthrough	Additional	No	radio	Type of redo pull-through procedure
redo_pullthrough_ oth	Additional	No	text	Other type of redo pull-through procedure
redo_pullthrough_ approach	Additional	No	radio	Approach redo pull-through procedure
redo_pullthrough_ date	Additional	No	date_dmy	Date redo pull-through procedure
pullthrough_ comp_class9	Additional	No	radio	Classification of complication

Value Labels	Branching Logic	Logic checks
Clavien-Dindo options previously listed	[reconstruction_comp(7)] = '1'	
1, Anoplasty | 2, Mini-PSARP | 3, Sphincter-sparing PSARP | 4, Perineal-sparing PSARP | 5, PSARP | 6, ASARP | 7, LAARP | 8, Open repair | 9, TUM | 10, PSARV(U)P | 77, Other | 99, Unknown	[reconstruction_comp(8)] = '1'	
	[redo_reconstruction(77)]=1	
	[reconstruction_comp(8)]='1'	Must be after [reconstruction_date]
Clavien-Dindo options previously listed	[reconstruction_comp(9)] = '1'	
Clavien-Dindo options previously listed	[reconstruction_comp(77)] = '1'	
0, No complications | 1, Wound infection | 2, Wound dehiscence | 3, Anastomotic leak | 4, Anastomotic stricture | 5, Rectourethral fistula | 6, Rectal/ mucosal prolapse | 7, Intra-abdominal infection | 8, Insufficient initial surgery requiring redo pull-through procedure | 9, Neurogenic bladder or urinary retention | 77, Other | 99, Unknown	[diagnosis_c]='2' AND [pullthrough]='1'	
	[pullthrough_comp(77)] = '1'	
Clavien-Dindo options previously listed	[pullthrough_comp(1)] = '1'	
Clavien-Dindo options previously listed	[pullthrough_comp(2)] = '1'	
Clavien-Dindo options previously listed	[pullthrough_comp(3)] = '1'	
Clavien-Dindo options previously listed	[pullthrough_comp(4)] = '1'	
Clavien-Dindo options previously listed	[pullthrough_comp(5)] = '1'	
Clavien-Dindo options previously listed	[pullthrough_comp(6)] = '1'	
Clavien-Dindo options previously listed	[pullthrough_comp(7)] = '1'	
1, Swenson | 2, Duhamel | 3, Soave | 77, Other | 99, Unknown	[pullthrough_comp(8)] = '1'	
	[redo_pullthrough]='77'	
1, Transanal only | 2, Transanal and laparoscopic assisted | 3, Transanal and laparotomy | 99, Unknown	[pullthrough_comp(8)] = '1'	
	[pullthrough_comp(8)]='1'	Must be after [pullthrough_date]
Clavien-Dindo options previously listed	[pullthrough_comp(9)] = '1'	

Supplementary File 1: Continued

Variable Name	Core /Additional	Required	Variable Type	Variable Label
pullthrough_ comp_class77	Additional	No	radio	Classification of complication
dilat	Additional	No	radio	Dilatations
dilat_pain	Additional	No	radio	Dilatations painful?
stoolreg	Additional	No	checkbox	Stool regulators
stoolreg_oth	Additional	No	text	Other stool regulator
botox	Additional	No	radio	Botox injections
botox_date	Additional	No	date_dmy	Date first Botox injection
rintala1	Additional	No	radio	Ability to hold back defecation
rintala2	Additional	No	radio	Feels or reports the urge to defecate
rintala3	Additional	No	radio	Defecation frequency
rintala3_1	Additional	No	radio	More or less than twice a day
rintala4	Additional	No	radio	Soiling
rintala5	Additional	No	radio	Accidents
rintala6	Additional	No	radio	Constipation
rintala7	Additional	No	radio	Social problems
rintala_score	Additional	Automatic	calc	Rintala bowel function score (1-20)

Value Labels	Branching Logic	Logic checks
Clavien-Dindo options previously listed	[pullthrough_comp(77)] = '1'	
0, No | 1, Yes | 99, Unknown		
1, Never | 2, Rarely | 3, Often | 4, Always | 99, Unknown	[dilat] = '1'	
0, None | 1, Diet | 2, Stool softener | 3, Oral stimulant / contact laxatives | 4, Enemas | 5, Rectal water irrigation systems | 77, Other | 99, Unknown		
	[stoolreg(77)] = '1'	
0, No | 1, Yes | 99, Unknown	[diagnosis_c]='2'	
	[botox]='1'	Must be after [dob]
0, No voluntary control | 1, Weekly problems | 2, Problems less than once a week | 3, Always | 4, Not applicable, patient has a stoma | 99, Unknown		
0, Absent | 1, Uncertain | 2, Most of the time | 3, Always | 4, Not applicable, patient has a stoma | 99, Unknown		
2, Every other day to twice a day | 1, More or less than twice a day | 3, Not applicable, patient has a stoma | 99, Unknown		
0, More than twice a day | 1, Less than three times a week	[rintala3] = '1'	
0, Daily soiling, requires protective aids | 1, Frequent staining, change of underwear often required | 2, Staining less than once a week, no change of underwear required | 3, Never | 4, Not applicable, patient has a stoma | 99, Unknown		
0, Daily, requires protective aids during day and night | 1, Weekly accidents, often requires protective aids | 2, Fewer than once a week | 3, Never | 4, Not applicable, patient has a stoma | 99, Unknown		
0, Manageable with enemas | 1, Manageable with laxatives | 2, Manageable with diet | 3, No constipation | 99, Unknown		
0, Severe social and/or psychic problems | 1, Problems causing restriction in social life | 2, Sometimes (foul odors) | 3, No social problems | 99, Unknown		
[rintala1]+[rintala2]+[rintala3]+[rintala4]+ [rintala5]+[rintala6]+[rintala7]	([rintala1] = '0' or [rintala1] = '1' or [rintala1] = '2' or [rintala1] = '3') and ([rintala2] = '0' or [rintala2] = '1' or [rintala2] = '2' or [rintala2] = '3') and ([rintala3] = '2' or [rintala3] = '1') and ([rintala4] = '0' or [rintala4] = '1' or [rintala4] = '2' or [rintala4] = '3') and ([rintala5] = '0' or [rintala5] = '1' or [rintala5] = '2' or [rintala5] = '3') and ([rintala6] = '0' or [rintala6] = '1' or [rintala6] = '2' or [rintala6] = '3') and ([rintala7] = '0' or [rintala7] = '1' or [rintala7] = '2' or [rintala7] = '3')	

PART 4

General discussion and
future perspectives

CHAPTER 8

General discussion and future perspectives

The aim of this thesis was to investigate the translation from clinical data to clinical care for ARM patients across Europe and Australia in terms of methodological implications and epidemiological comparisons, to ultimately improve health-related outcomes. This was studied in three parts. Initially, we have gained an understanding of the key components of design, development, quality assurance, and maintenance of rare disease patient registries, and their accompanying challenges. Subsequently, real-world data collected in patient registries specifically for ARM patients were extracted and analysed to add to the body of evidence on disease and treatment characteristics of these patients, and to compare these characteristics across Europe and Australia. Lastly, the knowledge and experience gained from analysing patient registries from a methodological perspective, as well as evaluating the data they contain from an epidemiological and clinical point of view, facilitated the initiation of novel patient registries for complex colorectal conditions in Europe, Australia, and New Zealand.

First, the main findings of this thesis will be elaborated upon in light of the objectives and existing literature. Next, methodological considerations of the conducted studies in terms of design, population, and data collection will be discussed. Finally, the clinical implications of the present thesis and perspectives for future research will be addressed, followed by concluding remarks.

Results in light of the objectives

The objectives of this thesis were formulated into research questions and were threefold.

1. What are the key components, main challenges, and quality measurements for the formation, use, and maintenance of patient registries for rare diseases in medical research and improvement of care?

To address the first research question, which explored the key components, main challenges, and quality measurements for the formation, use, and maintenance of patient registries for rare diseases in medical research and improvement of care, a systematic review of the existing literature was conducted (Chapter 2). The review included 37 rare disease patient registries across multiple countries, covering various diseases and their approaches on

design, maintenance, and quality management. The majority of the included studies focused on the design component of the registry. These registries were developed for the purpose of providing subjects for clinical studies, or facilitating research into clinical care, outcomes, epidemiology, and/or natural history of a disease. Whilst nearly all registries described their design, only about half of the studies reported some form of quality management or registry maintenance, such as automated data entry checks, monitoring, funding, or long-term goals. Maintaining and sustaining a rare disease patient registry were also infrequently described, and data quality and continued relevance seemed to be a challenge recognized by only a few. Evidently, there was an imbalance in terms of focus on the various registry components of the included studies, where most attention was aimed towards design, and only few registries recognized the value of maintenance and sustainability. These findings underscore the importance of critical assessments of existing registries and calls for recommendations on how to improve the quality and longevity of these registries, rather than the continued efforts on how to setup new ones. Recommendations published by important working groups in the field support these findings [1-7].

For this reason, a critical assessment of the quality of the pre-existing ARM-Net registry was conducted, with a focus upon the structure and data elements, collected data, and the surgeons' experience of using the registry (Chapter 3). Data capturing structure and data elements were assessed for completeness, consistency, usefulness, accuracy, validity, and comparability. Furthermore, an intra- and inter-user variability study was conducted through monitoring, and a questionnaire was developed to investigate the user experience. Most data elements were dedicated to collecting information on associated anomalies and surgical details. A quarter of the data elements were free text fields, with even a single free text field containing more than 500 different answers submitted. These free text fields resulted in the collection of widely varying data, from further specifications of predefined answer options, to providing additional information that could not be registered anywhere else in the registry. The collected data for the same set of patients showed discrepancies between the users, as well as between separate occasions of registration, especially for data pertaining to associated anomalies, surgical details, one-year follow-up, and family history. This demonstrated that the ARM-Net registry is vulnerable to inter- and intra-variability and emphasized that data capturing methods need to be improved to minimize this variability. Registration of patients was mostly

done by the treating paediatric surgeon, who were generally satisfied with the ARM-Net registry and found it easy to use. This quality assessment showed that the ARM-Net registry collects valuable information, but has outgrown itself from a methodological perspective. Continuously improving data quality of this registry, as well as other rare disease patient registries, is necessary to remain relevant for future research. Fortunately, several other registries have also conducted similar self-assessments to improve the quality of their data [8-10]. A survey sent out to leaders of 40 rare disease registries evaluated what quality criteria should be considered as essential features of rare disease registries, and this study confirmed that long-term sustainability plans, quality checking procedures, and a core data set should be in place [11]. Another study consulted experts in the field of rare diseases and registries, and emphasized the need for well-established quality criteria, self-assessments, and data collection that is interoperable with other registries, such as with common datasets [12]. Therefore, the findings of our systematic review and ARM-Net quality assessment were entirely in line with the existing literature and consensus amongst the registry experts.

2. How can real-world data from patient registries be utilized to describe and compare clinical and surgical characteristics of ARM patients across Europe and Australia?

Data from the ARM patient registries central to this thesis were extracted to explore the second research question. Firstly, focusing on the European part, data from the ARM-Net registry was extracted to create a general overview of patient- and treatment-related characteristics of the included ARM patients over a 10-year period of data collection (Chapter 4). After excluding patients with missing data, 2619 ARM patients registered through 34 European centres could be described in terms of patient demographics, disease characteristics including ARM type according to the Krickenbeck classification [13], associated anomalies, and surgical details including reconstruction type and complications. Sex distribution was equal, the most common ARM type was perineal fistula for both sexes, followed by vestibular fistula and cloaca in females, and rectobulbar and rectoprostatic fistula in males. Two-thirds of patients had one or more associated anomalies, mostly skeletal, cardiac, or renal, which was in concordance with the findings in other European studies [14-17]. Furthermore, most patients underwent a posterior sagittal anorectoplasty (PSARP) procedure at 4

months of age, and patients with associated anomalies were older at time of surgery compared with those without. Reconstruction was followed by anal dilatations, and about half of the patients were treated for constipation at least one year after surgery, in line with existing literature [18-21]. Besides providing a thorough overview of the clinical and surgical characteristics of ARM patients in many European clinical centres, this study also resulted in more in-depth studies on details pertaining to diagnostic and treatment options, and their consequences. Some new findings were that over 40% of patients undergoing anal dilatations experienced pain, and only one-third of all patients were screened for vesico-urethral reflux (VUR). Another interesting finding was that most (88-90%) patients with a perineal fistula or anal stenosis, as well as the majority (66%) of vestibular fistula patients underwent single-staged procedures, without prior defunctioning enterostomies. With the results from this study, we could conclude that real-world data from the ARM-Net patient registry can indeed be utilized to describe clinical and surgical characteristics of European ARM patients and be useful for future research and clinical applications.

After establishing a general overview of ARM patients in Europe from the ARM-Net registry, we investigated the data further to examine a more specific issue: surgical complications in these patients (Chapter 5). Patient-related characteristics such as sex, ARM type, associated anomalies, and age at time of reconstructive surgery were analysed for associations with complications after reconstructive surgery, and if applicable, after enterostomy formation and closure. Furthermore, the role of treatment-related factors in the development of these complications was studied, including reconstruction type and enterostomy formation, enterostomy type, and bowel section. We found that the ARM type recto-bladder neck fistula, the presence of any associated anomalies, and those undergoing a laparoscopic-assisted anorectoplasty (LAARP) procedure were independently associated with an increased risk for post-reconstructive complications. We also discovered that in patients with perineal or vestibular fistula, both ARM types that can be reconstructed primarily or staged (with a prior enterostomy), formation of an enterostomy did not lower the risk for developing post-reconstructive complications, contrary to other studies [22-24]. In the group that did receive an enterostomy, it was found that a divided type had higher complication rates after enterostomy formation than a loop type. This was an interesting finding, as in fact the majority (76%) of all patients with an enterostomy received a divided type,

perhaps related to previous recommendations from the literature. Finally, reconstructive approach per ARM type showed that anterior sagittal anorectoplasty (ASARP) was a risk factor for complications compared with PSARP in perineal, but not vestibular fistula patients, and LAARP was a risk factor in patients with rectourethral fistula. No studies comparing complication rates between ASARP and PSARP approaches in perineal fistula can be found in the current literature. With regards to LAARP versus PSARP, many studies have researched and compared outcomes, and most studies show that LAARP is not inferior and, when considering shortened length of stay and reduced invasiveness, possibly even preferable to PSARP [25-29]. However, a meta-analysis found no significant differences in rates of postoperative rectal prolapse, anal stenosis, anorectal manometry measurements, faecal incontinence scores, and voluntary bowel movements between the two types of reconstructive surgery [30].

To address the latter part of the second research question, data extracted from the RCH Colorectal Database were analysed to describe Australian ARM patients, and to compare them with the ARM-Net patients (Chapter 6). A total of 456 ARM patients had sufficient data in the RCH database. There was a slight, but insignificant, male preponderance, most patients had a perineal fistula, followed by vestibular fistula in females, and rectoprostatic and rectobulbar urethral fistulas in males. Furthermore, nearly 80% of patients had associated anomalies, which were mostly cardiac, skeletal, and renal. These disease characteristics were similar to the ARM-Net patients, although there were more RCH patients with rare ARM types and significantly more RCH patients had associated anomalies, specifically cardiac, renal, and tracheo-oesophageal, even though the same fraction of patients undergo full diagnostic screening in Australia and Europe [14, 31]. In terms of treatment-characteristics, RCH patients more frequently underwent multi-staged procedures with prior defunctioning enterostomies, especially in the perineal and vestibular fistula group. In this same group of ARM types, RCH patients were either reconstructed by cutback procedure or PSARP, where ARM-Net patients would mostly undergo PSARP. In rectourethral and recto-bladder neck fistula patients, RCH patients mostly underwent LAARP, while ARM-Net patients more often underwent PSARP. These different practices and preferences also coincided with distribution of complication rates, as RCH patients had less complications after LAARP, which was performed more frequently, and more complications after PSARP, which was performed less frequently, than in ARM-Net. These findings are

supported by the well-researched volume-outcome ratio, where increased surgeon volume is associated with better patient outcomes, such as less postoperative complications [32-35].

3. How can the knowledge and experience gained facilitate the establishment of new, and the improvement of existing, registries for patients with colorectal conditions?

After the knowledge gained on methodological aspects of rare disease patient registries, and more specifically, the ARM-Net registry, and the experience gained from conducting research with data extracted from ARM registries, new registries could be developed, and the ARM-Net registry improved. Based on the recommendations stemming from the systematic review and the quality assessment, including the user questionnaire, the ARM-Net registry requires expansion of the follow-up period to increase clinical relevance and enhancement of sustainability in the form of securing long-term sources of funding. In addition, maximization of completeness through built-in features of the data capturing platform, such as errors when items are left blank and automatic reminders for follow-up data entry, are needed. As the current capacity of the ARM-Net registry and the ARM-Net Consortium had insufficient subsidies to achieve these goals, collaboration and thereafter fusion with the registry of the European Reference Network for rare urogenital diseases and complex conditions (ERN eUROGEN) was sought. ERN eUROGEN is a virtual network where specialist healthcare providers are connected to share knowledge and expertise on highly specialized surgery for rare urogenital diseases and complex conditions [36]. Part of this network is the ERN eUROGEN patient registry, aiming to gather individual data from patients suffering from rare urogenital diseases and complex conditions, including ARM [37]. Data are collected through 1) the common data set developed by the Joint Research Centre (JRC) of the European Union Rare Diseases Platform [38], 2) a clinical practice snapshot consisting of questions that describe the care pathway of patients in the first year after the start of the treatment (for ARM specifically, the first year after reconstructive surgery), and 3) clinical follow-up forms completed every five years, for 25 years [39]. In this PhD trajectory, the datasets for both the clinical practice snapshot and clinical follow-up form for ARM patients were developed, in collaboration with clinical experts and patient advocacy group representatives, largely based on the existing ARM-Net registry and as part of the improvement plan. Data on patient demographics, disease

characteristics, diagnostic screening, associated anomalies, surgical and medical treatments, complications, functional outcomes, and participation in research were collected [39]. Currently the registry collects data from informed and consented patients with various urogenital and complex conditions treated at 56 healthcare providers in 20 different countries [37]. Data are collected in the online data capturing platform Castor, which also includes features to improve completeness [39].

A second novel registry that was developed with the knowledge gained from investigating the first two research questions, and the experience with building the ERN eUROGEN registry, was the Australia New Zealand Congenital Colorectal Registry (ANZCCoRe) (Chapter 7). This online, international, multi-centre patient registry that will collect clinical data both retrospectively and prospectively of both ARM and Hirschsprung disease (HD) patients. The purpose of the ANZCCoRe is to centralize clinical data of ARM and HD patients in order to provide a source for potential research participants, describe patient and disease characteristics, evaluate health-related outcomes, improve and standardize care, and to create and enhance collaborations between paediatric surgical centres across Australia and New Zealand. The data collection procedures will be similar to the ARM-Net and eUROGEN registries, with a first set of Core Data Elements containing the JRC common data elements, covering patient details, consent diagnosis, care pathway, and surgical treatments. This dataset is limited, should be considered the bare minimum, and is therefore mandatory. The second set of Additional Data Elements should also be collected if available, and contains elements on diagnostic screening, associated anomalies, medical and surgical treatment details, postoperative and stoma-related complications, and functional outcomes. The division of two datasets is aimed to minimize missing data and improve data quality. The data for the ANZCCoRe registry will be collected in the Research Electronic Data Capture (REDCap) platform, after an opt-out patient consent procedure. The registry will be continuously monitored for data quality with the data collection structure of two datasets, features built in REDCap, and periodic self-assessments and user feedback surveys. Although the registry has limitations, such as securing funding for long-term maintenance and collecting selected information; the process of defining, designing, and implementing the registry is a first step in finding the balance between what is ideal and what is feasible. With the ANZCCoRe registry as the

final product in the exploration of the three research questions, it thereby concludes the findings of this thesis.

Methodological issues and considerations

Design

The first study in this thesis, described in Chapter 2, was setup as a systematic review of the existing literature on the design, quality management, and maintenance of rare disease patient registries. However, albeit conducted in a systematic manner, the review did not meet all criteria of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocol [40]. Given the descriptive aim of this review, a single reviewer, rather than the recommended two blinded reviewers, screened and selected studies for inclusion, and the included studies were not subjected to a risk of bias assessment. Nevertheless, since the included studies were qualitative in nature and a meta-analysis was not an objective, the review presented a thorough and well-defined scope of the literature, providing an extensive overview of the collective studies included.

In Chapter 3, the quality assessment of the ARM-Net registry design and data collection was conducted based on several dimensions of data quality described by authors of the European Registration of Rare Disease Patients (EPIRARE) project [41, 42] and various other quality assessments found in the literature [1-4, 6, 8, 10, 43-45], rather than an existing validated format. For this reason, our study is comparable to other studies describing elements of data quality and adds to the existing literature.

The remaining studies in this thesis are all observational in nature. Considering ARM is a rare condition, where study methods such as randomized controlled trials are difficult to conduct, observational cohort studies form an appropriate design to evaluate outcomes, and determine possible associations between risk factors and outcomes [46]. More specifically, the studies in this thesis are conducted using registry data. An important limitation of registry-based studies is that the quality of the studies is highly dependent on the data quality of these registries. Data may have been entered incorrectly or interpreted differently and relations between factors and outcomes may have been influenced by other, unknown, confounding factors. However, as the registries have

been collecting data without predefined research objectives, selection bias is minimized, which is an important strength of using registries as a data source. Furthermore, the data is collected by paediatric surgeons that all conduct frequent consensus meetings together, which minimizes interpretation differences.

Population

Chapters 4, 5 and 6 of this thesis describe ARM patient populations derived from two large patient registries: the European ARM-Net registry and the Australian RCH Colorectal Database. The ARM-Net registry includes patients from multiple centres across 13 different countries in Europe. Although it was originally intended for all centres to register all ARM patients each year, local ethical requirements, including informed consent, were variable between centres and therefore the external validity of the results from this ARM population may not be maximized. However, this was applicable to only a handful of centres, and the ARM-Net registry is deemed to be representative for the ARM population in Europe. With respect to external validity of the RCH Colorectal Database, an important consideration is that this dataset includes only a single centre and may therefore not be representative of all Australian ARM patients. However, the RCH is the main referral centre for ARM in this region and uses an opt-out procedure, rather than informed consent, so the majority of the ARM patients should therefore have been included in the Colorectal Database.

When comparing patient and disease characteristics of the ARM-Net registry to other sources, like the European Surveillance of Congenital Anomalies (EUROCAT) network of registries, ARM-Net patients had higher incidences of associated anomalies, compared with the ARM patients in the 1980-2008 EUROCAT registries [47]. However, the ARM-Net registry included patients born from 2007 onwards, and the higher incidences found may reflect the increasing attention to and practices of diagnostic screening for associated anomalies [14, 31, 48]. Additionally, many associated anomalies that are registered in the ARM-Net registry, such as patent foramen ovale, may not have been registered in EUROCAT, as their data collection is based on the tenth edition of the International Classification of Diseases (ICD-10)[49], and may not reflect all possible associated anomalies. In line with the patients derived from both the ARM-Net registry and the RCH Colorectal Database, other series in the United States, Singapore, North Korea, India, Australia, Italy, The Netherlands, and France have found associated anomalies,

especially skeletal, spinal, cardiac, and genitourinary, to be common among ARM patients [15-17, 50-54]. Although all studies describe associated anomalies to be common, incidences vary widely. One explanation may be that discussion exists on which anomalies should be regarded, and although most agree that anomalies should be congenital and not acquired, severity and clinical consequences of specific anomalies, such as persistent ductus arteriosus or dilated pyelocaliceal system, remain a question. It may be argued that conditions such as these, that may not require management and could resolve with time, should not be included as associated anomalies, though spontaneous resolution is difficult to predict. Furthermore, most studies include the non-random association of vertebral, anorectal, cardiac, tracheo-oesophageal, renal, and limb (VACTERL) anomalies [55]. However, discussion as to which anomalies belong to this association persists [56], and other studies, including studies in the present thesis, also describe anomalies that do not belong to the VACTERL association, such as defects in the neurological, dermatological, gastrointestinal, or urogenital organ systems, which may explain the varying incidences of the umbrella term '*associated anomalies*'. Moreover, although the presence of associated anomalies implies that diagnostic screening has been conducted to detect these, the absence of associated anomalies may not. Therefore, there may be an underestimation of the incidence of associated anomalies, as a number of patients may not have been subjected to diagnostics and could remain undiagnosed.

Other methodological issues to be considered for the study population are loss to follow-up, especially with regards to bowel functioning after reconstructive surgery. Although the RCH Colorectal Database had near-complete data, the ARM-Net registry showed complete data for only 65% of patients at one-year follow-up data collection. Therefore, the results derived from that sub-population may be biased, and skewed to the more severe patients who tend to visit more frequently, which may also explain the higher frequency of patients on constipation regimens in ARM-Net, compared to the RCH cohort.

Data collection

Finally, methodological issues in data collection for the studies in this thesis circle back to data quality in registries. Completeness, accuracy, timeliness, usefulness, and consistency are all important dimensions of data quality that, to varying extents, are compromised in the datasets utilized. For

this reason, the datasets have undergone extensive data cleaning, but this may have resulted in loss of data. An important consideration that should be taken into account, especially for the ARM-Net registry, is the fact that multiple centres enter data, and this may especially have impact on the registration of complications. Surgical outcomes are affected by the surgeon's sex, ethnic background, and level of experience [57-60], and registration of these complications is also largely variable to subjectivity, feelings of shame, peer disapproval, and cultural discrepancies [61, 62]. Therefore, with over 30 centres providing input, the quality of complication registration may be questionable. However, complication rates were similar to the RCH Colorectal Database cohort, where only a handful of surgeons register complications. A final issue with data collection is that different types of persons were responsible for data entry in both the ARM-Net registry and RCH Colorectal Database. In the ARM-Net registry, a lead paediatric surgeon is responsible for data input for their centre, and whilst some may personally enter data of patients they treated, others may delegate this task to more junior surgical residents. Meanwhile, in the RCH Colorectal Database, a research assistant, often of undergraduate university level, is mainly responsible for data input, and may not possess the clinical knowledge required to fully comprehend medical notes to enter all data adequately. Therefore, both data sources have methodological implications with regards to data collection that should be considered when interpreting the results from the studies that utilize them.

Clinical implications

This thesis demonstrates how registries are indeed a good solution for conducting research in rare diseases, when other study methods such as randomized controlled trials are difficult to conduct, due to small sample sizes and scattered data. The results of this thesis have direct implications for clinical care across the areas of diagnostics, treatments, and postoperative care. One important finding with significant clinical implication was that only one-third of all ARM-Net patients were screened for VUR, and subsequently more than a third were diagnosed. In fact, nearly 20% of screened patients were diagnosed with high-grade VUR, which if left untreated, can cause serious renal damage, and ultimately, renal failure [63]. This underscores the necessity of VUR screening and warrants VUR screening in all ARM patients.

Regarding implications for clinical care in terms of treatment, it was found that for perineal fistula patients, reconstruction by anoplasty and mini-PSARP reduced the risk for complications, while ASARP increased this risk. Thus, the ASARP technique should not be the first choice of reconstructive surgery for these patients, and minimally invasive approaches should be preferred. When examining enterostomy formation in ARM types where enterostomy formation remains debatable, such perineal and vestibular fistula, it was found that an enterostomy did not protect from complications after reconstructive surgery. In other words, a primary repair did not increase, nor reduce the risk for developing post-reconstructive complications, compared to a multi-staged repair for perineal or vestibular fistula. Hence, a primary repair should be favoured over a staged repair with prior defunctioning enterostomy in this patient group, considering that enterostomies themselves may lead to complications [64, 65]. Nevertheless, when deciding to opt for a multi-staged repair, a divided enterostomy type showed a higher complication rates than loop type in our study, thus a loop type enterostomy seems the safer option in perineal and vestibular fistula patients. However, in a different ARM type, namely ARM without fistula, a defunctioning enterostomy did have a protective role against post-reconstructive complications, and therefore, these patients should not be subjected to a primary repair.

Another interesting finding was the identification of independent risk factors for post-reconstructive complications in the ARM-Net registry. Patients with a recto-bladder neck fistula, patients with one or more associated anomalies, and patients reconstructed by the LAARP procedure were at an increased risk for developing complications. An important clinical implication from this is that surgeons, physicians, and nurses involved with perioperative care should be especially mindful of complication-prevention within these high-risk groups. Furthermore, in the European rectourethral fistula cohort, the LAARP approach was associated with an increased risk for complications compared to PSARP, but this relationship was not found in the Australian subpopulation of rectourethral fistula patients. On the contrary, more Australian patients had complications after PSARP, which was performed less frequently than LAARP. This suggests that European surgeons were better at the PSARP procedure, which they performed more frequently, and Australian surgeons better at the LAARP approach, their most frequently performed surgery type for this patient group. These geographic variations in surgical approaches and the consequent distribution of complications confirm that surgeons should do what they are

good at, and that practice makes, maybe not perfect, but better. However, it would be most interesting if Australian surgeons would visit European centres and vice versa, so that they may train their skills, and rectourethral fistula patients across both continents, undergoing either type of surgery, have similarly low complication rates.

Post-operatively, a concerning 40% of patients treated with anal dilatations experienced pain. Clinical implications of this important finding might be that the indication and necessity of anal dilatations should be weighed thoroughly in each patient, considering inconclusive evidence regarding efficacy, high parental burden, and the possible trauma inflicted upon the patient [66-69]. Furthermore, at least one year after reconstructive surgery, more than half of the European patients were constipated and treated with diet, stool softeners, laxatives, or enemas. This suggests that other, perhaps more holistic, constipation treatment strategies such as herbal supplements, pre- and probiotics, and even behavioural and osteopathic therapy that have shown to improve outcomes, may be considered to play a selected role in current management [70-72]. Additionally, inspiration and advice should be sought from other centres with better functional outcomes one year post-operatively, such as the RCH in Australia, as only about a fifth of patients was still suffering from constipation.

Lastly, the discussions and new research questions raised by the results of this thesis are implications that not directly, but eventually, may result in improved clinical care. Certain findings might need to be studied further, other findings might stir controversy, and clinical variations should be debated, to ultimately gather evidence and reach a consensus on best practice.

Future perspectives and research

One of the perspectives which may already be observed in the immediate future, is the fusion and implementation of the ARM-Net registry within ERN eUROGEN, which has the funding and sources for ARM-Net to overcome and resolve the identified weaknesses in the quality assessment and analyses, and to continue to exist in a sustainable and relevant manner.

Another important aspect to promote registry longevity in the future is the involvement of patients and patient advocacy groups. Surgeons may

move between centres and countries or may retire, posing a challenge on continuous and consistent data entry. Patients, however, are often very motivated to contribute to research, and are a reliable source of data with regards to functional outcomes, or patient-reported outcome measures (PROMs). Although patients may move as well, they should continuously be able to enter data in a registry that pertain to their personal experiences. Patient participation in registries does not only promote longevity, but also creates a more complete picture of how a certain condition and the relevant procedures and treatments impact a patient's life, which is ultimately the information necessary to measure whether clinical care has improved. Additionally, it helps patients gain insight into their own condition, care pathway, and physician's decision-making.

Furthermore, physicians and researchers should learn to appreciate data and patient care from both a research and clinical perspective. Ideally, research data management should be taught in medical schools, where students learn how to identify which specific data elements are necessary, and how data should be collected to investigate a certain research question. On the other side, researchers should be exposed to a clinical environment, where they may witness decision-making, patient care, and how data may translate to symptoms and outcomes. This should build a bridge between registry developers, clinical researchers, and physicians, and enhance data collection procedures and data quality to be able to conduct better research. Other important roles that should be considered for future research with patient registries are data scientists, as they are specialized in computer science, data analytics, infrastructure, and statistical principles, and should be more involved with the development, maintenance, and quality monitoring of registries. Although data scientists may not have knowledge of the particular disease or condition, they are knowledgeable in data management, which is essentially the core of patient registries, and determines the quality of the research. Additionally, the cumulative workload that physicians and registry managers experience will be less burdensome by using programming code and machine learning-based natural language processing to automatize data extraction from the medical files by converting text into quantifiable code [73, 74], mining and analysis from registry data [75], and even data linkage with other registries [76].

Registries serve as a repository of potential participants that may be recruited for other research projects, without the time-consuming process of

identification and selection of patients. The collected data of these patients may then act as a foundation onto which additionally collected data can be built when investigating a more specific research question in a select patient group. Additionally, registries may give rise to registry randomized clinical trials (RRCTs), randomized trials that are embedded into a registry, utilizing the existing registry infrastructure, reducing costs and time for data collection and improving generalizability and follow-up periods compared to conventional RCTs [77].

Another implication for future research with patient registries is an increased involvement and support from authorities, with the European Commission of the European Union setting an important example. The European Registration of Rare Disease Patients (EPIRARE) project, aimed to address regulatory, ethical, and technical issues associated with the registration of rare disease patients, and the development of various European Reference Networks for rare diseases are all funded by the European Commission [42, 78]. In addition, the European Commission has recently launched another joined action with 18 million euros in funding to improve the diagnosis, treatment, and care of patients with rare diseases throughout the European Union by integrating the ERNs into national health systems [79]. Governmental bodies of other countries, like Australia and New Zealand, should follow the example set by the European Union and support initiatives like the ANZCCoRe, and the development of registries for other rare diseases.

Finally, several new clinical questions for future research have arisen from this thesis. An enterostomy was found to lower the risk for developing complications after reconstructive surgery in patients with ARM without fistula, but not in perineal and vestibular fistula. Although these patient groups differ in anatomy and surgical complexity, an exact explanation remains elusive, and further research is suggested. Another important issue regarding enterostomies, is to investigate whether enterostomy formation was planned as part of a multi-staged procedure, or whether it was to manage complications in patients that have initially undergone primary repairs, which may elucidate new risk factors for post-reconstructive complications. Also, improved data collection methods of both the ARM-Net registry and RCH Colorectal Database on spinal ultrasonography or magnetic resonance imaging (MRI) for diagnostic screening of tethered cord or other spinal anomalies, may result in high quality data to study the role

of ultrasonography as an equally valuable or possibly superior diagnostic method, considering the time consumption, costs, and invasiveness of MRI, as paediatric patients must undergo general anaesthesia [80]. Furthermore, data on sacral ratio of patients in the ARM-Net registry has been collected, but was not used in this thesis, because these data was available from only approximately half of the patients. Still, a suggestion for future research is to select this patient population and study the association between sacral ratio and bowel functioning. These two factors are widely assumed to be closely related and provide opportunities for better outcome prediction for patients, but this relationship is yet to be confirmed, or possibly, disputed. Moreover, with anal dilatations experienced as painful by a large group of patients combined with the questionable efficacy and high patient and parental burden, studies such as RRCTs or comparative retrospective cohort studies should be conducted to validate the use or discontinuation of anal dilatations. Lastly, an exciting and promising perspective for the future that builds on the collaboration that is established by this thesis, is to create exchange programs, where European surgeons travel to Australia to train their skills in enterostomy and LAARP surgery, and Australian surgeons visit European centres to train their PSARP skills, to lower complication rates worldwide.

Concluding remarks

The journey from data to clinical care in the field of rare diseases, particularly ARM in Europe and Australia, viewed from a methodological and epidemiological perspective, shows promising results to improve health-related outcomes. With this thesis, we have established the key components and steps to undertake when developing and maintaining a rare disease registry. Moreover, we have added substantial evidence to the growing understanding of ARM disease characteristics, and importantly, have shed light on the diversity of surgical and medical treatment strategies and have identified risk factors associated with complications after reconstructive surgery. Our findings show that, in the realm of rare diseases, an area where decision-making and clinical practices are mostly based on expertise and consensus, joined efforts may also yield evidence-based approaches. To pursue the ultimate aim of improving clinical care for ARM patients, collaboration, not only between surgeons, centres and countries, but also with patients, epidemiologists, data scientists, developers, and researchers, is absolutely fundamental. The only way forward is together.

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CHAPTER 9

Summaries (EN/NL)
Research Data Management
PhD Portfolio
List of Publications
Curriculum Vitae
Acknowledgement

Summary

Anorectal malformations (ARM) are a group of congenital defects affecting the rectum (the last part of the colon) and the anus. The anus may be in the incorrect location, may be too narrow, or may even be missing, so that the rectum ends in a different organ system, like the vagina, prostate, or bladder. There are various different types of ARM, such as perineal fistula, vestibular fistula, rectourethral fistula, recto-bladder neck fistula or cloacal malformations. These complex conditions require highly specialized reconstructive surgery early in life, often accompanied by a defunctioning enterostomy. Although outcomes have improved over the years, patients continue to be affected throughout their lives both physically, with bowel functioning problems such as faecal incontinence, and psychosocially with impaired mental and sexual health due to feelings of insecurity or embarrassment. Additionally, patients with ARM often present with associated anomalies in other organ systems, such as genital, spinal, vertebral, cardiac, tracheo-oesophageal, renal, or limb anomalies, potentially complicating management and quality of life even more. Evidently, ARM are impactful conditions, and quality research is warranted to improve health-related outcomes. With a prevalence of 1 in 2500 to 5000 live births, ARM are considered a rare disease, and small sample sizes and scattered data signify limited research possibilities.

However, patient registries may provide a solution for rare disease research. Patient registries are organized systems that use observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease or condition. The rise of these large online databases and data protection policies allows for different countries and centres to collaborate and share data to enhance research possibilities for rare diseases, including ARM. Collecting clinical data from different centres with varying practices may provide a rich source to evaluate, standardize, and improve clinical care.

The aim of this thesis is to investigate the translation from clinical data to clinical care for ARM patients across Europe and Australia in terms of methodological implications and epidemiological comparisons, to ultimately improve health-related outcomes. The registries that play significant roles for the ARM patients described in this thesis are the ARM-Network (ARM-Net) registry in Europe, and the Royal Children's Hospital (RCH) Colorectal Database in Australia.

Part 1: Background, key components, and challenges of rare disease patient registries

After a general introduction on the different concepts discussed in this thesis in Chapter 1, Chapter 2 explores the key components, main challenges, and quality measurements for the formation, use, and maintenance of patient registries for rare diseases in medical research. A review of the existing literature was conducted and included a total of 37 patient registries covering various rare diseases in multiple countries. The studies reporting on these registries focused mostly on design, and only few studies reported on data quality, maintenance, or sustainability. These findings underscored the importance of critical assessments and recommendations of improvement for existing registries. For this reason, a quality assessment of the ARM-Net registry was conducted and is elaborated upon in Chapter 3. Structure, data elements, collected data, and surgeons' experience when registering patients were assessed. Completeness, consistency, usefulness, accuracy, validity, and comparability of data elements were evaluated. The ARM-Net registry was found to collect valuable information, but has areas of weakness that should be improved, including vulnerability to missing data, requirement of extensive cleaning, and discrepancies between users. Nevertheless, surgeons found the registry easy to use and were generally satisfied.

Part 2: Clinical and surgical characteristics of ARM patients in Europe and Australia

Data from the ARM-Net registry were extrapolated to provide a general overview of the patient- and treatment-related characteristics of the ARM patients in the registry, which can be found in Chapter 4. The study describes 2619 patients, where the most common ARM type was perineal fistula for both sexes, followed by vestibular fistula and cloaca in females, and rectobulbar and rectoprostatic fistula in males. Two-thirds of patients had one or more associated anomalies, mostly skeletal, cardiac, or renal. Most patients underwent a posterior sagittal anorectoplasty (PSARP) reconstructive procedure at 4 months of age, followed by anal dilatations, which were considered painful in a concerning 42% of patients. About half of the patients were treated for constipation at least one year after surgery.

Chapter 5 delved deeper into the surgical details available in the ARM-Net registry, namely complications. Patient-related and treatment-related factors were analysed for associations with developing complications after reconstructive surgery, and if applicable, after enterostomy

formation and closure. We found that ARM type recto-bladder neck fistula, presence of associated anomalies, and undergoing a laparoscopic-assisted anorectoplasty (LAARP) were risk factors for complications after reconstruction. We also discovered that in patients with perineal or vestibular fistula, both ARM types that can be reconstructed primarily or staged (with a prior enterostomy), formation of an enterostomy did not lower the risk for developing post-reconstructive complications. Regarding enterostomy-related complications, a divided type was a risk factor for complications after formation, as well as placement in a bowel segment other than the descending colon/sigmoid junction, the segment most used. Remarkably, the majority (76%) of the ARM-Net patients with an enterostomy received a divided type.

In Chapter 6, epidemiological comparisons were drawn between patients derived from the Australian RCH Colorectal Database, and the previously described ARM-Net registry patients. It was found that these patient groups were somewhat similar in disease characteristics, although there were more RCH patients with associated anomalies and rare ARM types. However, in terms of management, the groups clearly differed. RCH patients more frequently underwent reconstructive surgery with a prior defunctioning enterostomy, especially in the perineal and vestibular fistula group. Furthermore, in this same group of ARM types as well as in rectourethral and recto-bladder neck fistula patients, types of reconstructive surgery also differed between RCH and ARM-Net. These different practices and preferences also coincided with distribution of complication rates, as RCH patients had less complications after types of surgery performed more frequently, and more complications after surgeries performed less frequently, than in ARM-Net.

Part 3: Innovation through collaboration: novel registries for patients with ARM

Chapter 7 describes the design and objectives of the novel Australia New Zealand Congenital Colorectal Registry (ANZCCoRe), an online, international, multi-centre patient registry that was developed with the knowledge and experience gained from the investigations of this thesis. The ANZCCoRe aims to centralize clinical data to provide a source for potential research participants, describe patient and disease characteristics, evaluate health-related outcomes, improve and standardize care, and to create and enhance collaborations between paediatric surgical centres

across Australia and New Zealand. The registry will be continuously monitored for data quality with the data collection structure of two datasets (a mandatory common dataset and an additional 'if-available' dataset), periodic self-assessments, and user feedback surveys. The ANZCCoRe is the final product of this thesis, and combines the knowledge gained from the literature, the experience gained from the quality assessment, and the clinical relevance of the data collected from the RCH Colorectal Database and the ARM-Net registry.

Part 4: General discussion and future perspectives

In Chapter 8, the findings previously touched upon are discussed in light of the objectives of this thesis and the existing literature. Furthermore, methodological issues and considerations are addressed, and include the limitations of the studies in terms of design, population, and data collection. Briefly, it should be considered that the majority of the studies in this thesis are observational in nature and based on registry data. An important limitation of registry-based studies is that the quality of the studies is highly dependent on the data quality of these registries. In addition, generalizability, or external validity, of the data derived from the European ARM-Net registry and the Australian RCH Colorectal Database may be limited due to variable ethical procedures (including informed consent) per centre. Also, comparability between the ARM-Net registry, with 34 centres from different countries and mostly surgeons entering data, and the RCH Colorectal Database, a single-centre registry with mostly students entering data, should be considered. Nevertheless, the results of the thesis have significant clinical implications. The importance of diagnostic screening for renal anomalies, reviewing the role of a defunctioning enterostomy in perineal and vestibular fistula patients, and mindful consideration of specific patient groups with higher risk for developing complications, are directly applicable to improve clinical care.

Although important questions have been explored and answered throughout the different sections of this thesis, new questions and perspectives for future research have been raised. Increased patient participation in registries, the role of data scientists and machine learning in more efficient and automatic data collection, comparing the value of ultrasonography and magnetic resonance imaging (MRI) in diagnosing tethered cord, and exploring the relationship between sacral ratio and bowel functioning are amongst the exciting new paths to embark on.

Samenvatting

Anorectale malformaties (ARM) zijn een groep aangeboren afwijkingen van het rectum (het laatste deel van de dikke darm) en de anus. De anus kan op de verkeerde plek zitten, te nauw zijn, of zelfs compleet afwezig zijn, waardoor het rectum in een ander orgaan kan eindigen, zoals de prostaat, vagina, of blaas. Er zijn verschillende ARM-types, zoals perineale fistel, vestibulaire fistel, rectourethrale fistel, blaashalsfistel, en cloacale malformatie. Deze complexe aandoeningen vereisen zeer gespecialiseerde reconstructieve chirurgie in het eerste levensjaar, vaak in combinatie met een tijdelijk deviërend stoma. Hoewel de resultaten in de loop der jaren aanzienlijk zijn verbeterd, blijven patiënten hun hele leven zowel fysiek, met darmproblemen zoals incontinentie voor ontlasting, als ook psychosociaal, met mentale en seksuele klachten als onzekerheid en schaamte, last hebben van deze aandoening. Daarnaast hebben patiënten met ARM ook vaak geassocieerde afwijkingen in andere orgaansystemen, zoals van het skelet, hart, slokdarm, nieren of genitaliën, wat de behandelingen en de kwaliteit van leven mogelijk nog ingewikkelder maken. Het is duidelijk dat ARM een impactvolle aandoening is, en onderzoek van goede kwaliteit is nodig om de gezondheidsgerelateerde uitkomsten voor deze patiënten te verbeteren. Met een prevalentie van 1 op de 2500 tot 5000 levendgeborenen wordt ARM als een zeldzame ziekte beschouwd, waarbij onderzoeksmogelijkheden door kleine aantallen en verspreide data beperkt zijn.

Patiëntenregisters kunnen echter een uitkomst bieden voor onderzoek bij zeldzame ziektes, zoals ARM. Patiëntenregisters zijn georganiseerde systemen die observationele onderzoeksmethoden gebruiken om uniforme data te verzamelen. Hiermee kunnen specifieke uitkomsten geëvalueerd worden voor een populatie die wordt gedefinieerd door een bepaalde ziekte of aandoening. De opkomst van deze grote online databases en de procedures om de data te beschermen, maken het voor verschillende landen en centra mogelijk om samen te werken en data te delen, om zo de onderzoeksmogelijkheden te vergroten. Het verzamelen van klinische data uit verschillende centra met verschillende praktijken kan een rijke bron vormen voor het evalueren, standaardiseren en verbeteren van de klinische zorg.

Het doel van dit proefschrift is om de vertaling van klinische data naar klinische zorg voor ARM-patiënten in Europa en Australië te onderzoeken in de vorm van methodologische implicaties en epidemiologische

vergelijkingen, om uiteindelijk de gezondheidsgerelateerde resultaten te verbeteren. De registers die een belangrijke rol spelen voor de ARM-patiënten die in dit proefschrift worden beschreven, zijn het ARM-Network (ARM-Net) register in Europa, en de Royal Children's Hospital (RCH) Colorectal Database in Australië.

Deel 1: Achtergrond, belangrijkste componenten en uitdagingen van patiëntenregisters voor zeldzame ziekten

Na een algemene introductie in Hoofdstuk 1 over de verschillende concepten die in dit proefschrift worden besproken, gaat Hoofdstuk 2 in op de belangrijkste componenten, uitdagingen en kwaliteitsmetingen voor het ontwerp, gebruik en onderhoud van patiëntenregisters voor zeldzame ziekten in medisch onderzoek. Er werd een overzicht van de bestaande literatuur uitgevoerd, waarbij in totaal 37 artikelen met registers over verschillende zeldzame ziektes en uit verschillende landen werden geïncludeerd. De artikelen beschreven vooral het ontwerp van de registers, en slechts enkele artikelen rapporteerden over kwaliteit van data, onderhoud of duurzaamheid. Deze bevindingen onderstreepten het belang van kritische beoordelingen en nieuwe aanbevelingen voor verbetering van bestaande registers. Om deze reden werd een kwaliteitsbeoordeling van het ARM-Net-register uitgevoerd, welke is beschreven Hoofdstuk 3. Structuur, data-elementen, verzamelde data en de ervaring van chirurgen bij het registreren van patiënten werden beoordeeld. Volledigheid, consistentie, bruikbaarheid, nauwkeurigheid, validiteit en vergelijkbaarheid van data-elementen werden geëvalueerd. Het ARM-Net-register bleek waardevolle informatie te verzamelen, maar heeft zwakke punten die moeten worden verbeterd, waaronder de kwetsbaarheid voor ontbrekende data, de noodzaak van uitgebreide data opschoning voor gebruik en discrepanties tussen gebruikers in gecollecteerde data. Niettemin vonden chirurgen het register makkelijk te gebruiken en waren ze over het algemeen tevreden.

Deel 2: Klinische en chirurgische kenmerken van ARM-patiënten in Europa en Australië

Data werden uit het ARM-Net-register gehaald om een algemeen overzicht te geven van de patiënt- en behandelingsgerelateerde kenmerken van de ARM-patiënten in het register. Deze data werden beschreven in Hoofdstuk 4. De studie beschreef 2619 patiënten, waarbij het meest voorkomende ARM-type voor beide geslachten een perineale fistel was, gevolgd door een vestibulaire fistel en cloaca malformatie bij vrouwen, en rectourethrale fistel

bij mannen. Twee derde van de patiënten had één of meer geassocieerde afwijkingen, meestal skelet-, hart- of nieraandoeningen. De meeste patiënten ondergingen op de leeftijd van 4 maanden een reconstructieve procedure middels een posterieure sagittale anorectoplastiek (PSARP), en werden daarna behandeld met anale dilataties, die bij een zorgelijke 42% van de patiënten als pijnlijk werden ervaren. Ongeveer de helft van de patiënten werd een jaar na de operatie nog behandeld voor obstipatie.

In Hoofdstuk 5 werd er dieper ingegaan op de chirurgische details die beschikbaar waren in het ARM-Net register, namelijk complicaties. Patiëntgerelateerde en behandelingsgerelateerde factoren werden geanalyseerd als potentiële risicofactoren voor het ontwikkelen van complicaties na reconstructieve chirurgie en, indien van toepassing, na aanleg en sluiting van een stoma. We ontdekten dat het ARM-type blaashalsfistel, de aanwezigheid van geassocieerde afwijkingen en het ondergaan van een laparoscopisch-geassisteerde anorectale plastiek (LAARP) risicofactoren waren voor complicaties na reconstructie. We vonden ook dat bij patiënten met een perineale of vestibulaire fistel, beide ARM-typen die zowel primair (zonder stoma) als met een deviërend stoma kunnen worden geopereerd, het aanleggen van een stoma niet het risico op het ontwikkelen van post-reconstructieve complicaties verlaagde. Wat betreft stoma-gerelateerde complicaties was een dubbelloops type stoma een risicofactor voor complicaties na aanleg, evenals plaatsing in een ander darmsegment dan de aflopende colon/sigmoïd-overgang, het segment dat normaliter wordt gebruikt. Opmerkelijk is dat de meerderheid (76%) van de ARM-Net-patiënten met een stoma een dubbelloops type had gekregen.

In Hoofdstuk 6 werden epidemiologische vergelijkingen gemaakt tussen patiënten afkomstig uit de Australische RCH Colorectal Database, en de eerder beschreven ARM-Net-register patiënten. Er werd vastgesteld dat deze patiëntengroepen enigszins vergelijkbaar waren wat betreft ziektekenmerken, hoewel er meer RCH-patiënten waren met geassocieerde afwijkingen en zeldzame ARM-typen. Qua behandeling verschilden de groepen echter duidelijk. RCH-patiënten ondergingen vaker reconstructieve chirurgie met een deviërend stoma, vooral in de perineale en vestibulaire fistelgroep. Daarnaast was er in deze groep ook verschil in reconstructieve procedures tussen RCH en ARM-Net, evenals bij patiënten met een rectourethrale en blaashalsfistel. Deze verschillende praktijken en voorkeuren vielen ook samen met de verdeling van de complicaties, waarbij

RCH-patiënten minder complicaties hadden na procedures die vaker werden uitgevoerd, en meer complicaties hadden na procedures die minder vaak werden uitgevoerd, vergeleken met ARM-Net.

Deel 3: Innovatie door samenwerking: nieuwe registers voor patiënten met ARM

Hoofdstuk 7 beschrijft het ontwerp en de doelstellingen van het nieuwe Australia New Zealand Congenital Colorectal Registry (ANZCCoRe), een online, internationaal, multi-centre patiëntenregister dat is ontwikkeld met de kennis en ervaring die is opgedaan tijdens de onderzoeken van dit proefschrift. De ANZCCoRe heeft als doel om klinische data te centraliseren, een bron te bieden waaruit potentiële onderzoeksdeelnemers kunnen worden geselecteerd, patiënt- en ziektekenmerken te beschrijven, gezondheidsgerelateerde resultaten te evalueren, de zorg te verbeteren en te standaardiseren, en om samenwerkingen tussen kinderchirurgische centra in Australië en Nieuw-Zeeland te creëren en te versterken. Het register zal continu worden gemonitord op de kwaliteit van data door middel van de structuur van twee datasets (een verplichte dataset en een aanvullende 'indien beschikbaar' dataset), periodieke zelfbeoordelingen en enquêtes over gebruikersfeedback. De ANZCCoRe is het eindproduct van dit proefschrift en combineert de kennis uit de literatuur, de ervaring die is opgedaan met de kwaliteitsbeoordeling en de klinische relevantie van het analyseren van de verzamelde data uit de RCH Colorectal Database en het ARM-Net register.

Deel 4: Algemene discussie en toekomstperspectieven

In Hoofdstuk 8 worden de eerdergenoemde bevindingen besproken in het licht van de doelstellingen van dit proefschrift en de bestaande literatuur. Bovendien komen methodologische kwesties en overwegingen aan de orde, waaronder de beperkingen van de onderzoeken op het gebied van opzet, populatie en datacollectie. Het is belangrijk in acht te nemen dat het merendeel van de onderzoeken in dit proefschrift observationeel van aard en gebaseerd zijn op data uit registers. Een belangrijke beperking van de op registers gebaseerde onderzoeken is dat de kwaliteit van de onderzoeken sterk afhankelijk is van de datakwaliteit van deze registers. Bovendien kan de generaliseerbaarheid, of externe validiteit, van de data afkomstig van het Europese ARM-Net-register en de Australische RCH Colorectal Database beperkt zijn als gevolg van verschillende ethische procedures (zoals informed consent) per centrum. Ook moet er rekening

worden gehouden met de vergelijkbaarheid tussen het ARM-Net-register, met 34 centra uit verschillende landen en voornamelijk chirurgen die data invoeren, en de RCH Colorectal Database, een register uit één centrum waarin voornamelijk studenten data invoeren. Niettemin hebben de resultaten van het proefschrift aanzienlijke klinische implicaties. Het belang van diagnostische screening op nierafwijkingen, het beoordelen van de rol van een deviërend stoma bij perineale en vestibulaire fistelpatiënten, en gepaste oplettendheid bij specifieke patiëntengroepen met een hoger risico op het ontwikkelen van complicaties, zijn direct toepasbaar om de klinische zorg te verbeteren.

Hoewel belangrijke vragen zijn onderzocht en beantwoord in de verschillende delen van dit proefschrift, zijn er nieuwe vragen en perspectieven voor toekomstig onderzoek naar voren gekomen. Meer aandacht voor datacollectie vanuit patiënten zelf, de rol van data wetenschappers en machine learning bij het vergemakkelijken en automatiseren van datacollectie, het vergelijken van de waarde van echografie en magnetic resonance imaging (MRI) bij het diagnosticeren van tethered cord, en het onderzoeken van de relatie tussen de sacrale ratio en het functioneren van de darmen behoren tot fascinerende nieuwe wegen om te bewandelen.

Research Data Management

Ethics and privacy

This thesis is based on the results of research involving human participants, which were conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct and Radboudumc policy. Furthermore, a Research Collaboration Agreement was signed between the Murdoch Children's Research Institute (MCRI) and the Radboudumc for the access, use, and protection of clinical data belonging to each party. Chapters 3, 4, 5, and 6 are based on results of existing pseudonymized clinical data from registries involving paediatric patients. The local Institutional Review Board of Radboudumc-Amalia Children's Hospital waived the requirement for informed consent for patient inclusion in the ARM-Net registry, as all data were pseudonymously extracted through patient medical files. Other European centres did require informed consent for including patients into the registry and have done so according to the local legal and ethical regulations. Solely the treating paediatric surgeons had code-breaking documents to re-identify pseudonymized data of their own patients. No informed consent was required for extraction of the existing pseudonymized data from the ARM-Net registry. Informed consent was also not required for data extraction from the The Royal Children's Hospital (RCH) Colorectal Database, as the patients whose data are in the registries had already been informed and had consented for their data to be used for research purposes. No new data was collected from patients. For the comparison of clinical data in Chapter 6, ethical approval was sought and approved from the RCH Human Research and Ethics Committee (HREC/93070/RCHM-2023). Chapter 3 included new data collected from surgeons who were part of the Anorectal Malformations Network (ARM-Net) through questionnaires. Surgeons consented to participation and their data were anonymized. Chapter 7 was conducted through a collaboration between MCRI and the European Reference Network (ERN) eUROGEN, and a Memorandum of Understanding was signed between the parties.

Data collection and storage

Collection, processing, analysing and publishing of data used for Chapter 6 was collaborated upon with the MCRI. MCRI provided the RCH Colorectal Database and the Radboudumc together with the ARM-Net Steering Group allowed for access to the ARM-Net registry. However, no transfer of data between the two institutes took place, as agreed upon in the Research

Collaboration Agreement. Both institutes were involved in the processing and analysis of their respective databases. Data were converged from the ARM-Net registry server to OpenRefine (v.3.4.1; 437dc4d, Google Inc. and contributors) and IBM SPSS Statistics (v.29, SPSS Inc., Chicago, Illinois, USA) for data cleaning and analysis purposes. Questionnaire data was collected in REDCap (v12.5.16, Vanderbilt University, Nashville, Tennessee, USA), and both the questionnaire and RCH Colorectal Database data were converged from REDCap into IBM SPSS Statistics (v.29, SPSS Inc., Chicago, Illinois, USA) for analysis. ARM-Net data was stored on the secured Radboudumc network server, and Radboudumc research team members had access only. RCH Colorectal Database and questionnaire data was stored on the secured MCRI network server. Access to the private network server was restricted to members of the research team only. RCH Colorectal data were only accessible to members of the MCRI research team and were stored on the MCRI network server, and access to the project folder on the MCRI network was restricted to members of the MCRI research team only. Publishing of project data was shared among the institutes.

Availability of data

All studies in this thesis are published open access. The data from Chapters 3, 4, 5, and 6 were existing data not owned by the authors and will therefore not be published. The data used may be available upon request via the ARM-Net registry and the RCH Colorectal Database. The pseudonymized dataset from Chapter 3 is available and can be found as ARM-NET UQ in the Radboud Data Repository (RDR) with restricted access and will be archived for 15 years. The conditions for access to the data are described in the DUA RUMC-RA-DUA-1.0.

Research data management was in compliance with the Radboudumc policy and approved by the Data Stewardship team of the Radboudumc Technology Centre.

PhD Portfolio

Department: Paediatric Surgery
PhD period: 01/04/2021 – 01/06/2024
PhD Supervisors: Prof. I. de Blaauw, Prof. S.K. King
PhD Co-supervisors: Dr I.A.L.M. van Rooij, Dr M. Trajanovska

Training activities	**Hours**
Courses	
European Joint Programme for Rare Diseases – European Reference Networks Workshop: Clinical research with databases (2021)	10.00
European Joint Programme for Rare Diseases - International Summer School on Rare Disease Registries and FAIRification of data (2021)	24.00
RIHS - Introduction course for PhD candidates (2022)	15.00
Investigator & Site Personnel Good Clinical Practice (2023)	6.00
Radboudumc - Scientific integrity (2024)	20.00
Meet the Expert "How to prepare for your PhD defense" (2024)	1.00
Seminars	0.50
Amalia Research Meeting (2024) - oral	
Conferences	
Pacific Association of Paediatric Surgeons – Annual Scientific Meeting (2021) - oral	40.00
Best of the Best – Paediatric Surgery 2022 Conference (2022) - oral	4.00
European Paediatric Surgeons' Association Annual Conference (2022) - poster (2x)	40.00
Anorectal Malformation Network Annual Meeting (2022) - oral	8.00
European Paediatric Surgeons' Association Annual Conference (2023) - oral	40.00
European Paediatric Colorectal and Pelvic Reconstruction Annual Meeting (2023) - oral	24.00
Nederlandse Vereniging van Kinderchirurgie Wetenschappelijke Vergadering (2024) - oral	8.00
Total	240.50

List of Publications

1. Hageman IC, van Overveld FJ, Rijkers GT. Visions of the Hereafter: Releasing the Brakes of the Immune System by Checkpoint Inhibition Immunotherapy. *Int J Immunol Immunother*. 2017;4(1):026.
2. Hageman IC, Tien MY, Trajanovska M, Palmer GM, Corlette SJ, King SK. Perioperative opioid use in paediatric inguinal hernia patients: A systematic review and retrospective audit of practice. *J Pediatr Surg*. 2022;57(7):1249-1257.
3. Hageman IC, van Rooij IALM, de Blaauw I, Trajanovska M, King, SK. A systematic overview of rare disease patient registries: challenges in design, quality management, and maintenance. *Orphanet J Rare Dis*. 2023;18(1):106
4. Hageman IC, van der Steeg HJJ, Jenetzky E, Trajanovska M, King SK, de Blaauw I, et al. A Quality Assessment of the ARM-Net Registry Design and Data Collection. *J Pediatr Surg*. 2023;58:1921–1928.
5. Hageman IC, Midrio P, van der Steeg HJJ, Jenetzky E, Iacobelli BD, Morandi A, et al. The European Anorectal Malformation Network (ARM-Net) patient registry: 10-year review of clinical and surgical characteristics. *Br J Surg*. 2024;111(2).
6. Hageman IC, Trajanovska M, van Rooij IALM, de Blaauw I, King SK. The Australia New Zealand Congenital Colorectal Registry (ANZCCoRe): driving innovation through collaboration. *J Pediatr Surg Open*. 2024;6(2):100121
7. Hageman IC, Trajanovska M, King SK, van der Steeg HJJ, Morandi A, Amerstorfer EE, et al. Anorectal Malformation Patients in Australia and Europe: Different Location, Same Problem? A Retrospective Comparative Registry-based Study. *J Pediatr Surg*. 2024:161879.
8. van der Zanden LFM, Hageman IC, Boormans L, Oomen L, Witjes WPJ. Chapter 6 - Development of the ERN eUROGEN registry. In: Feitz WFJ, Tidman J, editors. Rare and Complex Urology: Academic Press; 2024:49-57.

Curriculum Vitae

I was born on May 2nd, 1995, in Essen, Germany, and moved to Curaçao, together with my parents and my sister, when I was five years old. I graduated from the International School of Curaçao with an International Baccalaureate diploma and an extra course, necessary to be eligible for medical school, in 2013.

Moving from a small island to an even smaller town, I followed the pre-medical track of the Liberal Arts and Sciences program at University College Roosevelt in Middelburg, The Netherlands. Graduating cum laude in 2016 and determined to become a doctor, I pursued the Selective Utrecht Medical Master at Utrecht University. This program, aimed to train students to become clinicians as well as researchers, enabled me to conduct my final research project at the Murdoch Children's Research Institute (MCRI) in Australia. I spent 10 months in Melbourne researching the use of opioids before, during and after surgery in paediatric patients at The Royal Children's Hospital, under the supervision of prof. Sebastian King, paediatric surgeon.

Upon my return in Utrecht, I completed my medical studies with a senior internship at the department of plastic surgery at the Utrecht University Medical Centre, and the department of general surgery at the Diakonessenhuis hospital. Inspired by research, reconstructive surgery, international academics and travelling, I embarked on a quest to combine all. Prof. King introduced me to prof. Ivo de Blaauw, a paediatric surgeon at the Radboudumc, and together they familiarised me with the highly specialised and multifaceted care for anorectal malformation patients.

A fruitful collaboration was born, and a PhD with both prof. King and prof. de Blaauw as my supervisors allowed me to research anorectal malformation patients and the different treatment strategies across Europe and Australia, and the challenges and methods to conduct research for rare conditions. Furthermore, I met many enthusiastic researchers and surgeons with a passion to improve the care for these patients, travelled to multiple cities for conferences, and returned once again to my old desk at MCRI in Melbourne. I returned to The Netherlands in 2023 and finished my PhD mid 2024.

Since June 2024, I have been working as a doctor (not in training) at the surgery department of the OLVG hospital in Amsterdam.

Acknowledgement

Although it is my name that's on the cover of this thesis, I have could not have completed it without the help and support of others, to whom I would like to express my gratitude.

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After a not so successful meeting with a stiff, suit-and-tie professor, meeting Ivo was like a breath of fresh air, and I immediately understood why Bazz and Ivo had hit it off at one of the many colorectal conferences somewhere across the world. Ivo, dankjewel voor jouw vertrouwen vanaf het eerste moment dat wij elkaar met videobellen ontmoetten. Je liet me direct op mijn gemak voelen en hebt mij geholpen dit toch wat ongebruikelijke en niet al te makkelijke plan van mij tot werkelijkheid te maken. Dankjewel voor je flexibiliteit in de turbulentie van de wereld op dat moment, en je begrip voor mijn reislustige (onrustige? of eigenzinnige) aard. Iris, jouw kritische, betrokken supervisie moest ik aan wennen, maar ik kan met zekerheid zeggen dat ik je daar enorm dankbaar om ben, ik heb ontzettend veel van je geleerd en jij hebt mij laten ontwikkelen tot een echte onderzoeker. Dankjewel voor je ondersteuning en het meedenken in lastige tijden, voor een veilig gevoel als mijn vertrouwenspersoon. Ook wil ik jou en Ivo bedanken dat jullie mij geïntroduceerd hebben aan ARM-Net, inclusief Herjan natuurlijk. Herjan, dankjewel voor de fijne samenwerking, ondanks dat wij in heel verschillende fases van onze levens zitten, zaten wij met

onze PhD toch in hetzelfde schuitje. Ik ben trots op ons gezamenlijk artikel, één van de beste hoofdstukken van mijn proefschrift! Ik kijk er naar uit om straks jouw promotie mee te maken.

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Iris heeft mij ook geïntroduceerd aan eUROGEN, en in het bijzonder aan Loes, haar kantoormaatje. Bedankt Loes en Wout, voor het aanbieden van een passende en flexibele baan tijdens mijn promotietraject! Jullie hebben mij geholpen om mijn huur te betalen (toen ik ervoor koos om in zo'n beetje de duurste stad te gaan wonen) en introduceerden mij aan veel inspirerende mensen. Ik ben trots dat ik de eUROGEN registry heb kunnen helpen ontwikkelen. Dankjewel Loes, dat jij mij hebt geleerd om op een andere manier naar registries te kijken. Dit heeft een belangrijke bijdrage geleverd aan de analyse van de ARM-Net registry, en de ontwikkeling van de ANZCCoRe.

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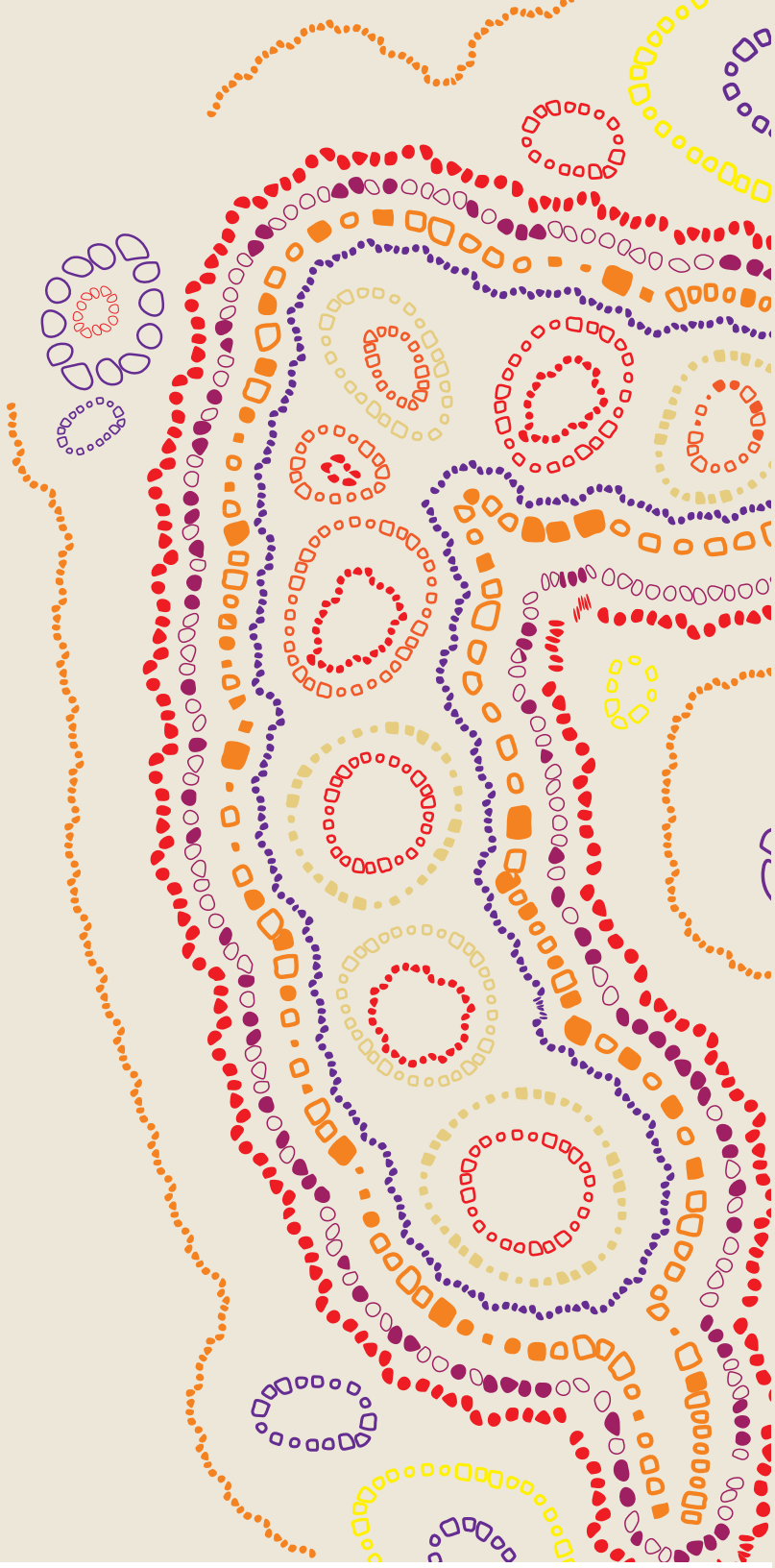

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