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INVITED REVIEW

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The I-CAH Registry: A platform for international collaboration for improving knowledge and clinical care in congenital adrenal hyperplasia

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Abstract

To provide an overview of the I-CAH Registry. Following the successful roll-out of the I-DSD Registry in the 2000s, it was felt that there was a need for a registry for congenital adrenal hyperplasia (CAH) and this was launched in 2014 as a dedicated module within the original registry. In addition to supporting and promoting research, the I-CAH Registry acts as an international tool for benchmarking of clinical care and it does this through the collection of standardised data for specific projects. Surveillance of novel therapies in the field of CAH can also be achieved via global collaborations. Its robust governance ensures adherence to the international standards for rare disease registries. Rare disease registries such as the I-CAH Registry are important tools for all stakeholders involved in the care of people with CAH.

KEYWORDS
CAH, DSD, network, rare disease, registry

1 | INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterised by a life-long deficiency of adrenal steroidogenic enzymes that lead to cortisol deficiency. In the commonest form of CAH due to 21-hydroxylase deficiency, cortisol deficiency is accompanied by a variable extent of mineralocorticoid deficiency and androgen excess.[1] Glucocorticoid (GC) replacement therapy in these patients aims to replace cortisol and prevent the corticotrophin (ACTH)-driven androgen excess. However, replacement therapy to normalise androgen levels can lead to excess GC exposure with associated growth concerns, obesity, hypertension, osteoporosis and an adverse cardiometabolic profile in adulthood.[2] Although CAH is the commonest cause of primary adrenal insufficiency in childhood, it is still a very rare condition, with an incidence of one in 15,000.[3] Continuing advances in our understanding of the condition coupled with recent therapeutic innovations will provide a wider range of management options. Within this context, multicentre collaboration through the collection of standardised data is going to prove vital in the assessment of novel therapies that will be introduced for CAH. This review describes the development of the I-CAH Registry and some of its activities.

2 | PURPOSE OF RARE DISEASE REGISTRIES

The aetiology, diagnosis, management and consequences of rare conditions can be collected in a specific manner in rare disease registries, enabling research to be performed on standardised data sets. This research can be aimed at improving patient care and to form the basis of best practice guidelines.[4] Rare disease registries can contribute to health care surveillance and allow the monitoring of new drugs and interventions in clinical care. These registries can also allow patients to become involved, which not only improves the quality of the data but also provides a springboard to the development of patient-reported outcomes. In addition, rare disease registries can support the development of new therapies and are often used by the industry for natural history data or for supporting postapproval surveillance of drugs.

3 | DEVELOPMENT OF THE I-CAH REGISTRY

The I-CAH Registry was preceded by the I-DSD Registry which was developed following the Consensus Workshop[5] on disorders/differences of sex development (DSD) hosted by the European Society of Paediatric Endocrinology (ESPE) and the Lawson Wilkins Paediatric Endocrine Society of North America in 2005. The idea of developing a registry was conceived due to a lack of an international database that collected standardised information on such a rare group of conditions. The initial registry was called the ESPE DSD Registry and was developed with a small project grant from ESPE in 2006 with partners from Glasgow, Cambridge, Luebeck, Pisa and Rotterdam. This registry evolved into the EuroDSD Registry, funded by EUFP7, between 2008 and 2011 and then into the International DSD (I-DSD) Registry funded by the UK Medical Research Council, between 2011 and 2017. During this period, the I-DSD Registry also played a vital role in other projects such as the Cooperation of Science and Technology (COST) Action DSDnet, which facilitated consultations with patients, researchers and health care professionals and led to user acceptability testing as well as guidance on the data sets that should be collected routinely. From 2018 onward, the registry has sustained itself through supporting research activity and symposia and has received funding from these sources as well as the industry. The development of the I-CAH Registry as an addition to the I-DSD Registry occurred in 2014 when it became evident that a registry would also be helpful to share data on rare enzymatic conditions that overlap with DSD but are under the wider umbrella of CAH and that the I-DSD module was not suitable for capturing some fields of CAH. This was also the time when the UK CaHASE consortium was highlighting the need for a standardised collection of outcomes in people with CAH.[6,7] Following consultation with a number of experts in the field of CAH, including those who were involved in the CaHASE consortium in the United Kingdom, the new CAH module was developed to collect information across the age span. Following their initial development, both the I-DSD and I-CAH Registries have undergone subsequent revisions, with the latest one being performed in 2020. In 2022, the Registry launched another module, I-TS, to collect standardised data on Turner Syndrome.

4 | GOVERNANCE OF THE I-CAH REGISTRY

The governance of the I-CAH Registry has been facilitated by the joint I-DSD/I-CAH/I-TS Steering Committee[8] which is composed of clinical and nonclinical experts, including patient representatives and representatives from professional societies. These representatives provide oversight of the Registry and are responsible for the overall direction of the initiative. The Steering Committee meets at regular intervals and oversees the activities of the Data Access Committee, the Care Quality Improvement Committee (CQIC) as well as the recently formed, Learning and Training Committee.[9–11] The Steering Committee also guides the Project Management Group which is based at the Office for Rare Conditions in Glasgow. Members of the Steering Committee and Data Access Committee work on a fixed-term basis and the day-to-day management of the registry including data governance is undertaken by the Project Management Group.[12] The Registry itself does not include any identifying information on patients directly, apart from date of birth. Instead, every participant is assigned a unique identifier generated automatically following entry of a case. This identifier needs to be retained and associated with local records at the contributing partner site. A record in the registry may also have a local identifier which is stored by the clinical partner, physically or electronically, separately to the registry. The unique identifier is used to track all information about the participant in the registry. The only way for research partners to find out more about the participants in the registry is to contact the clinical partners whose details are linked to the unique identifier.[13] Registry participants or their guardians are able to access their record on the registry by asking their primary clinician. They can also access their record electronically by providing their email to the clinician. Consent from patients is mandatory to insert the patient's data and there is an additional optional consent if the patient can be contacted for research purposes and sharing their data.

5 | A DESCRIPTION OF THE CONTENTS OF THE I-CAH REGISTRY

At last review (February 2023), there were 2690 cases of CAH from 92 centres in 32 countries (Figure 1). Among those, there were 18 centres from the United Kingdom and Ireland (Figure 2). Of the 2690 cases, 2410 (90%) were due to 21-hydroxylase deficiency, 90 (3.5%) were due to 11-β hydroxylase deficiency and the remainder included cases of 3β-hydroxylase deficiency ($n = 41$, 1.5%) and cytochrome P450 oxidoreductase deficiency ($n = 13$, 0.5%). The median year of birth of these cases was 2005 (10th centile: 1984, 90th centile: 2016) and the age of

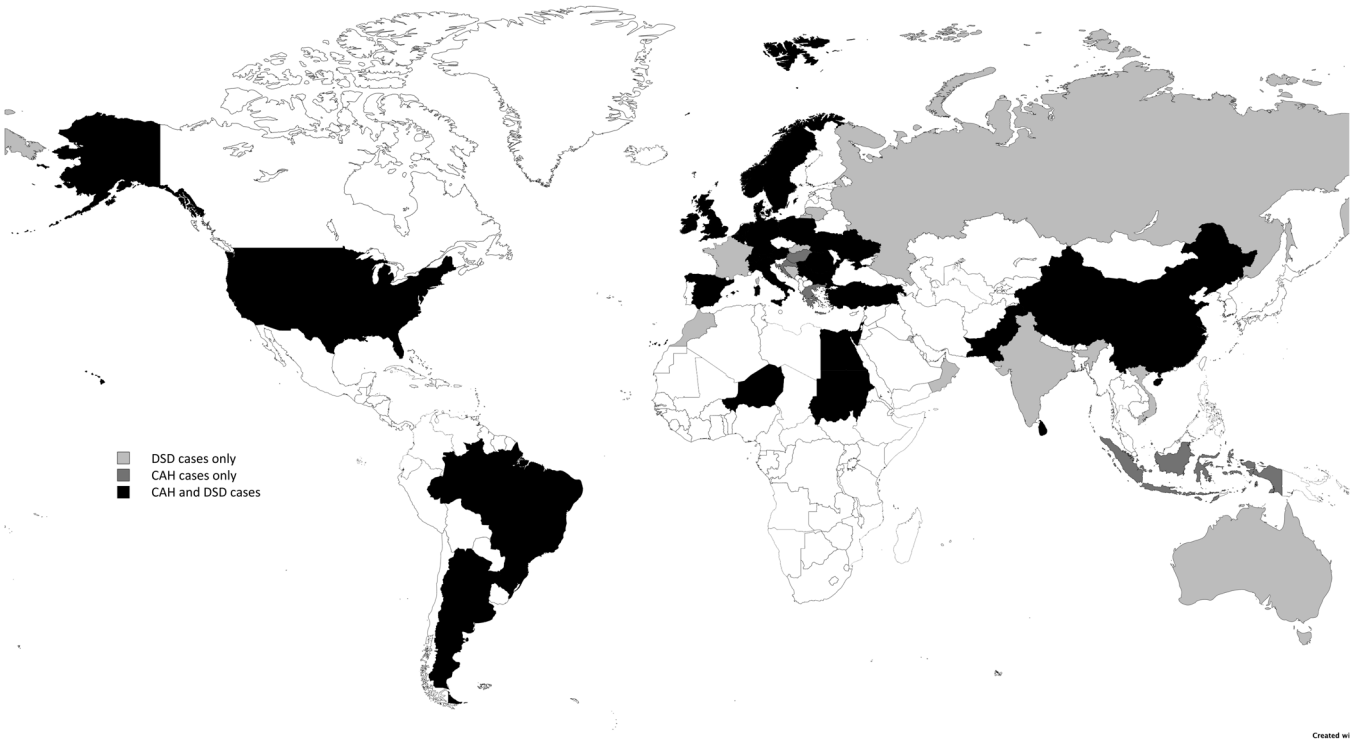

FIGURE 1 World map showing countries that have centres that report both congenital adrenal hyperplasia (CAH) and DSD cases (black), countries with centres that only report on CAH (dark grey) and countries that report DSD cases only (light grey).

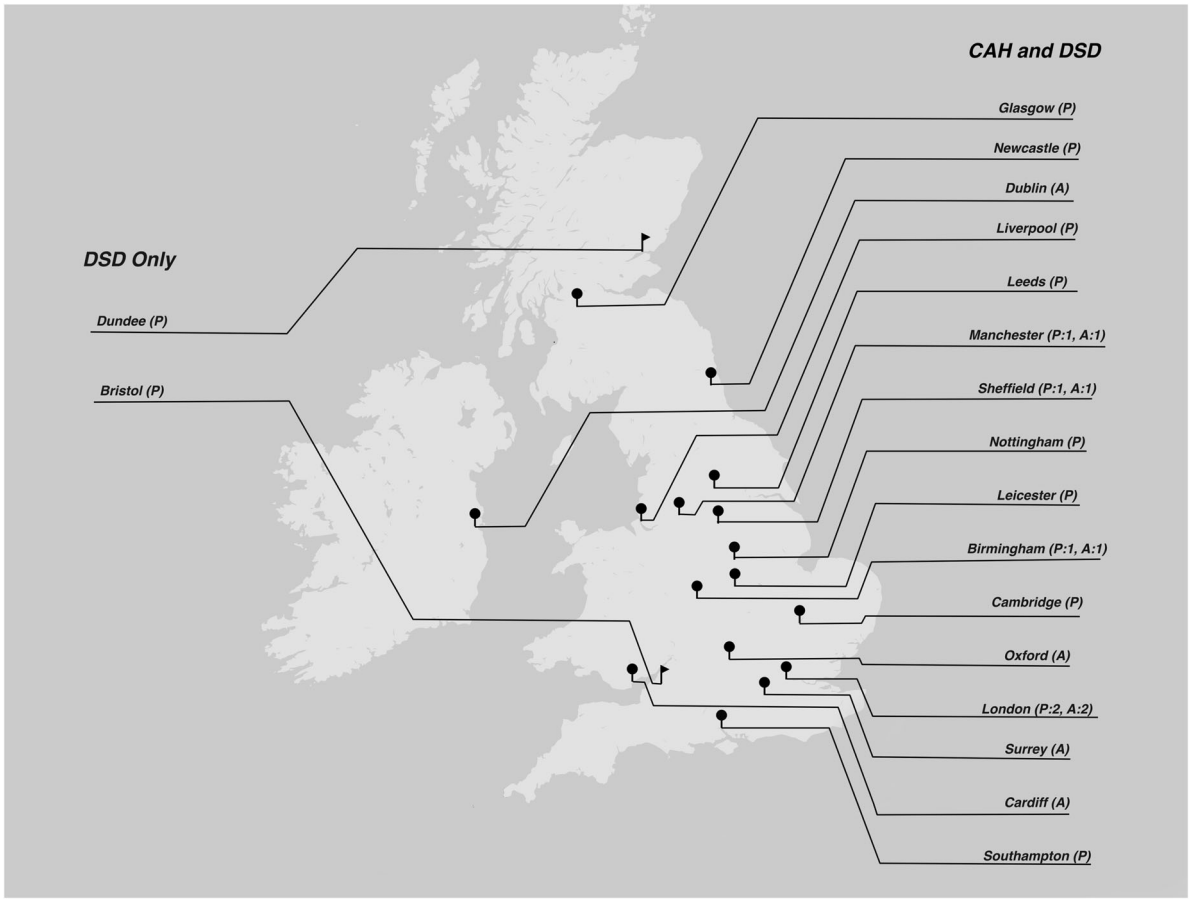

FIGURE 2 Map showing centres in the United Kingdom and Ireland that report both congenital adrenal hyperplasia (CAH) and DSD cases (circle) or only DSD (flag). Paediatric centres are indicated as P and adult centres as A. In cases of multiple adult or paediatric centres in any city, the number of centres is indicated in the parenthesis.

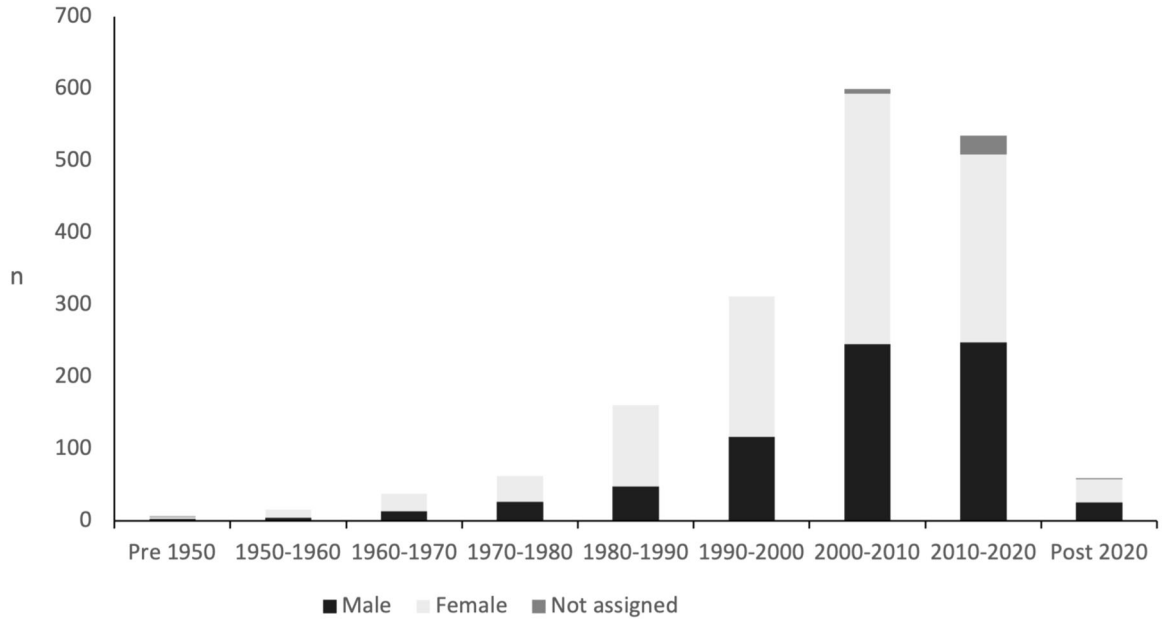

FIGURE 3 Number of patients registered in I-CAH and their sex assignment at birth according to year of birth decade.

presentation ranged from birth to 59 years. The sex assignment at birth of the patients registered in I-CAH according to year of birth decade is shown in Figure 3. More details on the data fields that the I-CAH Registry collects can be found in Table 1. The Registry has also undergone a quality assessment, which confirmed it has most of the elements that are considered vital features of a rare disease registry.[14] This quality assessment which was performed in 2017 showed that the data had a high degree of validity, consistency and accuracy and the completeness was maximal for specific conditions such as CAH. In terms of research output, the external validity was strong but the wide variety of cases needed further review. The internal validity of data was condition-specific and was also highest for conditions such as CAH. However, over time, many more cases of these conditions have been entered into the Registry and there is a constant need for quality checks. While having mandatory fields and validation functions help with ensuring data accuracy and completeness, the best exercise for quality control is the performance of studies as that allows reporting centres to complete relavant fields and also allows the research team to check the validity of the data. This also has a positive knock-on effect on subsequent studies that use the same data for other purposes. It is possible that the Registry may move to an active quality assurance programme but as this is resource intensive, it may need to be focussed on specific studies where the investigators require this extra level of assurance. All data that are used in studies and lead to a publication are returned by the investigators to the Registry team in case they need to be reused or rechecked at a later date for the purpose of research integrity. A new aspect of the registry is that it started providing the reporting centres with feedback on the quality of data they input through a centre-specific report, as seen here: https://sdmregistries.org/wp-content/uploads/2022/02/cah-benchmarking-report-template.pdf.

6 | DATA GOVERNANCE

The I-CAH Registry complies with the Findable, Accessible, Interoperable and Reusable principles for rare diseases registries which means that it adheres to international standards of the regarding quality, access control and structure as well as information sharing.[15] In terms of data ownership, the Office for Rare Conditions at the University of Glasgow is the owner of the I-CAH Registry platform, however, the patient participant or the legal guardian is the primary owner of the data and the institution of the clinician who has entered the data is the owner of the aggregated data of that patient participant. Information sharing between organisations adheres to the principles of the UK Data Protection Act (2018), the EU General Data Protection Regulation (GDPR) (2018), the UK GDPR (2021) and the 'Conditions of Ethical Approval' as stipulated by the West of Scotland Research Ethics Service.

7 | DATA ACCESS FOR RESEARCH

The I-CAH Registry has supported various research projects which have been published in peer-reviewed journals and disseminated in international conferences. There have been over 20 original data publications so far and 25 projects have been approved up to February 2023. Details of all projects are available on the research section of the website: https://sdmregistries.org/ongoing-studies/. Prospective investigators are advised to read the Data Access Policy and the information pack available and have to liaise with the Registries Project Management Team for advice on the study process and design before submitting their data request application for a new

TABLE 1 The data fields in the I-CAH Registry.

Core data	CAH first assessment	CAH longitudinal assessment (cont.)
Core information	Prenatal diagnosis	
Centre/country/register ID[a]	Prenatal dexamethasone therapy	
Consent for registry[b]	Age at first presentation	
Can be contacted for research purposes	Prader stage at first presentation	
Data can be shared for research purposes	Salt-wasting crisis at presentation	Diabetes mellitus type 1/diabetes mellitus type 2/hypertension/thyroid disease/osteoporosis/stroke/cardiovascular disease/smoking/anaemia/depression/anxiety/psychosis/other mental health problems
Core information	Adrenal crisis at first presentation	
Local ID	Father's height (cm)	Bone health and maturation
Country of usual residence	Mother's height (cm)	Date of test
Patient follow-up status	Mid parental height (cm)[a]	Bone age result (years)
First contact with centre		Bone mineral density (date and result)
	CAH longitudinal assessment	
Birth	Anthropometry	Puberty male
Date of birth[b]	Weight/height	Genital stage
Sex at birth[b]	Waist circumference/hip circumference (cm)	Pubic hair stage
Country at birth	BMI[a]	Axillary hair stage
Birth weight/birth length	BSA[a]	Testicular volume
Gestational age	Cushingoid	Puberty female
Birth head circumference	Virilisation	Breast stage
Details of the condition	Blood pressure	Pubic hair stage
Current gender[b]	Systolic/diastolic (mmHg)	Axillary hair stage
Karyotype[b]	Current medication	Menarche
Disorder type[b]	Daily adherence to therapy	Age at menarche
Type of CAH[b]	Has treatment changed since last visit[b]	Regular menstrual cycle
Date of condition onset	Why was the treatment changed	Adverse events: sick day episodes
Date of diagnosis	Glucocorticoids (dose, time)	Oral steroids
Associated conditions	Fludrocortisone (dose, frequency)	HC injection
Diagnostic biochemistry	Current GC replacement	Adrenal crisis
Diagnostic genetics	Salt replacement	Emergency management/predisposing condition/number of days
Participation in other Registries	Oestrogen/testosterone/GnRH analogues	Labs (type/result/value)
Family history	Antihypertensives/antidiabetic/antidepressants/other drugs	Sodium/potassium/renin/plasma renin activity/17-OHP/ACTH/Cortisol/DHEAS/androstenedione/total testosterone/dihydrotestosterone/11-deoxycortisol/LH/FSH/oestradiol/progesterone/inhibin-B/haemoglobin/haematocrit/SHBG/glucose/urine steroids by GCMS
Parental consanguinity	Comorbid condition and surgery	
History of impaired fertility	EUA	
History of a similar condition	Surgery	
Mother's height/father's height	Other congenital abnormalities	

Abbreviations: ACTH, corticotrophin; BMI, body mass index; BSA, body surface area; CAH, congenital adrenal hyperplasia; DHEAS, dehydroepiandrosterone; EUA, examination under anaesthetic; FSH, follicle stimulating hormone; GC, glucocorticoid; GCMS, gas chromatography mass spectometry; GnRH, gonadotrophin-releasing hormone; HC, hydrocortisone; LH, luteinizing hormone; OHP, 17-hydroxyprogesterone; SHBG, sex hormone binding globulin.

[a]Automatic fields.

[b]Mandatory fields.

study. Data requests can be submitted at any time but are reviewed by the Data Access Committee twice per year. Once a study is launched, the Registries Project Management Team identify the centres with the eligible cases and approach them with the details of the study to ask if they would like to participate in the study. If they agree to participate, they are provided with clear instructions on which fields to complete in the Registry. The progress of the study is monitored through regular meetings with the study team and annual reports to the Data Access Committee. On average, the time lag between a project being launched and a publication in a peer-reviewed journal is approximately 2 years. The publications arising from the real-world data in the registry cover a wide variety of research questions related to CAH. These include understanding the variability of adverse events related to CAH and setting international standards that will promote benchmarking of care.[16,17] The project that examined the acute adrenal insufficiency-related adverse events in children has been embraced by the CAH community and it is now repeated every 3 years as a care quality improvement (CQI) exercise. The treatment and therapy monitoring of CAH has also been reported in other publications.[16,18–22] Notably, the study by Pofi et al. used the Registry to study the clinical utility of measurements such as renin when performed in the real-world setting for managing CAH.[22] In the field of CAH, the recent study by Neumann et al. which reported that the growth outcomes of children with salt-wasting CAH who had early salt supplementation were similar to those who had no salt supplementation illustrated the utility of the Registry for performing pragmatic real-world clinical trials which could then be followed up with more rigorously designed clinical trials, if necessary.[19] Another example of the Registry's utility is in understanding current practice and helping to design new studies. Recently, Righi et al. studied the current practice of cardiometabolic monitoring in adults with CAH.[21] The results showed, at a centre level, that most centres that were surveyed routinely performed a more comprehensive assessment than recommended in the CAH practice guidelines[3]; furthermore, the study also noted that, at a patient level, those with specific morbidities such as hypertension were treated with a wide range of antihypertensives, thus calling for further studies comparing the effectiveness of different hypertensives.

8 | LEARNING AND TRAINING

The Registry has been supporting learning and training by organising an I-DSD Symposium every 2 years. The Symposium was held in Luebeck in 2004, 2006 and 2011 and since the development of the registry, it has been held biennially in Glasgow in 2013, Ghent in 2015, Copenhagen in 2017 and Sao Paulo in 2019. In 2021, the meeting was held virtually followed by Bern in 2022. The remote meeting in 2021 was very successful and for that reason, it was decided to hold a virtual meeting in the gap year between the biennial face-to-face meetings. The remote meetings have taken the shape of user group meetings where the focus has increasingly shifted to an update on studies that are being performed in I-DSD/I-CAH/I-TS. The first postgraduate course in DSD took place in Bern in 2022 before the scientific meeting with the second one to happen in June 2024 in Stockholm.

9 | ENGAGEMENT WITH STAKEHOLDERS

The Project Management Team offers monthly drop-in sessions where people interested in the Registry can join and ask questions. An I-DSD Training Workshop is also held before the biennial I-DSD Symposium and is included as part of the postgraduate course in DSD. This comprises interactive small group sessions that are aimed at improving clinical and research skills, covering a wide range of topics, from how to use the I-DSD/I-CAH/I-TS Registries to how to perform bioinformatic analysis and interpret endocrine tests. More information regarding this can be found at https://sdmregistries.org/9th-i-dsd-symposium-2022-programme/. In the past, I-DSD also participated in the EU COST Action DSDnet and organised joint patient and professional workshops.[23,24] This COST Action also determined the priorities of further research.[25]

10 | QUALITY IMPROVEMENT PROJECTS

One of the aims of the I-CAH Registry is to contribute to the improvement of care of patients with CAH and other rare conditions. The CQIC provides oversight and direction to the CQI registry projects and guides the development of other related activities. A number of quality improvement projects have arisen from the real-world data of the registry and these include the I-CAH acute adrenal insufficiency project where the aim is to provide a clinical benchmark to the participating centres.[16] All centres that participate in this project receive a regular individualised report which provides information on the quality of the data in the I-CAH Registry and the quality of care, as reflected by sick day episodes and adrenal crises rates. A new CQI project on the management of CAH in infancy utilises the I-CAH Registry to investigate the variation in clinical management of infants with 21-hydroxylase deficiency CAH in the first 3 months of life (https://sdmregistries.org/cah-in-infancy-project/). A recently completed project has shown that adults with CAH can suffer from multiple cardiometabolic and bone comorbidities and are often exposed to a wide range of therapies to manage these comorbidities.[21] Further exploration of such real-world data will not only allow a better understanding of the natural history of the CAH complications but may also provide real-world evidence for therapeutic rationalisation.

11 | FUTURE DIRECTIONS

The I-CAH Registry is a rare disease registry that can serve several roles with regard to all aspects (pathophysiology, aetiology, epidemiology, management and surveillance) of the condition. It can be used as a clinical tool of benchmarking clinical outcomes to improve the quality of care of patients with CAH. A survey in 2014 revealed

that some of the burdens of participating in a registry included lack of workforce, lack of time and difficulties in consenting patients.[23] Acknowledging these efforts, the I-DSD/I-CAH/I-TS Registries have started to offer a research participation award to centres that provide the largest number of cases and are involved as co-authors in the largest number of papers. It is hoped that these forms of recognition will also generate interest among the wider network.

In the future, the Registry intends to collect patient-report outcomes directly from patients on quality of life, adverse events and endocrine management. There is also a need to explore other methods of data flow between different databases where there are matching fields and where the appropriate data governance approvals exist. The experience with I-DSD, I-CAH and I-TS has shown that one platform can be used for collecting detailed routinely collected information on multiple conditions that affect sex development and maturation and over time, this will allow the Registry to consider developing modules for conditions such as hypogoandotrophic hypogonadism or Klinefelter Syndrome. Last, while supporting research will continue to remain a major focus of the Registry, it is also clear that reporting centres welcome projects that have a CQI component. Previous consultation with stakeholders that was performed through an EU COST Action, DSDnet and that included patients, parents, scientists and health care providers in the field of DSD and CAH, highlighted a number of priorities[26] and the long-term mission of the Registry is to ensure that the projects that are performed match the priorities of these stakeholders.

12 | CONCLUSIONS

The I-CAH Registry constitutes an international platform with the main aim of improving the knowledge of CAH among clinicians, patients and researchers. It achieves this through a robust governance structure that supports a data-driven network that pursues research and quality improvement projects.

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