THE ASSESSMENT OF OUTCOMES IN RARE ENDOCRINE CONDITIONS

Dr Salma Rashid Ali
BMedSci (Hons), MBChB, MRCPCH, PgCert (Merit)

Submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy

College of Medical, Veterinary and Life Sciences
University of Glasgow

Abstract

Endocrine pathology in children may manifest in infancy or adolescence by either a deficiency or excess of one or more hormones, with a range of metabolic sequelae. Almost all conditions are associated with long-term morbidity, societal and healthcare implications. Optimal patient management requires an awareness of these conditions and specialist expertise within a multidisciplinary setting. However, due to the rarity of some of these conditions, the end result is often substantial variation in patient care.

The focus of this thesis was on the exchange of real-world data and knowledge for rare endocrine conditions through local, regional and international networks including detailed disease registries (I-DSD, I-CAH), facilitating the development of clinical benchmarks, with the overall aim of improving patient care.

Rare disease registries enable pooling of data for research and surveillance and are regarded as essential for networks such as the European Reference Network for Rare Endocrine Conditions (Endo-ERN). It was unclear how many cross-border registries exist for rare endocrine conditions and the extent of involvement of expert centres with these registries. This was investigated by a database search to identify cross-border international endocrine registries. Concurrently, an international survey of 71 Endo-ERN reference centres was performed. Of the 42 conditions with orphacodes covered within Endo-ERN, international registries existed for 33 (78%), with Endo-ERN expert centres aware of 11 (41%) of these registries. Despite awareness of these registries, some experts did not use the registries. The I-DSD/I-CAH registries were amongst the most commonly identified and used registries, thus, providing an ideal platform for the study of core clinical outcomes at an international level.

With the recent global expansion in the number of rare disease registries, it was imperative that a process for quality evaluation of registries was developed, in order to ensure the sustainability of registries in the longer term and the exchange of high quality data for investigating core clinical outcomes. Rare disease registry leaders representing 40 registries were surveyed to ascertain the level of consensus regarding the quality criteria that should be considered essential features of a disease registry. Over 95% of leaders indicated that

essential quality criteria should include establishment of a good governance system, procedures for checking data quality and construction of an IT infrastructure complying with Findable, Accessible, Interoperable and Reusable (FAIR) principles. Rare endocrine registries, identified in the database search and Endo-ERN mapping exercise, performed self-evaluation of these quality criteria, with the methodology applicable to all rare disease registries.

The initial mapping exercise of Endo-ERN reference centres highlighted the need to improve the awareness and signposting of existing registries through a simple platform that can be used by the whole endocrine community. Standardised data collection on the conditions covered within Endo-ERN as well as information on the incidence, prevalence and natural history of rare endocrine conditions is also important for networks such as Endo-ERN. Web-based methods of capturing presentation of rare endocrine conditions were explored and the European Registries for Rare Endocrine Conditions (EuRRECa) was developed to achieve this objective. Analysis of data entered by clinicians via the e-Reporting platform (e-REC) within EuRRECa revealed increasing popularity of the platform since its inception in 2018, with a total of 9,715 and 4,243 new cases reported in adults and children, respectively, over this time. Conditions affecting sex development were most commonly encountered in children (40% of all reported conditions), with a median of 0.6 (range 0, 38) cases reported per centre per month. The EuRRECa platform has the potential to provide the infrastructure for future research activity, with the overall aim of improving patient care.

Disorders or differences of sex development (DSD) and congenital adrenal hyperplasia (CAH) were used as models of rare endocrine conditions where there was a paucity of real-world data in large, multi-centre, international cohorts relating to prevalence, morbidity (acute adrenal insufficiency (AI) related adverse events in CAH) and psychosocial outcomes in children with DSD. Provision of optimum healthcare for infants with atypical genitalia requires a clear understanding of the occurrence of this condition. Thus, to study the presentation of DSD at a national level in Scotland, a nationwide study of the prevalence and management of atypical genitalia was performed. A prospective, electronic survey of clinicians within managed clinical networks in Scotland with cross verification of cases at cytogenetic labs was undertaken over a 6 year

period. The birth prevalence of term infants with atypical genitalia was 1:1,881 and 1 in 3,318 required specialist input over the first 3 months of life. The birth prevalence of a case of atypical genitalia where sex assignment was delayed beyond birth was estimated at 1 in 11,097 births. The study provided new clinical benchmarks for comparing and improving the delivery of care in centres that manage these rare conditions.

Another study investigated the occurrence of sick day episodes (SDE) and adrenal crises (AC), factors which may influence these outcomes and inter-centre variability for these events in children. Data from 518 children from 34 centres in 18 countries showed that infectious illness was the most frequent precipitating event, reported in 1,105 (72%) of SDE. Interestingly, children from high income countries had significantly higher rates of SDE compared with children from low-middle incomes, 0.75 (0, 13.3) vs 0.11 (0, 12.0), $p<0.001$. Risk factors for SDE were younger age (1-4 years), adolescence (15-18y), male sex and normal or lower doses of glucocorticoids, all $p<0.05$. These new clinical benchmarks were used to produce centre-specific reports for I-CAH centres. As these data were increasingly used as benchmarks in CAH care, a need for further research to improve and standardise the definition and management of SDE and AC was highlighted. An international survey of 56 expert centres revealed a good level of consensus on specific aspects that may lead to greater benchmarking of care. Over 60% of centres were in agreement regarding the criteria that should be considered essential for diagnosis of an adrenal crisis and these criteria included hypotension, hyponatraemia, hyperkalaemia and clinical improvement following parenteral glucocorticoids.

To date, there is a paucity of information on health-related quality of life (QoL) outcomes in parents and children with DSD and a lack of instruments available for evaluating these outcomes. The final part of the project explored the use of parent reported outcome (PRO) measures in clinical practice as part of routine healthcare evaluation in parents of children with DSD and other endocrine conditions. The study found that parents of children with DSD had greater concerns regarding their child’s future than parents of children with other endocrine conditions. To further investigate the psychosocial concerns amongst parents of children with DSD and reduce respondent burden, short

questionnaires that could be used in routine outpatient settings were developed using previous QoL-DSD data from 132 patients that had completed validated long questionnaires. Initial validation of the short questionnaire was performed in 24 patients. Results showed good agreement between the short and the long questionnaires in 11 out of 12 (92%) scales on the parent self-report and 4 out of 5 (80%) scales on the parent proxy-report. Following further psychometric validation in larger cohort, these QoL tools may be used to establish national and international benchmarks for psychosocial outcomes in parents and young children with DSD and CAH.

The final chapter (Chapter 10) summarises my work for this thesis, highlighting its strengths and limitations as well as providing perspectives into the future directions of this work.

Table of Contents

List of Tables

List of Figures

Publications relating to this thesis

Ali SR, Bryce J, Krone NP, Claahsen-van der Grinten HL, Ahmed SF. Current management of acute adrenal insufficiency related adverse events in children- results of an international survey of specialist centres. *Horm Res Paediatr*. 2022;95:363-373.

Ali SR, Bryce J, Kodra Y, Taruscio D, Persani L, Ahmed SF. The quality evaluation of rare disease registries- an assessment of the essential features of a disease registry. *Int J Environ Res Public Health*. 2021;18:11968.

Ali SR, Bryce J, Smythe C, Hytiris M, Priego AL, Appelman-Dijkstra NM, Ahmed SF. Supporting international networks through platforms for standardised data collection – the European Registries for Rare Endocrine Conditions (EuRRECa) model. *Endocrine*. 2021;71:555-560.

Ali SR, Bryce J, Haghpanahan H, Lewsey JD, Tan L, Atapattu N, Birkebaek NH, Blankenstein O, Neumann U, Balsamo A, Ortolano R, Bonfig W, Claahsen-van der Grinten HL, Cools M, Costa E, Darendeliler F, Poyrazoglu S, Elsedfy H, Finken MJJ, Fluck CE, Gevers E, Korbonits M, Guaragna-Filho G, Guran T, Guven A, Hannema SE, Higham C, Hughes IA, Tadokoro-Cuccaro R, Thankamony A, Iotova V, Krone NP, Krone R, Lichiardopol C, Luczay A, Mendonca BB, Bachega T, Miranda MC, Milenkovic T, Mohnike K, Nordenstrom A, Einaudi S, van der Kamp H, Vieites A, de Vries L, Ross RJM, Ahmed SF. Real world estimates of adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2021;106:e192-203.

Ali SR, Bryce J, Tan LE, Hiort O, Pereira AM, van den Akker ELT, Appelman-Dijkstra NM, Bertherat J, Cools M, Dekkers OM, Kodra Y, Persani L, Smyth A, Smythe C, Taruscio D, Ahmed SF. The EuRRECa project as a model for data access and governance policies for rare disease registries that collect clinical outcomes. *Int J Environ Res Public Health*. 2020;17:8743.

Ali SR, Macqueen Z, Gardner M, Sandberg DE, Kyriakou A, Mason A, Shaikh MG, Wong SC, Ahmed SF. Parent reported outcomes in young children with disorders/differences of sex development. *Int J Pediatr Endocrinol*. 2020;2020:3.

Ali SR, Lucas-Herald A, Bryce J, Ahmed SF. The role of international databases in understanding the aetiology & consequences of differences/disorders of sex development. *Int J Mol Sci*. 2019;20:4405.

Ali SR, Bryce J, Cools M, Korbonits M, Beun JG, Taruscio D, Danne T, Dattani M, Dekkers OM, Linglart A, Netchine I, Nordenstrom A, Patocs A, Persani L, Reisch N, Smyth A, Sumnik Z, Visser WE, Hiort O, Pereira AM, Ahmed SF. The current landscape of European registries for rare endocrine conditions. *Eur J Endocrinol*. 2019;180:89-98.

Nowotny HF, Bryce J, Ali SR, Giordano R, Baronio F, Chifu I, Tschaidse L, Cools M, Van den Akker ELT, Falhammar H, Appelman-Dijkstra NM, Persani L, Beccuti G, Ross IL, Grozinsky-Glasberg S, Pereira AM, Husebye ES, Hahner S, Ahmed SF, Reisch N. Outcome of COVID-19 infections in patients with adrenal insufficiency and excess. *Endocr Connect*. 2023. Epub ahead of print.

Lawrence N, Bacila I, Dawson J, Bryce J, Ali SR, van den Akker ELT, Bachega TASS, Baronio F, Birkebaek NH, Bonfig W, van der Grinten HC, Costa EC, de Vries L, Elsedfy H, Güven A, Hannema S, Iotova V, van der Kamp HJ, Clemente M, Lichiardopol CR, Milenkovic T, Neumann U, Nordenström A, Poyrazoğlu Ş, Probst-Scheidegger U, De Sanctis L, Tadokoro-Cuccaro R, Thankamony A, Vieites A, Yavaş Z, Ahmed SF, Krone N. Analysis of therapy monitoring in the international congenital adrenal hyperplasia registry. *Clin Endocrinol (Oxf)*. 2022;97:551-561.

Lucas-Herald A, Ali SR, McMillan C, Rodie ME, McMillan M, Bryce J, Ahmed SF. I-DSD – The first 10 years. *Horm Res Paediatrics*. 2022. Epub ahead of print.

Rodie ME, Ali SR, Jayasena A, Alenazi NR, McMillan M, Cox K, Cassim SM, Henderson S, McGowan R, Ahmed SF. A nationwide study of the prevalence & initial management of atypical genitalia in the newborn in Scotland. *Sex Dev*. 2021;5:1-8.

Bacila I, Freeman N, Daniel E, Šandrk M, Bryce J, Ali SR, Abali Z, Atapattu N, Bachega T, Balsamo A, Birkebaek N, Blankenstein O, Bonfig W, Cools M, Costa E, Darendeliler F, Einaudi S, Elsedfy H, Finken MJJ, Claahsen-van der Grinten HL, Guran T, Guven A, Hannema S, Higham C, Iotova V, van der Kamp H, Korbonits

M, Krone R, Lichiardopol C, Luczay A, Mendonca B, Milenkovic T, Miranda MC, Mohnike K, Ortolano R, Thankamony A, Tomlinson JW, Vieites A, de Vries L, Ahmed SF, Ross RJM, Krone NP. International practice of corticosteroid replacement in congenital adrenal hyperplasia: data from the I-CAH registry. *Eur J Endocrinol*. 2021;184:553-563.

Pofi R, Prete A, Thornton-Jones V, Bryce J, Ali SR, Ahmed SF, Köhler B, Balsamo A, Acerini C, Cannuccia A, Guven A, Guran T, Darendeliler F, Higham C, Bonfig W, De Vries L, Mendonca B, Iotova V, Korbonits M, Krone NP, Krone R, Lenzi A, Arlt W, Ross RJ, Isidori AM and Tomlinson JW. Plasma renin measurements are unrelated to mineralocorticoid replacement dose in patients with primary adrenal insufficiency. *J Clin Endocrinol Metab*. 2020;105(1):dgz055.

Flück C, Nordenström A, Ahmed SF, Ali SR, Berra M, Hall J, Köhler B, Pasterski V, Robeva R, Schweizer K, Springer A, Westerveld P, Hiort O, Cools M, On behalf of COST Action BM1303 working group. Standardised data collection for clinical follow-up and assessment of outcomes in differences of sex development (DSD): Recommendations from the COST Action DSDnet. *Eur J Endocrinol*. 2019;181:545-564.

Ahmed SF, Ali SR. Section 7. Sex development. Chapter 7.2.2. Disorders of Sex Development. In: Wass J, Arlt W, Semple R (Eds) *Oxford Textbook of Endocrinology and Diabetes* 3e; Oxford University Press; 2019.

Oral presentations at conferences

Ali SR, Gardner M, Xin Y, O'Toole S, Flett M, Lee B, Steven M, Sandberg DE, Ahmed SF. Development and validation of a short version of the quality of life DSD questionnaire (QoL-DSD) for parents of young children with disorders/differences of sex development. ENDO, 11-14th June 2022, Atlanta, USA.

Ali SR, Bryce J, Priego AL, Cools M, Danne T, Katugampola H, Dekkers OM, Hiort O, Linglart A, Netchine I, Nordenström A, Patócs A, Pereira AM, Persani L, Reisch N, Smyth A, Šumnik Z, Taruscio D, Visser WE, Appelman-Dijkstra NM, Ahmed SF. European registries for rare endocrine conditions (EuRRECa): Results from the e-reporting platform for rare conditions (e-REC). European Registries for Rare Endocrine Conditions Annual Meeting, 14th February 2022, held online due to Covid-19 pandemic.

Ali SR, Bryce J, Kodra Y, Taruscio D, Persani L, Ahmed SF. Quality assurance and evaluation. European Registries for Rare Endocrine Conditions Annual Meeting, 14th February 2022, held online due to Covid-19 pandemic.

Ali SR, Bryce J, Krone NP, Claahsen-van der Grinten HL, Ahmed SF. Current management of acute adrenal insufficiency related adverse events in children-results of an international survey of specialist centres. International Disorders of Sex Development Annual Symposium, Congenital Adrenal Hyperplasia Workshop, 8-9th July 2021, held online due to Covid-19 pandemic.

Ali SR, Bryce J, McMillan M, O'Connell M, Davies JH, Ahmed SF. Using the I-DSD/I-CAH/I-TS registries for quality improvement in clinical care. International Disorders of Sex Development Annual Symposium, Quality Improvement Workshop, 8-9th July 2021, held online due to Covid-19 pandemic.

Ali SR, Bryce J, Kodra Y, Taruscio D, Persani L, Ahmed SF. Developing a list of affiliate registries. European Registries for Rare Endocrine Conditions Annual Meeting, 12th April 2021, held online due to Covid-19 pandemic.

Ali SR, Bryce J, Priego AL, Cools M, Danne T, Katugampola H, Dekkers OM, Hiort O, Linglart A, Netchine I, Nordenström A, Patócs A, Pereira AM, Persani L, Reisch N, Smyth A, Šumnik Z, Taruscio D, Visser WE, Appelman-Dijkstra NM, Ahmed SF. European registries for rare endocrine conditions (EuRRECa): Results from the e-reporting platform for rare conditions (e-REC). European Registries for Rare Endocrine Conditions Annual Meeting, 12th April 2021, held online due to Covid-19 pandemic.

Ali SR, Bryce J, Haghpanahan H, Lewsey JD, Tan L, Atapattu N, Birkebaek NH, Blankenstein O, Neumann U, Balsamo A, Ortolano R, Bonfig W, Claahsen-van der Grinten HL, Cools M, Costa E, Darendeliler F, Poyrazoglu S, Elsedfy H, Finken MJJ, Fluck CE, Gevers E, Korbonits M, Guaragna-Filho G, Guran T, Guven A, Hannema SE, Higham C, Hughes IA, Tadokoro-Cuccaro R, Thankamony A, Iotova V, Krone NP, Krone R, Lichiardopol C, Luczay A, Mendonca BB, Bachega T, Miranda MC, Milenkovic T, Mohnike K, Nordenstrom A, Einaudi S, van der Kamp H, Vieites A, de Vries L, Ross RJM, Ahmed SF. Real world estimates of adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia. Glasgow Clinical Academic Research Annual Meeting, 21st October 2020, held online due to Covid-19 pandemic.

Ali SR, Bryce J, Haghpanahan H, Lewsey JD, Tan L, Atapattu N, Birkebaek NH, Blankenstein O, Neumann U, Balsamo A, Ortolano R, Bonfig W, Claahsen-van der Grinten HL, Cools M, Costa E, Darendeliler F, Poyrazoglu S, Elsedfy H, Finken MJJ, Fluck CE, Gevers E, Korbonits M, Guaragna-Filho G, Guran T, Guven A, Hannema SE, Higham C, Hughes IA, Tadokoro-Cuccaro R, Thankamony A, Iotova V, Krone NP, Krone R, Lichiardopol C, Luczay A, Mendonca BB, Bachega T, Miranda MC, Milenkovic T, Mohnike K, Nordenstrom A, Einaudi S, van der Kamp H, Vieites A, de Vries L, Ross RJM, Ahmed SF. Adrenal insufficiency related adverse events in congenital adrenal hyperplasia. International Disorders of Sex Development and International Congenital Adrenal Hyperplasia Annual User Group Meeting, 9th September 2020, held online due to Covid-19 pandemic.

Ali SR, Bryce J, Haghpanahan H, Lewsey JD, Tan L, Atapattu N, Birkebaek NH, Blankenstein O, Neumann U, Balsamo A, Ortolano R, Bonfig W, Claahsen-van der Grinten HL, Cools M, Costa E, Darendeliler F, Poyrazoglu S, Elsedfy H, Finken MJJ, Fluck CE, Gevers E, Korbonits M, Guaragna-Filho G, Guran T, Guven A,

Hannema SE, Higham C, Hughes IA, Tadokoro-Cuccaro R, Thankamony A, Iotova V, Krone NP, Krone R, Lichiardopol C, Luczay A, Mendonca BB, Bachega T, Miranda MC, Milenkovic T, Mohnike K, Nordenstrom A, Einaudi S, van der Kamp H, Vieites A, de Vries L, Ross RJM, Ahmed SF. Real world estimates of adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia. Scottish Paediatric Endocrine Group Annual Scientific Meeting, 30-31st January 2020, Glasgow, UK.

Ali SR, Bryce J, Cools M, Korbonits M, Beun JG, Taruscio D, Danne T, Dattani M, Dekkers OM, Linglart A, Netchine I, Nordenstrom A, Patocs A, Persani L, Reisch N, Smyth A, Sumnik Z, Visser WE, Hiort O, Pereira AM, Ahmed SF. The current landscape of European registries for rare endocrine conditions. Rare Endocrine Diseases Annual Meeting, 12-13th December 2019, Glasgow, UK.

Ali SR, Bryce J, Muir T, Okure A, Cools M, Danne T, Dattani M, Dekkers OM, Hiort O, Linglart A, Netchine I, Nordenström A, Patócs A, Pereira AM, Persani L, Reisch N, Smyth A, Šumnik Z, Taruscio D, Visser WE, Ahmed SF. European registries for rare endocrine conditions (EuRRECa): Results from the platform for e-reporting of rare endocrine conditions (e-REC). European Society for Paediatric Endocrinology Annual Meeting, 19-21st September 2019, Vienna, Austria.

Ali SR, Macqueen Z, Gardner M, Sandberg DE, Kyriakou A, Mason A, Shaikh MG, Wong SC, Ahmed SF. A health-related quality of life tool for parents of young children with disorders of sex development. International Disorders of Sex Development Annual Symposium, 4-6th July 2019, Sao Paulo, Brazil.

Ali SR, Daniel E, Bryce J, Ikiroma A, Lewsey JD, Ross RJM, Ahmed SF, On Behalf of the I-CAH Consortium. Development of an international benchmark for sick day episodes as a core clinical outcome in people with congenital adrenal hyperplasia. International Disorders of Sex Development Annual Symposium, 4-6th July 2019, Sao Paulo, Brazil.

Rodie ME, Ali SR, Jayasena A, Alenazi NR, McMillan M, Cox K, Cassim SM, Henderson S, McGowan R, Ahmed SF. A nationwide study of the prevalence & initial management of atypical genitalia in the newborn. International Disorders of Sex Development Annual Symposium, 4-6th July 2019, Sao Paulo, Brazil.

Ali SR, Bryce J, Muir T, Okure A, Cools M, Danne T, Dattani M, Dekkers OM, Hiort O, Linglart A, Netchine I, Nordenström A, Patócs A, Pereira AM, Persani L, Reisch N, Smyth A, Šumnik Z, Taruscio D, Visser WE, Ahmed SF. European registries for rare endocrine conditions (EuRRECa): Results from the platform for e-reporting of rare endocrine conditions (e-REC). European Registries for Rare Endocrine Conditions Annual Meeting, 11th March 2019, Budapest, Hungary.

Ali SR, Daniel E, Bryce J, Ikiroma A, Lewsey J, Krone R, Acerini C, Krone N, Das U, Tomlinson J, Korbonits M, Higham C, Darendeliler F, Guran T, Guven A, Attapatu N, Milenkovic T, Raducanu-Lichiardopol C, Hannema S, Claahsen H, Finken M, Baronio F, Balsamo A, Einaudi S, de Vries L, Luczay A, Neumann U, Blankenstein O, Mohnike K, Bonfig W, Elsedfy H, Birkebaek N, Iotova V, Bachega T, Mendonca B, Correa Costa E, Guaragna-Filho G, Rey R, Cools M, Ross RJM, Ahmed SF. Real world estimates of adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia. Glasgow Paediatric Research Day, 8th November 2019, Glasgow, UK.

Ali SR, Bryce J, Cools M, Korbonits M, Beun JG, Taruscio D, Danne T, Dattani M, Dekkers OM, Linglart A, Netchine I, Nordenstrom A, Patocs A, Persani L, Reisch N, Smyth A, Sumnik Z, Visser WE, Hiort O, Pereira AM, Ahmed SF. The current landscape of European registries for rare endocrine conditions. European Society for Paediatric Endocrinology Annual Meeting, 27-29th September 2018, Athens, Greece.

Ali SR, Macqueen Z, Gardner M, Sandberg DE, Kyriakou A, Mason A, Shaikh MG, Wong SC, Ahmed SF. Parent reported outcomes in conditions affecting sex development. International Disorders of Sex Development and International Congenital Adrenal Hyperplasia Annual User Group Meeting, 26th September 2018, Athens, Greece.

Achievements and awards

Awards

European Society for Paediatric Endocrinology registration grant for high scoring abstract, July 2021 – Current management of acute adrenal insufficiency related adverse events in children- results of an international survey of specialist centres.

Glasgow Children's Hospital Charity research project grant, February 2020 – Development and validation of a short version of the quality of life DSD questionnaire (QoL-DSD) for parents of young children with disorders/differences of sex development.

University of Glasgow PhD conference support award, September 2019 – European registries for rare endocrine conditions (EuRRECa): Results from the pilot phase of the platform for e-reporting of rare endocrine conditions (e-REC).

Prizes

Best poster presentation, Glasgow Paediatric Research Day, November 2020 – Real world estimates of adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia.

Yorkhill Prize for postgraduate research, University of Glasgow, October 2020 – Real world estimates of adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia.

Best short oral presentation, International Disorders of Sex Development Symposium, São Paulo, July 2019 – A nationwide study of the prevalence & initial management of atypical genitalia in the newborn in Scotland.

Acknowledgements

Firstly, I would like to express my sincere gratitude to my principal supervisor, Professor Faisal Ahmed, for his support and guidance throughout the duration of my PhD studies.

I would also like to thank Dr Guftar Shaikh for his exceptional mentorship and both academic and clinical supervision during this time.

My sincere thanks to all members of the Child Health team including Ms Karyn Cooper, Mr Martin McMillan, Dr Angela Lucas-Herald and colleagues from the Office for Rare Conditions for their help and support at various stages of this journey. A special thanks to Dr Jillian Bryce for her constant support, sharing her knowledge and IT skills with me and assistance in data extraction from the I-DSD/I-CAH and EuRRECa registries platforms.

I am grateful to the University of Glasgow for funding via the Gardiner Clinical Lectureship in Child Health, Diurnal Ltd and Neurocrine Biosciences for unrestricted education grants, and the EU Health Programme for funding the EuRRECa project. I am also thankful to the Glasgow Children's Hospital Charity for a project grant for the PRO study. The I-CAH/I-DSD registries were developed using research grants from the Medical Research Council, the Seventh EU Framework Program, the ESPE Research Unit and an educational grant from Diurnal Ltd.

I am also very grateful to the local and international clinicians who made many of my research collaborations possible and to all of the patients and their families who took part in my studies. A special thank you to Prof David Sandberg and Dr Melissa Gardner from the University of Michigan for their help and guidance with the PRO studies.

I would also like to thank my family and parents-in-law, Mr Arshad Ali and Mrs Nassim Ali for supporting my educational endeavours. Finally, a big thank you to my husband, Khalid, and my children Hannah, Harris and Ayla for their patience, love and support.

I would like to dedicate this thesis to my parents, Mrs Nargis Rashid and Mr Abdul Rashid, I am forever indebted to your unwavering encouragement and guidance.

Author's Declaration

I declare, except where reference is made to the contribution of others, that all work presented in this thesis was performed by myself and has not been submitted for any other degree at the University of Glasgow, or any other institution.

Dr Salma Rashid Ali

I certify that the work reported in this thesis has been performed by Dr Salma Rashid Ali and that during the period of study, she has fulfilled the conditions of the ordinances and regulations governing the Degree of Doctor of Philosophy, University of Glasgow.

Professor Syed Faisal Ahmed

Abbreviations

21-OHD CAH	21-hydroxylase deficiency congenital adrenal hyperplasia
AC	Adrenal crisis
ACTH	Adrenocorticotrophic hormone
AI	Adrenal insufficiency
AMH	Anti-müllerian hormone
BSA	Body surface area
BSPED	British Society for Paediatric Endocrinology and Diabetes
CAH	Congenital adrenal hyperplasia
CAIS	complete androgen insensitivity syndrome
CRH	corticotropin-releasing hormone
DHAS	Dehydroepiandrosterone sulphate
DSD	Differences or disorders of sex development
EFA	Exploratory factor analysis
EMS	External masculinisation score
Endo-ERN	European reference network for rare endocrine conditions
Endo-ERN MTG	European reference network for rare endocrine conditions main thematic group
Endo-ERN RC	European reference network for rare endocrine conditions reference centre
e-REC	e-reporting platform for rare endocrine conditions
ERN	European reference network
EuRRECa	European registries for rare endocrine conditions
FAIR data	Findable, accessible, interoperable, reusable data
FC	Fludrocortisone
FL	Factor loading
FSH	Follicle stimulating hormone
GC	Glucocorticoid
HC	Hydrocortisone
hCG	Human chorionic gonadotrophin
HPA axis	Hypothalamic-pituitary-adrenal axis
HRQoL	Health-related quality of life
I-CAH	International congenital adrenal hyperplasia registry

I-DSD	International disorders of sex development registry
LH	Lutenising hormone
PAI	Primary adrenal insufficiency
PPR	Parent proxy-report questionnaire
PRO	Parent reported outcomes
PROM	Parent reported outcome measures
PROMIS	Patients reported outcomes measurement information system
PSR	Parent self-report questionnaire
QoL	Quality of life
QoL-DSD Long PPR	Long version of the quality of life DSD questionnaire parent proxy-report
QoL-DSD Long PSR	Long version of the quality of life DSD questionnaire parent self-report
QoL-DSD Short PPR	Short version of the quality of life DSD questionnaire parent proxy-report
QoL-DSD Short PSR	Short version of the quality of life DSD questionnaire parent self-report
RAA system	Renin-angiotensin-aldosterone system
RD	Rare disease
SDE	Sick day episodes
SDSD	Scottish disorders of sex development
SPEG	Scottish Paediatric Endocrine Group
SV	Simple-virilising
SW	Salt-wasting

CHAPTER 1

Introduction

1 Introduction

1.1 Rare endocrine conditions

1.1.1 Overview

Rare diseases or rare conditions are defined by the European Union (EU) as life-threatening or chronic debilitating conditions with a prevalence rate of less than 5 per 10,000 and affect approximately 30 million people across Europe (EU Regulation #141/2000).

Rare endocrine conditions in children and adults may manifest by either a deficiency or an excess of one or more hormones, hormone resistance, tumour growth in endocrine organs, or diseases with consequences for the endocrine system. There are over 440 distinct rare conditions that affect the endocrine system (Reincke and Hokken-Koelega 2021) and these include inherited conditions (e.g. congenital adrenal hyperplasia), cancer (e.g. multiple endocrine neoplasia syndromes) and conditions associated with metabolic sequelae such as diabetes, disorders of calcium and bone metabolism, lipid metabolism, hypogonadism, adrenal, pituitary and thyroid dysfunction. Almost all conditions span across the entire lifetime and are associated with long-term morbidity, including societal and healthcare costs.

The epidemiology of rare endocrine conditions is highly variable from very rare, rare, to low-prevalence conditions. In 2019, Rare Disease UK (https://www.raredisease.org.uk) estimated that it takes on average 4 years for a patient to receive a rare condition diagnosis. Thus, optimal patient management for patients with rare endocrine conditions requires an awareness of these conditions and specialist expertise within a multidisciplinary setting. However, due to the rarity of several of these conditions, the end result is often a substantial variation in patient care.

Increasing the exchange of data and knowledge via collaboration through international networks facilitates a greater understanding of the aetiology of rare endocrine conditions and enables the development of novel and effective therapeutic strategies. A holistic approach to patient-centered research that

encompasses the physical, psychological and social impact of these rare conditions is key (de Graaf, de Vries et al. 2021).

1.1.2 Networks for expert care and research

Collaboration through a network of clinical and research centres would help to reduce the variation in care for individuals with rare conditions. Networks for expert care for rare endocrine conditions such as DSD exist at a regional, national and international level (Ahmed, Bryce et al. 2014). In Scotland, expert clinical care is coordinated through multidisciplinary managed clinical networks (MCNs) such as the Scottish DSD Network (www.sdsd.scot.nhs.uk) and the Scottish Paediatric Endocrine Group (www.speg.scot.nhs.uk), established in 2005 and 2009, respectively. Within these networks, paediatric endocrine services are delivered by local multidisciplinary teams and supported by regional tertiary centres. This model ensures that services are patient-centered, delivered locally where possible and supported by agreed clinical standards.

The Chicago consensus conference on differences of sex development in 2005 (Lee, Houk et al. 2006) led to the development of national DSD networks at an accelerated pace and many European countries including Germany currently have networks to support professionals, patients and families and provide links to support organisations (www.netzerk-is.de). Examples of international cooperation in DSD research include EU funded projects such as EuroDSD which connected 13 research groups from 6 European countries, integrating molecular and genome-wide research to categorise patients with poorly defined DSD. Another example is DSD-life, an initiative which studied quality of life outcomes in adult patients with DSD (Thyen, Ittermann et al. 2018). The Cooperation of Science and Technology (COST) programme action- ‘DSDnet’, also provided a framework for collaboration between researchers, patients and support groups with the development of position papers on diagnostic procedures and best practice guidance on clinical management (Hiort, Cools et al. 2019). In addition, the creation of the International DSD (I-DSD) registry, with the initial help of ESPE in 2007 and the EU in 2008, as part of the EuroDSD project, provided valuable insight into many aspects of DSD including epidemiology and long-term outcomes (Lucas-Herald, Rashid Ali et al. 2022).

The International Rare Diseases Research Consortium (IRDiRC), launched in 2011 is an initiative of the EU. The IRDiRC is a global consortium that unites national and international governmental and non-profit funding bodies, companies (including pharmaceutical and biotech enterprises), umbrella patient advocacy organisations and scientific researchers to promote international collaboration and advance rare diseases research worldwide (Cutillo, Austin et al. 2017). It was originally conceived with the vision of enabling all people living with a rare disease to receive an accurate diagnosis and care within one year of coming to medical attention with two main goals of contributing to the development of 200 new therapies and diagnosing more rare diseases by the year 2020. The goal to deliver 200 new therapies was achieved in early 2017.

The European Union Committee of Experts on Rare Diseases (EUCERD) established criteria for the designation of centres of expertise within member states in 2011. These criteria included the capacity to produce and adhere to good practice guidelines for diagnosis and care, quality management to ensure quality of care, a high level of expertise and contribution to research and multidisciplinary collaboration with other centres of expertise at a national and international level.

In 2017, European Reference Networks (ERNs), virtual networks of expert reference centres, started across Europe. ERNs aim to manage rare medical conditions that require specialist input and a concentration of knowledge and resources (Moliner 2010, Azzopardi-Muscat and Brand 2015). They are based on directive 2011/24/EU of the European Parliament and state that citizens with rare, low prevalence and complex diseases have the right to cross-border healthcare. The Directive became law in EU member states in 2013 and emphasises the value of eHealth and the importance of interoperability in national health IT systems in facilitating information sharing. Currently, 24 ERNs are active covering a range of conditions including bone disorders, childhood cancer and immunodeficiency and these virtual networks bring together experts from across the EU.

The ERN for rare endocrine conditions (Endo-ERN; endo-ern.eu) is the largest ERN with 111 reference centres from 27 member states and includes patient representatives in all condition groups. Endo-ERN currently includes 42

conditions with orphacodes that are organised into eight broad categories termed ‘Main Thematic Groups (MTGs)’, covering the spectrum of congenital and acquired endocrine conditions. These are adrenal disorders, disorders of calcium and phosphate homeostasis, disorders of sex development and maturation, genetic disorders of glucose and insulin homeostasis, genetic endocrine tumour syndromes, disorders of growth and genetic obesity, pituitary disorders and thyroid disorders. It is estimated that these reference centres may care for over 60,000 patients with the above groups of conditions (Pereira and Hiort 2021).

The main objectives of Endo-ERN are to increase awareness and knowledge regarding diagnosis and treatment of rare endocrine conditions and to reinforce research and epidemiological surveillance of rare endocrine conditions. The network also aims to optimise the communication and interaction interfaces between healthcare professionals and patients and to validate the current standards of care with the creation of a single, easy to access platform containing all information. Rare patient cases may be discussed virtually through a dedicated and secure IT platform, the clinical patient management system (CPMS), constructed by the EU Commission specifically for ERNs (Mönig, Steenvoorden et al. 2021, White, Wagner et al. 2022). These virtual discussions ensure that medical knowledge and multidisciplinary expertise are shared across different countries, facilitating access to diagnosis, treatment and providing high quality and cost-effective healthcare for patients with these rare conditions.

With the support of professional endocrine societies such as the European Society for Endocrinology (ESE) and European Society for Paediatric Endocrinology (EPSE), Endo-ERN has created defined structures for sharing knowledge and care for rare endocrine conditions. However, long-term funding and resources required to support these infrastructures and promote these networks amongst health professionals and patient communities is required to enable sustainability and expansion of their activities.

1.1.3 Benchmarking and continuous quality improvement

Benchmarking is an approach for implementing best practices, often at best cost in healthcare and involves comparing indicators of practice amongst collaborating centres (Ettorchi-Tardy, Levif et al. 2012). A key feature includes

its integration within a continuous and participatory policy of continuous care quality improvement (CQI). Identification of a point of comparison, the benchmark, is used to compare indicators of practice.

Benchmarking is a fairly recent concept in healthcare, emerging in the mid-90s, and initially utilised to compare hospital outcomes to rationalise their funding (Camp 1998, Dewan, Daniels et al. 2000). Benchmarking is becoming increasingly common in healthcare settings including research in rare conditions. The driving forces behind this increasingly more accepted concept include the need to control healthcare costs, the need to structure risk management and quality of care and the need to satisfy patient expectations (Ellis 2006).

In the context of rare disease research, benchmarking may focus on gathering indicators for long-term monitoring or outcome or facilitate a comparison of morbidity outcomes in rare conditions (e.g. the incidence of adrenal crises in patients with CAH amongst different centres), promoting further research and collaboration amongst healthcare professionals, the patient community and industry. Benchmarking in healthcare is a process of comparative evaluation and identification of the underlying causes leading to optimal performance (Ellis 2006). It is imperative that the benchmarking process involves a sustained effort to measure outcomes, compare these outcomes against those of other centres (at a local, national or international level) to learn how these outcomes were achieved and apply the lessons learned in order to improve practice, and ultimately patient care. Also imperative to benchmarking is the need for reliable and up-to-date data, ongoing data surveillance and collaboration amongst participating centres. A nine-step benchmarking process is outlined in Figure 1-1 (Pitarelli E. 2000).

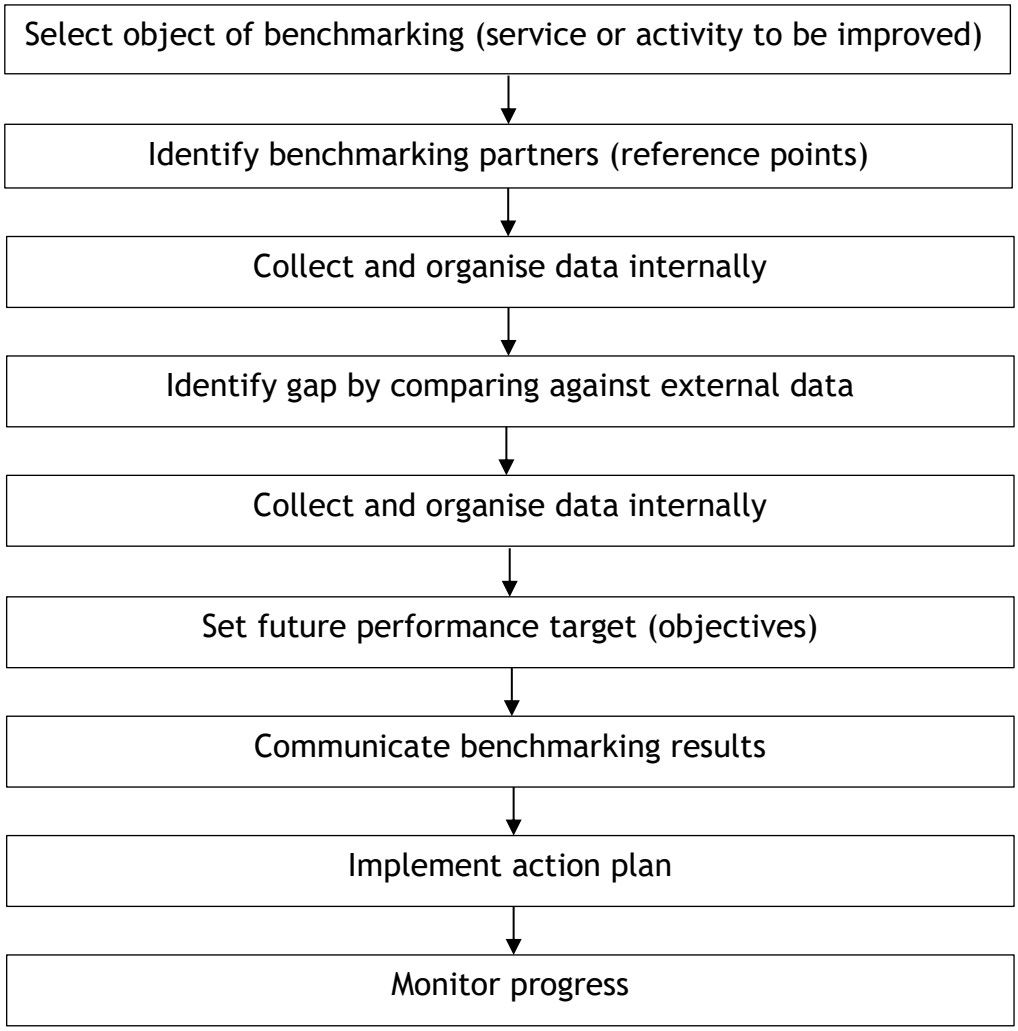


Figure 1-1. The benchmarking process (adapted from Pitarelli and Monnier 2000)**.**

1.2 Rare disease registries for endocrine conditions and the collection of real-world data

1.2.1 The role of rare disease registries in studying disease outcomes in rare endocrine conditions

The management of rare endocrine conditions requires coalesced efforts over the life-time of the patient to reduce morbidity and mortality in affected individuals. Rare endocrine conditions pose a challenge due to knowledge gaps regarding long-term prognosis and lack of expert and evidence based multidisciplinary care resulting in substantial variation in care.

A patient disease registry is an organised system that uses methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves one or more predetermined scientific, clinical, or policy purposes (Gliklich and Dreyer 2010). Detailed disease registries have the potential to improve patient care and healthcare planning in those with rare conditions. Registries enable pooling of data for research activities and surveillance and allow the creation of a virtual environment of collaboration, facilitating communication between professionals and affected individuals. Multicentre collaboration between centres of expertise within registries can also play a vital role in the development of clinical benchmarks, thereby acting as a platform for quality improvement. In addition, the use of cross-border international registries offers clear benefits for collaboration and standardised data collection for rare conditions. A requirement for international registration of patients with rare conditions is widely recognised and supported by the EU International Rare Disease Consortium (irdirc.org) (Taruscio, Mollo et al. 2014).

Over 800 rare disease registries are reported to exist in Europe and some of these registries operate on an international, national or regional scale (Taruscio, Vittozzi et al. 2015, Baldovino, Moliner et al. 2016). European initiatives including Orphanet (https://www.orpha.net/) and RD-Connect (http://catalogue.rd-connect.eu/) are free online databases providing information and data on rare diseases, orphan drugs and existing registries (Thompson, Johnston et al. 2014). Over the last decade, advances in information

technology, as well as a greater willingness to collaborate has resulted in the development of several secure, web-based registries for discrete groups of endocrine conditions including disorders of sex development (I-DSD, www.i-dsd.org), congenital adrenal hyperplasia (I-CAH, www.i-cah.org), Cushing Syndrome (ERCUSYN, www.lb.de/ercusyn/), adrenal tumours (ENSAT, www.ensat.org) and common and rare forms of diabetes (SWEET, www.sweet-project.eu). Some registries, such as ENSAT, have placed a greater emphasis on research and biobanking whilst others, such as SWEET, have placed a greater focus on service development. Others, such as the I-DSD and I-CAH registries have explored how the involvement of patients can be maximised through the development of a patient accessible module. Several active users of these registries and their coordinators are also already participating in Endo-ERN.

With the recent expansion in rare disease registries, focus needs to be placed on ensuring that registries are of high quality and compliant with ethical and legal standards. High quality registries can provide access to data on a platform that ensures data security and patient confidentiality. In addition, understanding clinical outcomes for rare endocrine conditions requires the collection of long-term follow-up data and this is only possible if registries are sustained over a long period of time. The long-term sustainability of a detailed disease registry can increase significantly if the data that are stored within the registry are FAIR (findable, accessible, interoperable and reusable). This involves designing a registry to comply with international standards of quality, structure and content, access control and also adopting common methods for information/patient discoverability and sharing (Kodra, Weinbach et al. 2018). Thereby, users can more easily compare, pool and analyse patient datasets, using sufficient numbers of cases for meaningful clinical research and public health purposes in areas identified as high priority by the endocrine community. A high-quality disease registry also requires clear governance structures and the effort involved in providing this is often under-estimated (Ali, Bryce et al. 2020).

Although registries are regarded as essential for networks such as Endo-ERN, knowledge on the range of registries that exist for cross-border sharing of information on rare endocrine conditions in Europe is scarce. Furthermore, the

extent of awareness, participation and availability of registries amongst health professionals for the wide range of conditions within Endo-ERN is unclear.

1.2.2 The European registries for rare endocrine conditions (EuRRECa) platform

With the development of Endo-ERN in 2017, consideration has been given on how to pool resources and develop a virtual environment that serves the objectives of this ERN and acts as a model for the wider endocrine community. The European Commission's delegated decision of March 2014 (2014/286/EU) which sets out the criteria and conditions that ERNs must fulfil with regard to the exchange of expertise, information systems and e-health tools, explicitly states that ERNs need established procedures and a framework for ensuring the management, safeguarding and exchange of data. The latter includes the gathering of data on established outcomes, process indicators and patient registries for the specific area of expertise covered by the ERN. The ERNs also need to fulfill minimum interoperability requirements and use standardised information and coding systems that comply with national or international systems. The size and the wide range of conditions within Endo-ERN allow it to act as a model for a large group of rare conditions that require a common core endocrine registry and an electronic surveillance system to capture activity, epidemiology and natural history of these conditions.

The European Registries for Rare Endocrine Conditions (EuRRECa) project (www.eurreca.net) was launched in 2018 and is funded by the EU Health Programme; it is also supported by the European Society for Paediatric Endocrinology (ESPE) and the European Society of Endocrinology (ESE). EuRRECa aims to support the needs of the wider endocrine community by maximising the opportunity for collaboration between patients, health professionals and researchers across Europe and beyond (Ali, Bryce et al. 2021). The EuRRECa platform comprises an electronic reporting system (e-reporting for rare endocrine conditions, e-REC) and a registry which collects a core dataset (EuRRECa core registry) (Figure 1-2). EuRRECa has the capacity to support Endo-ERN by providing clear data on the conditions covered within the ERN as well as understand the incidence, prevalence and natural history of rare endocrine conditions, thereby providing the infrastructure for future research activity.

Participation in EuRRECa is open to all members of Endo-ERN and other professionals providing endocrine care.

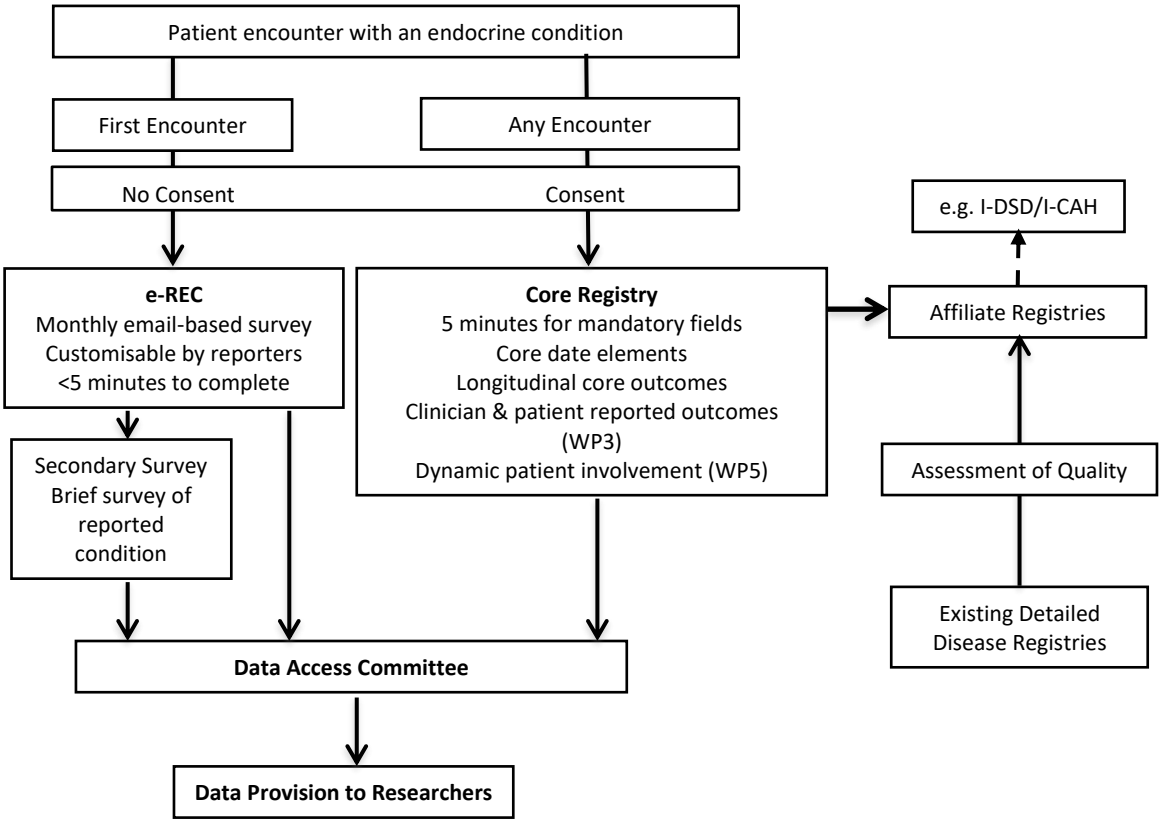


Figure 1-2. The concept of the European registries for rare endocrine conditions (EuRRECa).

Within e-REC, registered users are asked to report new cases of any of the conditions that have been included in Endo-ERN and this process does not require informed consent from patients. On reporting a case, no personally identifiable information is collected. The e-REC allows continuous reporting of core indicators of activity and enables clinical networks such as Endo-ERN to embark on its stated mission of objectively mapping conditions and related activity, providing a better understanding of the occurrence of the rare conditions covered within Endo-ERN.

The EuRRECa core registry collects a core dataset that has been evaluated against existing FAIR standards (Kodra, Weinbach et al. 2018). The fields have a high level of interoperability for a wide range of rare conditions including those that are covered within Endo-ERN (https://eurreca.net/data-elements/). The fields that are used to collect core information include the core data elements that are recommended by the European platform on rare diseases (EU RD

platform) for data collection and a high proportion of them have universal identifiers. By using Orphacodes and LOINC codes, the data are highly interoperable with other registries that use the same approach. Clinicians require informed consent from patients prior to entering patient data into the EuRRECa core registry. The EuRRECa core registry also incorporates patient centered outcome measures and in the future, will signpost participants to high-quality, disease-specific registries. Access to the data within e-REC and the EuRRECa core registry, by stakeholders, is governed by the EuRRECa data access committee.

The EuRRECa project complies with the UK Data Protection Act (2018) and General Data Protection Regulation (GDPR 2016/679) and the e-REC and the core registry have been approved by the UK Research Ethics Service. The project aims to promote good standards of practice by adherence to the highest standards of data security and is subject to stringent governance (Ali, Bryce et al. 2020).

1.2.3 The International disorders of sex development (I-DSD) and congenital adrenal hyperplasia (I-CAH) registries

Disorders of differences of sex development (DSD), including congenital adrenal hyperplasia (CAH), are an example of a group of rare endocrine conditions where there is a lack of knowledge regarding aetiology and long-term outcomes, with research limited by the low prevalence of individual conditions. The consensus workshop on DSD which was jointly hosted by the European Society of Paediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society of North America in 2005, highlighted the need for standardised data collection and data sharing across geographical boundaries for this group of conditions (Lee, Houk et al. 2006). At that time, despite the existence of regional and national databases in centres of expertise, international uniformity was lacking, a desirable feature when dealing with a rare group of conditions.

With the initial help of ESPE followed by the European Union, through an EUFP7 funded project, a European web-based registry and research environment for DSD, EuroDSD, was developed between 2008 and 2011. The registry gained international popularity beyond Europe and in 2011 it secured a five year international partnership grant from the UK Medical Research Council (MRC) to

become the I-DSD Registry (https://home.i-dsd.org/). By 2013, many cases of CAH were being entered into the I-DSD registry. To further facilitate this, a CAH module was developed by an international network of researchers and clinicians looking after people with CAH. The mirror site, which used the same registry platform but could be entered through a separate website, was subsequently titled the I-CAH Registry and was launched in 2014. Over the last few years, the I-DSD Registry has also included cases of Turner Syndrome (TS) and in 2020, work commenced on developing another mirror site (I-TS) which uses the same registry platform as I-DSD and I-CAH. More recently, the I-DSD/I-CAH registries have been supported from funding from a wide range of sources that includes fees incurred by investigators for obtaining data for research, project grants from UK NIHR, the Chief Scientist Office of Scotland, income from the biennial I-DSD symposium and unrestricted education grants from the pharmaceutical industry.

The I-DSD/I-CAH registries provide a means of connecting clinical and research centres around the world and allow the collection of real-world data within a secure environment (Lucas-Herald, Rashid Ali et al. 2022). The registries support primary and secondary research, provide a platform for pharmacovigilance and act as a tool for monitoring clinical and patient-centered outcomes for improving patient care. The registries also facilitate the development of support networks for individuals with a wide range of conditions affecting sex development and maturation. Currently, the I-DSD/I-CAH registries network comprises 260 centres in 63 countries on all continents. Of these, 115 centres from 40 countries use the registries to enter patient data and over 5,500 cases have been entered to date (Figure 1-3). The remaining 145 centres receive newsletters and participate in the other activities such as education events and surveys. Of the cases, the current age of the patients ranges from newborn to 72 years, with a median of 17 years. A total of 54% of these individuals are male and the most commonly registered diagnosis is CAH (n, 1507, 28%) (Figure 1-4).

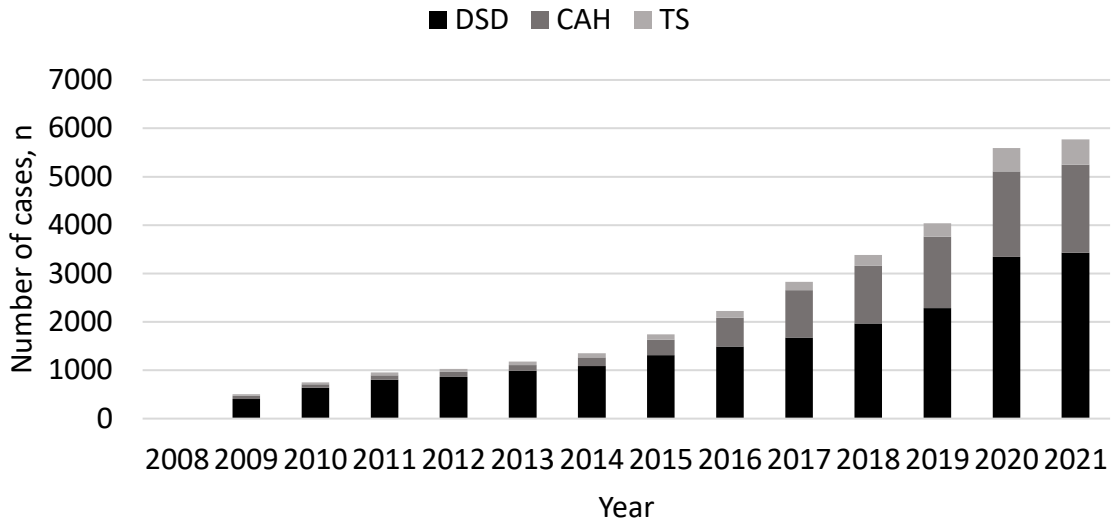


Figure 1-3. Cumulative groups of conditions within the I-DSD/I-CAH/I-TS registries.

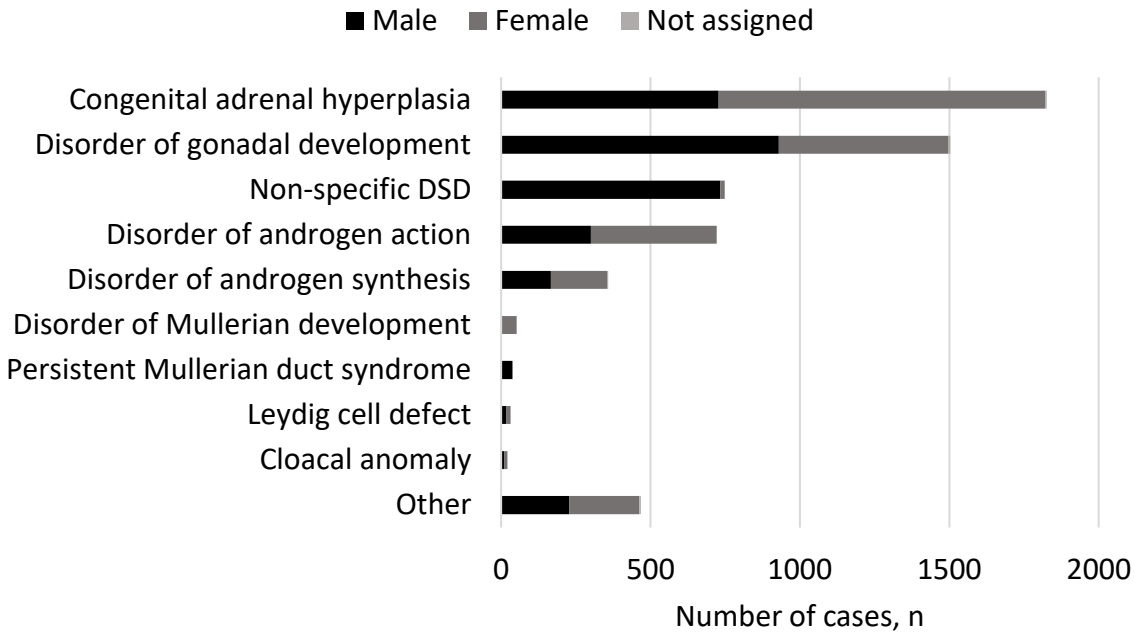


Figure 1-4. Patient diagnoses and sex within the I-DSD/I-CAH/I-TS registries.

The registries are approved by the National Research Ethics Service in the United Kingdom as research databases of information that is collected as part of routine clinical care. Pseudonymised information can be shared for a range of purposes that have the ultimate aim of improving the health of people with these conditions. Participation in research is a vital component of the project and since 2010, over 20 original data communications, with data from 86 centres, have been published in peer reviewed journals. Of the cases on the registry, 3,383 (59%) have been included in at least one published study, with a range of 0-8 studies per case and the most commonly studied condition to date is CAH

(1399 (41%) of cases in published studies) (Lucas-Herald, Rashid Ali et al. 2022). It is increasingly becoming recognised that participation in registries and related activities is an essential feature of complex and specialist clinical services that deliver care in the field of rare diseases (Ahmed, Achermann et al. 2021). However, challenges still exist in the participation of registry related activities including lack of time or dedicated personnel for data entry and quality control (Kyriakou, Dessens et al. 2016).

The I-DSD registry has previously undergone quality assessment and has most features that experts would identify as essential features of a rare disease registry (Kourime, Bryce et al. 2017). The registry has also created a detailed data dictionary that paves the way to making the data discoverable. In the future, to improve the quality of the data further, the I-CAH registry aims to provide its users with feedback on the quality of data they enter through a centre specific report provided at regular intervals.

The I-DSD/I-CAH registries are managed and administered by a joint steering committee with representation from patients and cross-border professional societies. The registries also have a data access committee that reviews new research proposals and a care quality improvement committee that oversees activities that use the registries for improvement of the quality of care for people with these conditions. Day to day management of the project is undertaken by the project management group which is based at the Office for Rare Conditions at the University of Glasgow. In addition, the I-DSD/I-CAH network is involved in training and learning events including the biennial DSD symposium and more recently the two-day DSD postgraduate course which is held prior to the scientific symposium.

1.3 Disorders (or differences) of sex development (DSD)

1.3.1 Incidence and aetiology

Differences or disorders of sex development (DSD) is an umbrella term that covers several conditions that affect sexual development and maturation that most often present in infancy or in the adolescent period. The birth prevalence of atypical genitalia has been reported to be as high as 1 in 300 births (Ahmed, Dobbie et al. 2004), however, the prevalence of complex anomalies that may lead to true genital ambiguity may be as low as 1 in 5,000 births (Thyen, Lanz et al. 2006). DSD conditions are characterised by atypical chromosomal, gonadal or phenotypic sex (Hughes 2008) and may be further classified based on karyotype into sex chromosome DSD (e.g. Turner syndrome), 46, XX DSD (Congenital Adrenal Hyperplasia) and 46, XY DSD (proximal hypospadias), or based on aetiology into disorders of gonadal development, disorders of androgen synthesis, disorders of müllerian development and other conditions affecting sex development (Figure 1-5). DSD encompass a range of conditions with a spectrum of accompanying features from those conditions requiring minimal medical input (e.g. proximal hypospadias) to those presenting with life-threatening problems (e.g. adrenal crises in CAH secondary to 21-hydroxylase deficiency).

Primary Root: 46 XY, 46 XX, 45 X/46 XY, 46 XX/46 XY, 45 X, 47 XXY, Presumed XY, Presumed XX, Other

Secondary Root	Disorder of gonadal develop-ment	Disorder of androgen synthesis	Disorder of androgen action	Disorder of androgen excess	Leydig cell defect	Persistent Mullerian duct syndrome	Defects of Mullerian develop-ment	Non-specific disorder of under-masculinisation	Other
Actual diagnosis	Complete gonadal dysgenesis Partial gonadal dysgenesis Gonadal regression Ovo-testicular DSD Testicular DSD	StAR P450 scc 3β-HSD CYP17 17βHSD 5α reductase P450 OR	PAIS CAIS Other	21α-hydroxylase def 11β-hydroxylase def Aromatase P450 OR Maternal androgens	Leydig cell hypoplasia LH deficiency	AMH low AMH normal AMH not known	MURCS MRKH Uterine Didelphys Other	Isolated hypospadias Isolated bilateral cryptorchidism Isolated micropenis Anomalies EMS >8 Anomalies EMS 5-8 Anomalies EMS <5	Cloacal Anomaly Bladder Exstrophy Other

Figure 1-5. Classification of DSD.

1.3.2 Pathways of sex development

Primordial germ cells migrate to the genital ridge from the yolk sac at approximately 6 weeks of gestation in the human embryo. Wilms Tumour 1 (WT1) and Steroidogenic Factor 1 (SF1) genes result in the development of bipotential gonads from these cells. Usually, in the presence of a Y chromosome, the development of Müllerian structures is inhibited by the production of Anti-Müllerian Hormone (AMH). With the production of testosterone by the Leydig cells, the mesonephric (Wolffian) duct increases in size and differentiates into the epididymis, vas deferens and prostate. 5-dihydrotestosterone (DHT) is produced by the conversion of testosterone by the enzyme 5α-reductase, resulting in the development of male typical external genitalia and testicular descent. If there is no Y chromosome present, the Müllerian structures usually develop into female typical internal genitalia and ovaries develop. The absence of DHT also results in the development of female typical external genitalia (Figure 1-6). There are many factors involved in the differentiation of the sex organs into male or female and there is potential for a disruption of this process at multiple different stages (Davies R 2020). The clinical phenotype therefore depends on the nature of the disruption.

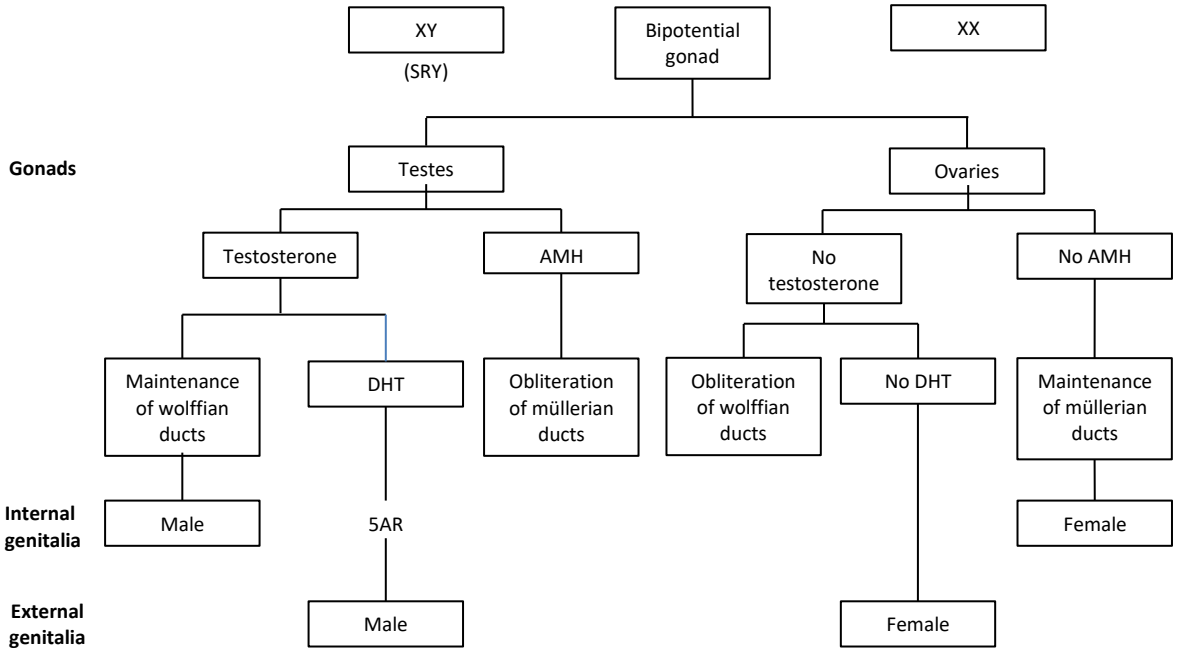


Figure 1-6. Normal pathways of sex development (adapted from Davies et al. 2020).

1.3.3 Clinical presentation

Most infants with a suspected DSD will present with overt genital ambiguity, a family history of DSD, a discordance between genital appearance and prenatal karyotype, apparent female genitalia with an enlarged clitoris and posterior labial fusion, an inguinal/labial mass, or apparent male genitalia with bilateral undescended testes, microphallus, proximal hypospadias, distal or mid-shaft hypospadias with undescended testis (Ahmed, Achermann et al. 2021).

Detailed physical examination and documentation of the genitalia is vital. Scoring systems used when evaluating the external genitalia of infants with a suspected DSD include the external masculinization score (EMS) (Ahmed, Khwaja et al. 2000) (Figure 1-7), which scores external genitalia individually for scrotal fusion, microphallus, location of urethral meatus and the location of each gonad. The external genitalia score (EGS) is a gender-neutral alternative to the EMS (van der Straaten, Springer et al. 2020).

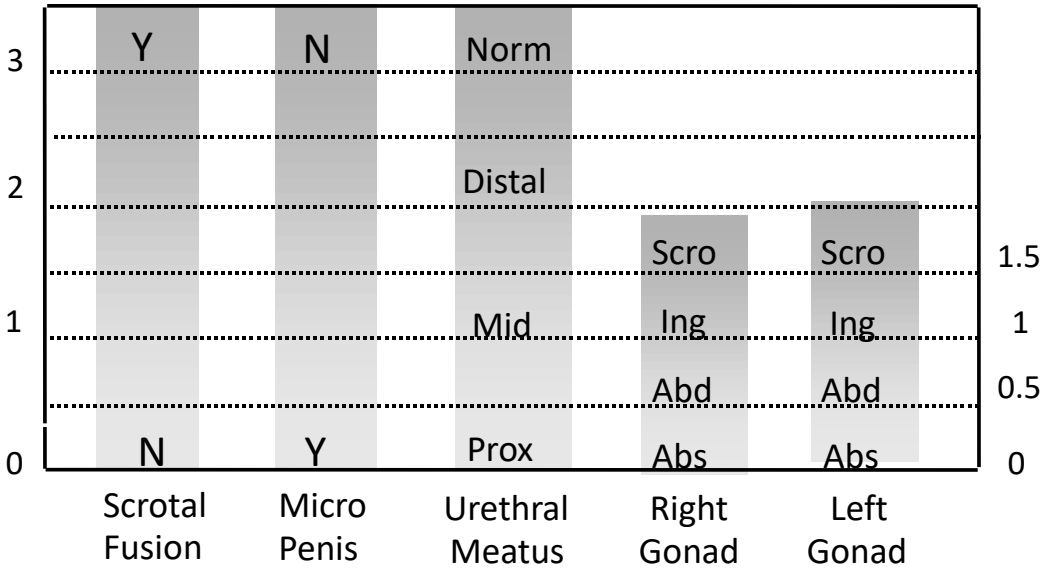


Figure 1-7. External masculinisation score (EMS). Adapted from Ahmed et al. 2000. Each clinical feature of the genitalia can be individually scored to provide a score out of 12. Scr, labioscrotal; Ing, inguinal; Abd, abdominal; Abs, absent on examination.

In one specialist centre, out of 63 unselected cases with proximal hypospadias (penoscrotal, scrotal, perineal) who were studied for all known causes of hypospadias with clinical as well as molecular biological techniques, an underlying aetiology was identified in 31% of cases (Boehmer, Nijman et al. 2001). Recent guidance recommends that further evaluation and investigation

should be performed in all children with an EMS of less than 11 and all children with familial hypospadias (Ahmed, Achermann et al. 2021).

1.3.4 Management

The management of children with DSD should include a multidisciplinary (MDT) approach led by one professional, for example, the paediatric endocrinologist in the case of the newborn, with involvement from a MDT which may be accessed via a regional DSD network. The members of the core clinical MDT should include specialists in paediatric endocrinology, paediatric urology, clinical psychology, radiology, nursing, neonatology in the case of newborns and an adolescent gynaecologist in older children. Parents and patients should be involved in discussions regarding management and psychosocial care. In addition, peer groups, such as the CAH support group (livingwithcah.com) and DSD support groups (dsdfamilies.org) can provide a valuable source of support and information for patients and families (Cull and Simmonds 2010).

Specialist centres should be able to complete first-line investigations including QF-PCR, karyotype or microarray and an ultrasound scan of the pelvis, in a timely manner for deciding upon sex assignment and excluding immediate medical concerns (Ahmed, Achermann et al. 2021). The clinical team should then decide upon second-line investigations to investigate the underlying aetiology that will guide long-term management. Second-line investigations may include urea and electrolytes, glucose, androgen profile, AMH, FSH, LH, ACTH, DHAS and a urinary steroid profile.

Guidance regarding the management of DSD have been developed by clinical networks at regional (https://www.clinicalguidelines.scot.nhs.uk), national (Bever, Brüggenwirth et al. 2020, Ahmed, Achermann et al. 2021) and international levels (Cools, Nordenström et al. 2018). Whilst it is expected that centres that belong to these networks would practice according to this guidance, recent evidence suggests that the approach to evaluating cases of DSD can vary widely between centres at a local as well as at an international level (Kyriakou, Dessens et al. 2016). In addition, for this group of rare conditions, it is vital that clinical experience is shared through national and international clinical and research networks. However, a recent international survey has also shown that

engagement in research and participation in registries is variable amongst centres that deliver DSD care (Kyriakou, Dessens et al. 2016). Variation in care pathways, especially at the point of initial presentation, is often felt to be the most important cause of the diagnostic odyssey that is experienced by patients with rare conditions (Tumiene and Graessner 2021).

European networks such as Endo-ERN and EuRRECa provide platforms to promote best practice for these conditions and enable continuous monitoring of clinical activity, whilst the I-DSD/I-CAH registries play an important role in supporting research, training and benchmarking. Virtual forums such as the clinical patient management system (CPMS) which is available to centres affiliated to Endo-ERN, can also promote good clinical practice and be used for remote discussion of complex DSD cases requiring expert input.

1.4 Congenital adrenal hyperplasia (CAH)

1.4.1 Incidence

Congenital adrenal hyperplasia are a group of rare autosomal recessive disorders and are the most common cause of primary adrenal insufficiency in children (Wijaya, Huamei et al. 2019, Capalbo, Moracas et al. 2021). Based on neonatal screening and data from global and national case registries, the worldwide incidence in the classic form ranges from 1 in 14,000 to 1 in 18,000 (van der Kamp and Wit 2004, Speiser, Arlt et al. 2018), with most recent data suggesting an incidence of 1 in 18,248 births in the UK. In Scotland, approximately 3-4 new cases of CAH are diagnosed per year.

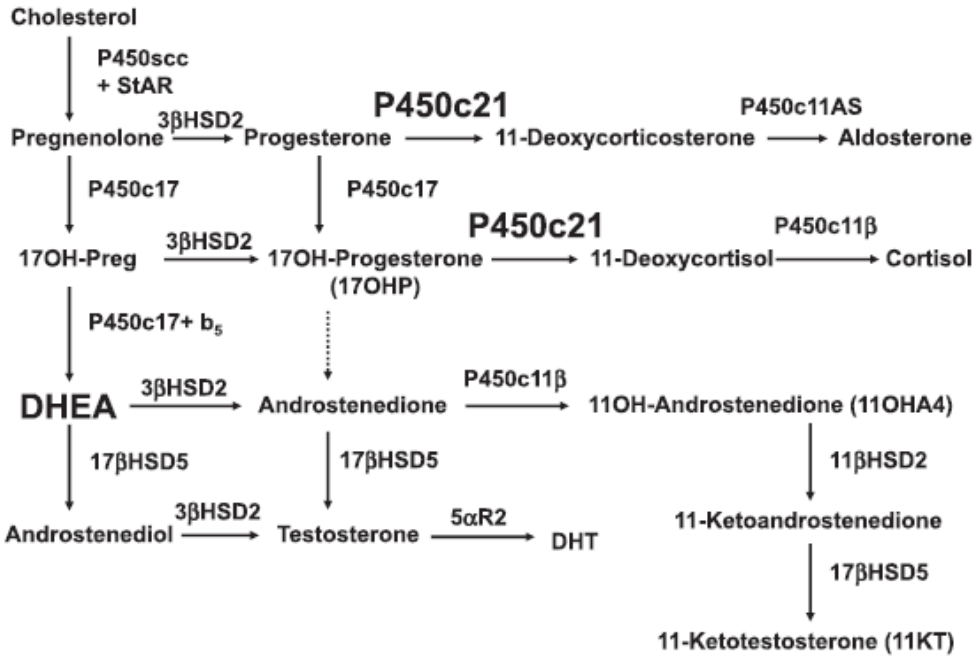
CAH is included in the newborn screening programme in around 40 countries, including all 50 states in the USA and specific regions of 17 additional countries. Some studies have shown that screening markedly reduces the time to diagnosis in infants with classic CAH, consequently reducing morbidity and mortality (Balsamo, Cacciari et al. 1996, Brosnan, Brosnan et al. 1999), with diagnosis more likely to be delayed in males due to the lack of genital ambiguity. However, a recent UK based study showed no increase in infant mortality for CAH in the absence of screening (Hird, Tetlow et al. 2014) and CAH is not currently included as part of the newborn screening programme in the UK. Overall, infant deaths from CAH are now reported to be rare at around 0-4% in developed countries even in the absence of screening (Dörr, Wollmann et al. 2018).

1.4.2 Steroid biosynthesis in the adrenal cortex

Steroidogenesis in the adrenal cortex entails conversion of cholesterol to active steroid hormones and involves many enzymes, cofactors and accessory proteins. Mutations have been described in most of the genes encoding these proteins. Those that disrupt cortisol synthesis with compensatory elevations in ACTH cause CAH. The enzymatic conversions required to synthesize cortisol are summarised in Figure 1-8. Steroidogenesis is initiated by the conversion of cholesterol to pregnenolone, catalysed by the cholesterol side-chain cleavage enzyme, CYP11A1 and steroidogenic acute regulatory protein (StAR). Pregnenolone is

converted to progesterone by 3ß-hydroxysteroid dehydrogenase (3ß-HSD) which also converts 17-hydroxypregnenolone (17-OH Preg), dehydroepiandrosterone (DHEA) and androstenediol to 17-hydroxyprogesterone (17 OHP), androstendione and testosterone, respectively. 17α-hydroxylase (CYP17A1) converts pregnenolone to 17-OH Preg and progesterone to 17 OHP; 17,20-lyase activity can convert 17OH-Preg to DHEA. POR deficiency diverts steroids into the "backdoor pathway" of dihydrotestosterone biosynthesis, contributing to prenatal female virilisation. Steroid 11-hydroxylase (CYP11B1, P450c11ß) and aldosterone synthase (CYP11B2, P450c11AS, P450aldo) are closely related enzymes that catalyze the final steps in the synthesis of glucocorticoids and mineralocorticoids, respectively. CYP11B1 is expressed abundantly in the zona fasciculata, where it converts 11-deoxycortisol to cortisol and 11 deoxycorticosterone (DOC) to corticosterone. The synthesis of sex steroids also requires the action of the 17 ß-hydroxysteroid dehydrogenases (17 ß HSD).

A



B

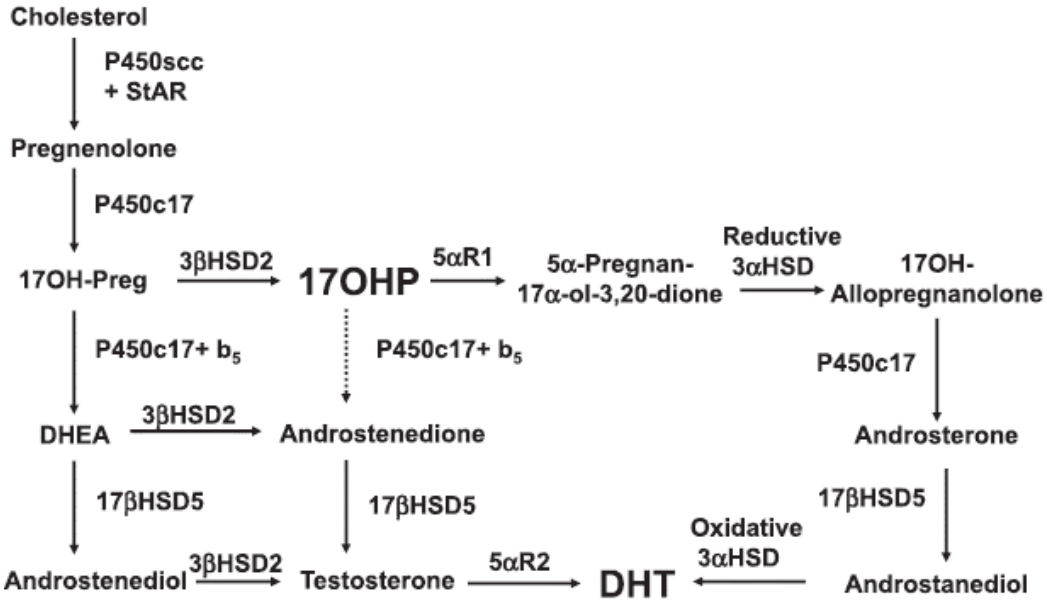


Figure 1-8. Normal fetal adrenal steroidogenesis (A) and the three pathways leading to increased androgens in the absence of 21-hydroxylase activity (B) (adapted from Speiser et al. 2018).

In CAH, the most common underlying mutation occurs in the *CYP21A2* gene that encodes 21-hydroxylase and 21-hydroxylase deficiency (21-OHD) accounts for more than 95% of cases (White and Speiser 2000). This enzyme converts progesterone to deoxycorticosterone and 17-OHP to 11-deoxycortisol, with these products being precursors for aldosterone and cortisol. A block in the pathways to aldosterone and cortisol synthesis results in accumulation of steroid precursors. These are diverted to sex hormone biosynthesis with overproduction of adrenal androgens and genital virilisation in the female fetus.

In addition to the classic pathway via DHEA, androstenedione, and testosterone, the most potent endogenous androgen, dihydrotestosterone (DHT), can also be synthesized via an alternative or “backdoor” pathway that bypasses the classical pathway intermediates (Auchus 2004) (Figure 1-8). This alternative pathway is physiologically active during the sixth to tenth week of fetal development and into the second trimester. To enter the alternative pathway to DHT, progesterone, or 17OHP are 5α-reduced by steroid 5α-reductase type 1 (SRD5A1) to yield 5α-dihydroprogesterone and 17α-hydroxydihydroprogesterone, respectively. These are subsequently 3α-reduced to allopregnanolone and 17α-hydroxyallopregnanolone. CYP17A1 converts allopregnanolone to 17α-

hydroxyallopregnanolone and then to androsterone by its 17,20-lyase activity. Androsterone can then be activated to DHT by sequential 17β-reduction and 3α-oxidase reactions. Excessive 17-OHP accumulation is a key characteristic of 21-OHD, thus it is highly likely that the alternative pathway to DHT is a major contributor to fetal female virilisation in 21-OHD. Alternative pathway steroid metabolites can be detected in patients of all ages with 21-OHD, most prominently in the neonate. Studies indicate that the high concentrations of 17-OHP in individuals with 21-OHD drive DHT production by the alternative pathway (Kamrath, Hochberg et al. 2012).

1.4.3 The role of the adrenal hormones

The adrenal gland develops from two separate embryological tissues; the adrenal medulla is derived from neural crest cells and the adrenal cortex is derived from mesoderm. In a foetus, the adrenal glands are first detectable from the sixth week of development. The adrenal glands are positioned just above the kidneys, hence the alternative name of 'suprarenal glands'. The outer part of each gland, the adrenal cortex, consists of three layers, the zona glomerulosa, zona fasciculata and zona reticularis, which produce mineralocorticoids (mainly aldosterone), glucocorticoids (mainly cortisol) and androgens, respectively. The innermost aspect of the adrenal gland, the adrenal medulla, contains chromaffin cells which secrete catecholamines (adrenaline and noradrenaline).

Glucocorticoids and mineralocorticoids are important in long-term reactions at moments of stress. Glucocorticoids are mainly involved in the regulation of glucose metabolism, through the conversion of protein and fats into glucose resulting in an increase in blood glucose levels, and they have a role in the inhibition of inflammation and immune functions. Mineralocorticoids regulate sodium, potassium and water balance, causing accumulation of sodium ions and water in the kidneys, resulting in an increase in blood circulating volume and blood pressure.

The hypothalamic-pituitary-adrenal (HPA) axis signalling pathway involves the release of corticotrophin releasing hormone (CRH) from the hypothalamus. CRH then stimulates the release of adrenocorticotrophic hormone (ACTH) from the

anterior pituitary gland and ACTH stimulates the release of cortisol from the adrenal cortex (Figure 1-9 A). Cortisol exerts a negative feedback effect on CRH and ACTH production from the hypothalamus and pituitary glands, respectively. In response to reduced renal perfusion, renin is released from the kidney and stimulates the production of angiotensin from the liver, which in turn stimulates the production of aldosterone from the adrenal cortex. This sequence of events, referred to as the renin-angiotensin-aldosterone (RAA) system, has an important role in blood pressure homeostasis.

In primary adrenal insufficiency (PAI) (e.g. CAH), there is a block in the production of cortisol from the adrenal cortex and the resultant absent or low levels of cortisol stimulate the hypothalamus and pituitary to increase production of CRH and ACTH, respectively (Figure 1-9 B). Reduced production of aldosterone in PAI promotes activation of the RAA system, resulting in high serum renin levels. Secondary adrenal insufficiency may occur due to hypothalamic or pituitary disease. In pituitary disease, absent or low ACTH production results in reduced cortisol, subsequently, lack of negative feedback on the hypothalamus results in increased CRH production (Figure 1-9 C). In hypothalamic disease, reduced CRH production results in reduced ACTH and cortisol production from the pituitary and adrenal gland, respectively (Figure 1-9 D).

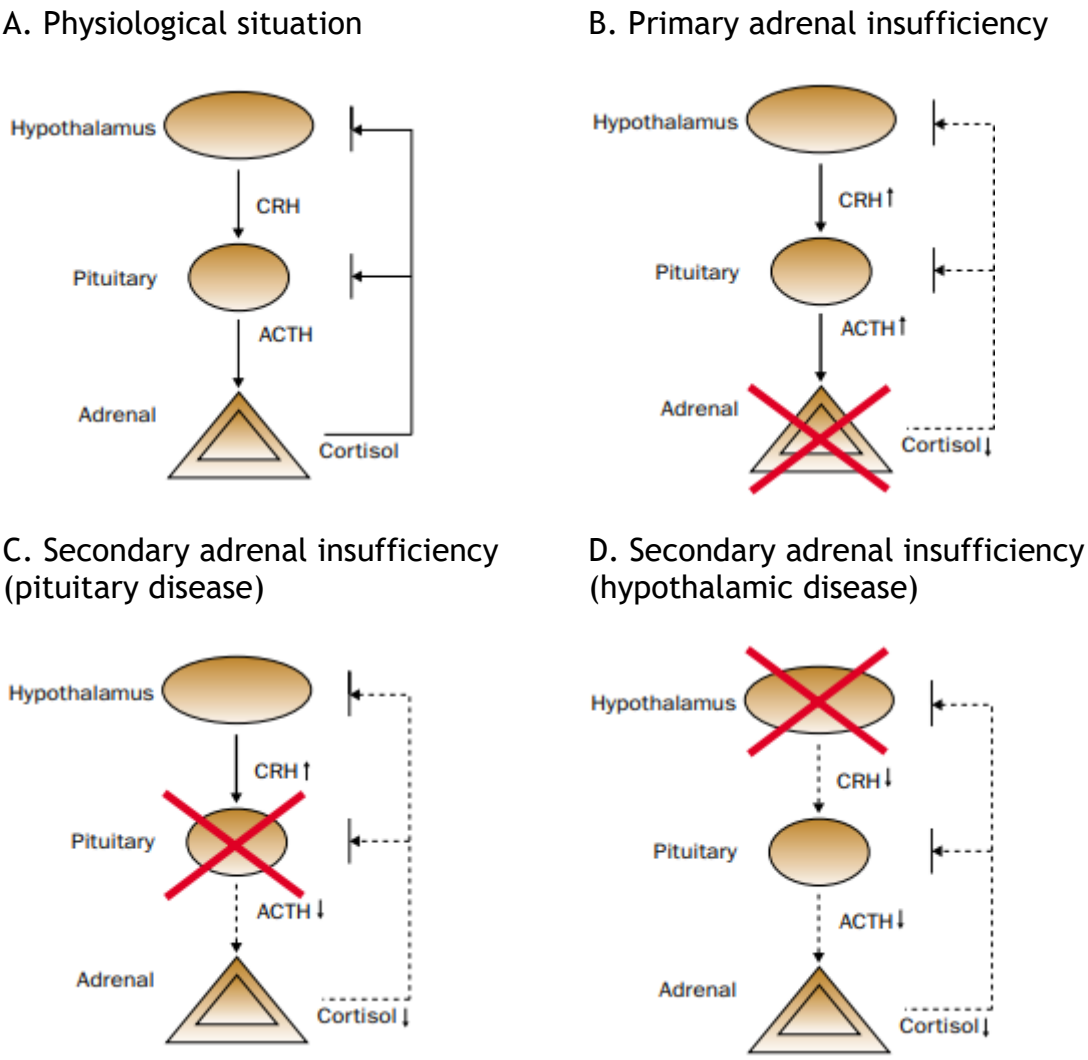


Figure 1-9. Primary and secondary adrenal insufficiency (adapted from Arlt et al. 2003).

1.4.4 Clinical presentation

21-OHD CAH is the most common cause of CAH and other causes of CAH, including 11-β hydroxylase deficiency, 17α-hydroxylase deficiency, 3-β-hydroxysteroid dehydrogenase deficiency, p450 oxidoreductase deficiency and congenital lipoid adrenal hyperplasia collectively account for less than 5% of all CAH cases (Speiser, Arlt et al. 2018). The 21-OHD phenotype is dependent on residual enzyme activity and 21-OHD CAH may be categorised into classic or non-classic types.

Classic CAH often presents in infancy with elevated steroid precursors and overproduction of adrenal androgens due to lack of negative feedback control on the HPA axis, resulting in variable degrees of genital virilisation in a genetically female fetus and no genetic ambiguity in the genetic male fetus. Müllerian duct development is normal, except for the formation of a urogenital sinus with

conjoined urethra and vagina, thus reproductive potential exists despite atypical genitalia (Speiser, Arlt et al. 2018). Classic CAH may be further classified into salt-wasting (SW) and simple-virilising (SV) subtypes depending on the presence or absence of mineralocorticoid deficiency, respectively (Table 1-1). Around 75% of classic CAH cases are of the salt-wasting phenotype (White and Speiser 2000). In patients with SW CAH, there is little or no residual enzyme activity, resulting in cortisol and aldosterone deficiency. These patients may present with 'salt wasting crises' with hyponatraemia, hyperkalaemia, hypovolaemia, acidosis or shock. Thus, prompt treatment is required to avert morbidity and mortality. Patients with SV CAH, associated with residual enzyme activity of 1 to 5% are less likely to have SW crises (White and Speiser 2000).

Table 1-1. Forms of congenital adrenal hyperplasia (CAH).

	Classic	**Simple-virilising**	**Non-classic**
Aldosterone	Low	Normal	Normal
Age at diagnosis	Infant	Infant/child	Child/adult
Virilisation	Severe	Moderate to severe	None/mild
Incidence	1/15,000	1/50,000	1/500

The adverse effects seen in patients with CAH occur due adrenal excess and from chronic glucocorticoid treatment (Figure 1-D). Poorly controlled CAH with adrenal androgen excess may cause advanced skeletal maturation and reduced adult height, central precocious puberty, acne, female hirsuitism, male pattern baldness, irregular menses and reduced fertility potential (Merke and Auchus 2020). Males with poor control may develop small testes, impaired gonadal function and benign testicular adrenal rest tumours (TARTs) (Mendes-Dos-Santos, Martins et al. 2018).

Non-classic CAH, associated with milder allelic variants with residual enzyme activity of 20 to 50%, may present later in adolescence or adulthood with variable degrees of androgen excess, however, patients may be asymptomatic (Falhammar and Nordenström 2015). Children may present with premature adrenarche, acne and advanced skeletal maturation. Adolescent or adult

females may present with hirsuitism, oligomenorrhoea, acne and subnormal fertility (Figure 1-10). Moreover, the mild subclinical impairment of cortisol synthesis in non-classic CAH generally does not lead to adrenal crises. The prevalence of non-classic CAH is estimated to be 1 in 500 to 1 in 1,000 in the general white population, with higher rates of up to 1 in 50 to 1 in 100 among populations with a smaller gene pool, particularly in remote geographic regions and areas with high rates of consanguineous marriages (Hannah-Shmouni, Morissette et al. 2017).

Adrenal crises, resulting from suboptimal replacement of glucocorticoids, are a life-long risk for patients with CAH and a leading cause of mortality in this condition (Falhammar, Frisén et al. 2014).

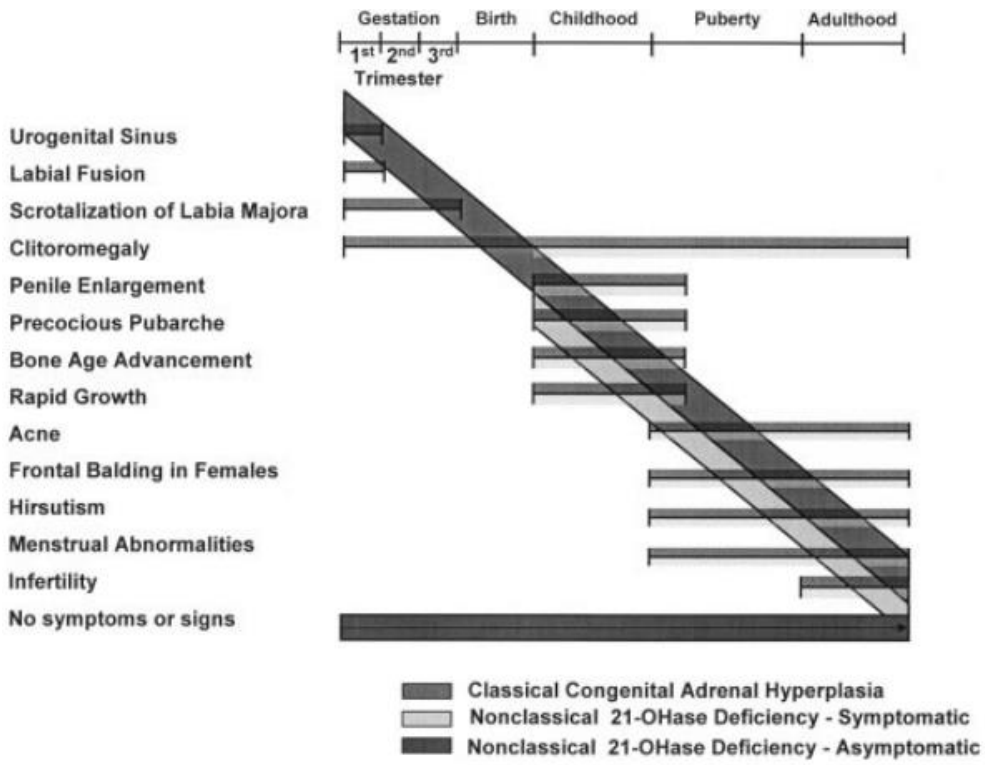


Figure 1-10. Clinical spectrum of classic and non-classic CAH (adapted from New MI et al. 1983).

1.4.5 Medical management

In classic CAH, life-long treatment with glucocorticoids and if necessary, mineralocorticoids is required. The goals of therapy in children are to maintain normal growth, puberty and development whilst preventing adrenal crises, the effects of excess androgen secretion and other long-term complications

including cardiometabolic morbidity (Falhammar, Frisén et al. 2015, Gomes, Mendonca et al. 2020). The Endocrine Society guidelines on the management of CAH due to 21-hydroxylase deficiency (Speiser, Arlt et al. 2018) include recommendations for maintenance glucocorticoid and mineralocorticoid treatment doses (Table 1-2). Despite these recommendations, recent studies using data from the I-CAH registry have shown that there is wide variation in international practice regarding glucocorticoid replacement regimens in children (Bacila, Freeman et al. 2021).

Table 1-2. Maintenance therapy in children with classic CAH (adapted from Speiser et al. 2018).

Medication	Total daily dose	Frequency
Glucocorticoids: Hydrocortisone tablets	10-15 mg/m^2	3 times daily
Mineralocorticoids: Fludrocortisone tablets	0.05-0.2 mg	1-2 times daily
Sodium chloride supplements	1-2 g (17-34 mmol/day) in infancy	Several feedings

Treatment with glucocorticoid in CAH aims restore negative feedback on pituitary ACTH, thereby reducing adrenal androgen excess and aims to replace cortisol. Hydrocortisone is the preferred glucocorticoid for use in growing children as it is associated with the best long-term outcomes with regards to metabolic, cardiovascular and bone health and its shorter half-life reduces the risk of adverse effects including growth suppression (Speiser, Arlt et al. 2018) (Table 1-3).

Table 1-3. Glucocorticoid preparations for CAH.

Glucocorticoid preparations		
Hydrocortisone tablets	10-15 mg/m^2/day in 3 divided doses	• May be crushed and suspended • 5 mg size not available in many countries
Prednisolone syrup, tablets	Use at one quarter to one fifth hydrocortisone dose	• Readily available • Prednisolone generally not preferred in children
Compounded hydrocortisone preparations		• Expensive • Serious errors reported
Immediate-release hydrocortisone granules (Infacort®, Alkindi®)		• 0.5 mg, 1 mg, 2 mg and 5 mg sizes • Approved in EU and USA • Limited availability in some countries
Modified-release hydrocortisone (Plenadren®)	Adults only	• No published data in CAH • Evidence of benefits in AI • Twice daily dosing
Modified and delayed-release hydrocortisone (Chronocort®)	Adults only	• Studies in progress. • Twice daily dosing- two thirds at 2300 hours and one third at 0700
Continuous subcutaneous hydrocortisone using insulin pump	Research phases only	• Expensive • Risk of device failure

Nevertheless, current treatment regimens are unable to adequately mimic the circadian rhythm of cortisol and the physiological stress response (Mah, Jenkins et al. 2004, Porter, Blair et al. 2017). Thus, treatment is an ongoing balancing act to prevent the side-effects from excess androgens due to undertreatment against the effects of excess cortisol from overtreatment (Figure 1-11) and an individualised approach should be adopted.

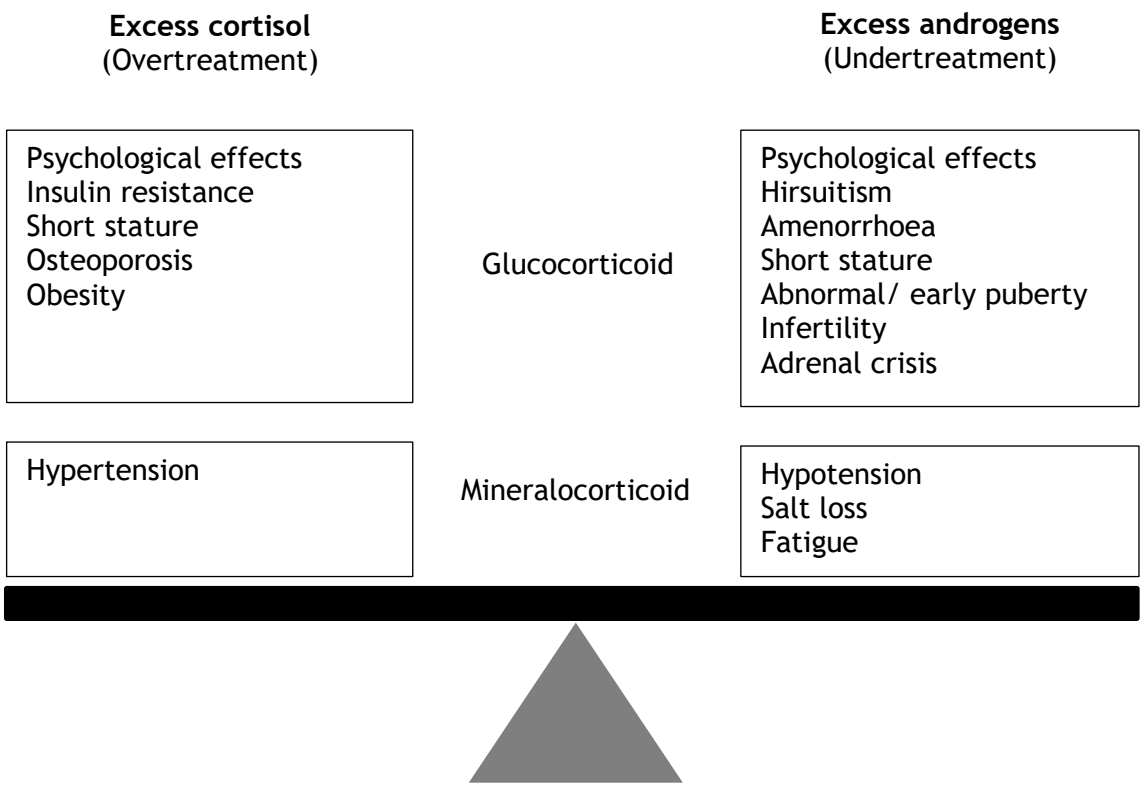


Figure 1-11. Balance between overtreatment and undertreatment in the management of children with CAH (adapted from Han TS et al. 2013).

A natural history study from NIH, the largest longitudinal study of patients with 21-OHD CAH followed 57 patients from childhood to adulthood with a median follow-up of 18.6 years. The study showed that the hydrocortisone dose at the beginning and at the end of the study was >17mg/m^2/day and 17-OHP and androstenedione levels were controlled in only 28% of visits (Torky, Sinaii et al. 2021). Other studies have shown that long-acting glucocorticoids cannot mimic cortisol circadian rhythm and do not control morning androgens in CAH (Debono, Mallappa et al. 2015). Prednisolone replacement in primary adrenal insufficiency is associated with an increased mortality (Ngaosuwan, Johnston et al. 2021), whilst dexamethasone is associated with low bone mineral density and increased body mass index (Whittle and Falhammar 2019). Recently, phase 3 trials of an oral modified release hydrocortisone, licensed for use in children over the age of 12 years which aims to mimic the circadian rhythm have demonstrated normalisation of 17-OHP levels and better disease control on a lower daily dose of hydrocortisone (median dose 20mg/day) with fewer adrenal crises and less frequent sick day dosing than patients on standard therapy (Merke, Mallappa et al. 2021).

In patients with CAH, treatment with mineralocorticoids is achieved with fludrocortisone and monitoring of electrolytes, plasma renin and blood pressure is required. All infants with classic CAH benefit from glucocorticoids and mineralocorticoids within the first year of life due to the low sodium content of infant diets and the relative aldosterone resistance in early infancy (Martinerie, Pussard et al. 2009). Physiological considerations in childhood and adolescence include a high sensitivity to androgens and sex steroids, reduced sensitivity to growth suppression by glucocorticoids than during infancy and increased metabolic cortisol clearance due to decreased 11ß-hydroxysteroid dehydrogenase type 1 activity (Charmandari, Brook et al. 2004). Other studies have shown that fludrocortisone in mild aldosterone deficiency results in lower glucocorticoid dose and better height outcome (Balsamo, Cicognani et al. 2003). In contrast to glucocorticoid treatment, fludrocortisone does not need to be increased during illness.

1.4.6 Monitoring

Current guidelines recommend 3 monthly follow-up for children younger than 18 months and 4 to 6 monthly follow-up for older children (Speiser, Arlt et al. 2018) (Table 1-4).

Steroids can be measured in blood, urine, saliva and dried filter paper samples and fluctuate with both the circadian rhythm and the timing of glucocorticoid intake (Debono, Mallappa et al. 2015, Bacila, Adaway et al. 2019).

Table 1-4. Therapy monitoring in CAH, parameters and goals.

Parameter	Goals
History	
Symptoms of adrenal insufficiency	No signs of adrenal insufficiency
Adrenal crisis prevention	Patient/parent education regarding sick day rules
	Emergency injection kit provided
	Steroid emergency card/medical alert provided
Menstrual cycle	Regular menstrual cycle
Physical examination	
Height	Linear growth within target range
Weight	Within age and sex-dependent reference range
Pubertal development/Tanner stage	Normal pubertal development
Blood pressure	Within age and sex-dependent reference range
Cushingoid features	No signs of hypercortisolism
Glucocorticoid treatment	
17-OHP	Suppressed or normal values indicate overtreatment
Androstenedione	Values within the normal age- and sex-specific range
Testosterone	Values within the normal age- and sex-specific range
ACTH	Not useful for disease control; normal values indicate overtreatment
Mineralocorticoid treatment	
Renin	Normal or mildly high values for age
Imaging	
Bone age yearly (children >2 years/adolescents)	Bone age within 2 SD
Scrotal ultrasound every 2-5 years (adolescents)	No gonadal masses

1.4.7 Acute adrenal insufficiency related adverse events in children

Acute adrenal insufficiency (AI) related adverse events include adrenal crises (AC) and their prodrome, sick day episodes (SDE). A sick day episode (or stress event) may be defined as an event that requires an increase in glucocorticoid from maintenance dose requirements. Currently, there is no consensus as to what events constitute SDE and there is wide variation with regards to glucocorticoid (hydrocortisone) dose adjustments that should be implemented in the event of SDE in children, also known as sick day or stress dosing. Parents are provided with specific guidance in the form of sick day management plans that explain when to increase glucocorticoid doses from baseline and the duration for which the increased dose is to be administered to their child. However, studies have shown that despite repeated patient education with regards to sick day dosing regimens, both adults and children still to appear to be at risk of repeated SDE and AC (El-Maouche, Hargreaves et al. 2018).

Recent guidelines have attempted to define SDE in children by categorising the requirement for an increase in glucocorticoid based on the type of event e.g. non procedural stressful events (fever >38ºC, gastroenteritis with vomiting or diarrhoea) or surgical procedures, with corresponding sick day regimens (Allolio 2015, Rushworth, Torpy et al. 2019, Claahsen-van der Grinten, Speiser et al. 2022) (Table 1-5). However, the majority of protocols and guidance for the prevention and treatment of SDE and AC are based on clinical experience and expert opinion. Additional considerations in the management of SDE include the frequent intake of simple and complex carbohydrates to prevent hypoglycaemia in children (El-Maouche, Hargreaves et al. 2018) and it is recommended that this guidance should be included as part of patient education regarding sick day dosing rules. In patients with non-classic CAH, the Endocrine Society Clinical Practice Guideline suggests sick day dosing in untreated individuals with a suboptimal ACTH test in the case of severe illness, major surgery, major trauma or childbirth (Speiser, Arlt et al. 2018).

Table 1-5. Suggested management and glucocorticoid sick day dosing for children with acute adrenal insufficiency secondary to CAH (adapted from Claahsen-van der Grinten et al. 2022).

Stress event/ sick day	Glucocorticoid dose adjustment
Major illness or high-grade fever (>39ºC in children)	Triple usual dose and administer every 6 hours
Gastroenteritis with diarrhoea and/or vomiting (with or without fever)	Triple usual dose and administer every 6 hours Repeat oral dose if vomiting occurs within 1 hour Consider early parenteral hydrocortisone
Minor illness or low-grade fever (>38ºC in children	Double or triple usual dose and administer every 6-8 hours
Exhausting physical exercise	Add 1 usual dose 30 to 60 minutes before exercise
Major surgery	Hydrocortisone intravenous bolus 50-100 mg/m^2) followed by infusion of 100 mg/m^2 over 24 hours Alternatively, divided doses every 6 hours, intravenous hydrocortisone 100 mg/m^2/day
Short surgery	Hydrocortisone intramuscularly or intravenous bolus 50 mg/m^2 just before general anaesthesia Alternatively, triple usual morning dose before oral intake with-held
Bowel procedures requiring overnight laxative	Double or triple usual dose prior to laxative and repeat every 6 hours if tolerated Alternatively, intramuscular hydrocortisone 50 mg/m^2 with laxative
Dental surgery	Extra morning dose 1 hour prior to surgery
Minor procedures with no sedation	No adjustment required

Adrenal crises (AC) are a life-threatening complication for patients with AI and a leading cause of death in patients with CAH (Shulman, Palmert et al. 2007, Falhammar, Frisén et al. 2014). Patients with CAH have a life-long risk of AC due to an inherent inability to produce enough glucocorticoid in response to stress. Thus, AC occur when the physiological requirement for cortisol is greater than the amount present in the circulation, for example, during periods of stress or infection. In children, AC are most often triggered by infectious illnesses including gastrointestinal and respiratory tract illnesses (Reisch, Willige et al. 2012, El-Maouche, Hargreaves et al. 2018, Tresoldi, Sumilo et al. 2020). Characteristic features of an AC may include hypotension, weakness, lethargy and abdominal pain in the presence of biochemical abnormalities including hyponatraemia, hyperkalaemia, hypoglycaemia or hypocalcemia (Hahner, Ross et al. 2021). Despite characteristic features and typical biochemistry, there is no

universally agreed definition of an ‘adrenal crisis’ (Rushworth, Torpy et al. 2017, Rushworth, Torpy et al. 2019). Even with over 50 years of experience with glucocorticoid therapy in CAH, the prevention and management of AC in children remains challenging due to the rarity of the condition, varying presentations and a lack of consensus and evidence-based recommendations regarding it’s definition and management. This has resulted in the adoption of pragmatic definitions of AC (Allolio 2015, Arlt and Society for Endocrinology Clinical 2016, Husebye, Pearce et al. 2021, Nowotny, Ahmed et al. 2021). Nevertheless, there is increasing consensus that the avoidance of acute adverse events due to AI is one of the most important outcomes that can be routinely measured in patients with CAH (Grossman, Johannsson et al. 2013, Regan, Vaidya et al. 2019).

An AC is a medical emergency requiring immediate intravenous (IV) hydrocortisone and rehydration with intravenous fluids (isotonic saline infusion). Cortisol dose escalation during SDE is the cornerstone to preventing AC and this includes the requirement to increase oral glucocorticoid dose or the administration of intramuscular (IM) or IV glucocorticoids if oral medication is not tolerated (e.g. diarrhoea or vomiting) (Arlt and Society for Endocrinology Clinical 2016). Thus, it is recommended that all patients carry medic alert cards or bracelets and that patient education regarding the risk and management of AC is carried out at regular intervals (Repping-Wuts, Stikkelbroeck et al. 2013).

Recent studies have reported an AC incidence of 5.2 to 10.9 per 100 patients years (Odenwald, Nennstiel-Ratzel et al. 2016, Rushworth, Falhammar et al. 2016, El-Maouche, Hargreaves et al. 2018, Ishii, Adachi et al. 2018) in children with CAH, with a mortality rate of 0.5 per 100 patient years (Jenkins-Jones, Parviainen et al. 2018). Other studies have estimated that deaths from AC contribute 42% of all deaths in CAH (Falhammar, Frisén et al. 2014). It is possible that some of this variation in the reported incidence of AC is related to lack of universally accepted definitions of AC and SDE or there may be other factors that influence this variation, some that are patient dependent and some that reflect on health care delivery (Jenkins-Jones, Parviainen et al. 2018, Dineen, Thompson et al. 2019).

Some studies evaluating the risk of illness sequelae in patients with CAH have reported an association with medication dosages, for example, higher doses of

fludrocortisone have been associated with increased rates of SDE in childhood (El-Maouche, Hargreaves et al. 2018). The latter may reflect a more severe phenotype of disease requiring higher doses of fludrocortisone and therefore a greater susceptibility to adverse events. Other studies have shown higher hospital admission rates amongst girls compared with boys (Rushworth, Chrisp et al. 2017, El-Maouche, Hargreaves et al. 2018) with younger children having a greater risk of hospitalisation than older children (White and Arlt 2010, Eyal, Levin et al. 2019). These results may reflect parental reluctance to administer sick day doses of glucocorticoids or intramuscular hydrocortisone to very young children or poorer recognition of illness in younger children. Furthermore, pre-hospital and in-hospital management of children with CAH can vary significantly between hospitals (Chrisp, Maguire et al. 2018).These findings emphasise the importance of standardisation of practice and determining other factors, other than solely patient factors, when taking into account rates of illness. Thus, the potential value of multi-centre studies using larger national and international datasets to provide an evaluation of illness sequelae and associated factors in rare conditions such as CAH must be explored.

Other studies have suggested that patients with CAH may have a greater predisposition to infectious diseases. A UK primary care database study analysing drug prescriptions and clinical diagnoses showed increased rates of infectious illnesses (respiratory tract, urinary tract and gastrointestinal) in patients with CAH (Tresoldi, Sumilo et al. 2020). Nevertheless, it is unclear whether this risk is due to the underlying disease or an effect of treatment with glucocorticoids. A single-blind randomised trial showed that patients treated with once daily modified-release hydrocortisone had more normal immune cell profiles and less infections than those on standard glucocorticoid treatment (Isidori, Venneri et al. 2018), however, further research is required.

There remains a need to improve our understanding of the current definitions and management of acute AI related adverse events amongst clinicians from expert centres at an international level. Moreover, a greater standardisation of the definition of these events as well as their prevention and management would facilitate benchmarking and improvement in clinical care.

1.5 Health-related quality of life (HRQoL) and psychosocial outcomes in DSD and CAH

1.5.1 Overview

Patients with DSD and CAH are known to be at risk of psychosocial co-morbidity (Schützmann, Brinkmann et al. 2009, Suorsa, Mullins et al. 2015), with a wide range of effects on psychosocial and psychosexual adjustment (Table 1-6). Thus, the management of DSD and CAH requires a multidisciplinary approach and early psychosocial screening is recommended (Ernst, Gardner et al. 2018, Crerand, Kapa et al. 2019), with the aim of enhancing positive psychosocial adaptation in children and caregivers (Schaeffer, Tryggestad et al. 2010, Bakula, Sharkey et al. 2017).

Distress related to associated feelings of shame and stigma secondary to having the condition, uncertainties regarding diagnosis and poor coping strategies may lead to a greater risk of adverse psychosocial outcomes which may be greater than the severity of the DSD or extent of genital ambiguity itself (Brinkmann, Schuetzmann et al. 2007, Rolston, Gardner et al. 2015, Alpern, Gardner et al. 2017). Recent studies indicate clinically significant levels of depression and anxiety amongst caregivers of children with these conditions (Pasterski, Mastroyannopoulou et al. 2014, Perez, Delozier et al. 2019). Despite evidence that parents of children with DSD have significant psychosocial co-morbidity and high levels of stress, there are a paucity of studies evaluating the generic (or 'non categorical') effects of psychosocial adaptation and family dynamics including psychosocial distress experienced by parents of young children with DSD, factors influencing adherence to treatment regimens, stress associated with clinic visits and clinical examination, the impact on the individual in terms of body or self-image and other problems of psychosocial adaptation (Stout, Litvak et al. 2010, Sharkey, Bakula et al. 2018) (Table 1-10). Thus, routine screening of parents and patients for both generic and condition-specific risk factors are indicated as part of ongoing clinical care (Ernst, Gardner et al. 2018, Crerand, Kapa et al. 2019). This lack of information is most likely due to a paucity of instruments that can be used in parents of young children to assess psychosocial outcomes.

Previous studies investigating psychological outcomes in individuals with DSD or CAH have often focused on a limited set of endpoints including the role of prenatal androgens on gender development (i.e. gender identity, gender role, sexual orientation) (Long, Wisniewski et al. 2004, Pappas, Wisniewski et al. 2008, Bakula, Mullins et al. 2017) in older children, adolescents and adults (Lee, Schober et al. 2012).

The development and validation of quality of life instruments or tools used to collect patient/parent-reported experiences of care that can be performed in a routine clinic setting and that inform the need for future clinical psychology input are vital.

Table 1-6. Selected generic and CAH-specific risk factors for psychosocial and psychosexual adaptation (adapted from Claahsen-van der Grinten et al. 2022).

A. Generic (non-categorical)
Males and females
Challenges to parenting with: - accompanying caregiver psychological distress - negative emotional spillover effects from parent to child - perceived child vulnerability and overprotectiveness
Burdens of clinic visits and adherence to treatment regimens; emergency room visits and hospitalisations
Threats to body-image and self-esteem
Higher rates of missed school and peer victimisation
Academic challenges
Problems of psychosocial adaptation (ie, increased psychological symptomatology in youth and adults compared with healthy comparison groups
Systemic weaknesses in the process of transitioning from paediatric to adult care
Career barriers for people with chronic illness
B. CAH-specific (categorical)
Female-specific
Early reactions to newborn with atypical genitalia (experiences in medical environment)
Stigma (anticipated or experienced) stemming from atypical genitalia and its modulation by culture
Tension between person-first (ie, CAH as a medical condition) vs identity-first (intersex and LGBT advocacy)
Secrecy
Genital examinations and medical photography
Gender of rearing in Prader V cases
Genital surgery decision making and: - consequences for sexual function - outcomes of postponing surgery
Gender identity
Effects on social support
Model of care
Males and females
Terminology
Early puberty/attenuated adult height; growth hormone treatment
Neurocognitive sequelae
Prenatal dexamethasone
Hyponatraemic episodes
Fertility problems (ie, testicular adrenal rest tumours in males)

1.5.2 Parent reported outcome measures

Generally, there has been growing interest in adopting standardised tools for assessing subjective experiences of patients and incorporating reports of parent/caregiver proxies in young children in the context of ongoing patient care. The assessment of a child's adaptation to their medical condition is also becoming increasingly common (Janssens, Thompson Coon et al. 2015) with the use of parent-proxy reporting playing an important role in overcoming challenges associated with assessing the subjective experience of young children (Varni, Limbers et al. 2011). Parent reported outcome measures (PROMs) can be generic, such as the scales comprising the 'Patients Reported Measurement Information System' (PROMIS) (Irwin, Gross et al. 2012) and the 'Patient Health Questionnaire for Depression and Anxiety' (Kroenke, Spitzer et al. 2009) or can be condition-specific, for example, the Pediatric Asthma Scale (Yeatts, Stucky et al. 2010). Previous work has also highlighted the need for the integration of assessment tools into clinic settings for parents and patients (Sandberg, Gardner et al. 2017). Currently, there is a lack of DSD-specific measures that can be routinely incorporated into clinical practice to enable assessment and monitoring of parent and patient needs at a single point in time or longitudinally, thereby facilitating opportunities for targeted and timely psychological, medical or surgical interventions. Guidance from the Endocrine Society has endorsed the further development and validation of tools for evaluating quality of life in patients with DSD and their families (Speiser, Arlt et al. 2018) and the 2006 Consensus Statement on the Management of Intersex Disorders outlined the importance of a mental healthcare component to promote positive adaptation in individuals with DSD (Lee, Houk et al. 2006).

1.5.3 Parent reported outcome questionnaires

Recently, a methodological gap was addressed by the development of DSD-specific health-related quality of life (HRQoL) measures for parents of children under 7 years of age including a parent-proxy measure and a self-report measure (Alpern, Gardner et al. 2017) and these measures were validated in a cohort of parents of 132 young children. Along with a need to develop standardised questionnaires that incorporate DSD-specific and generic items to assess the impact of DSD on parents and children, there is a need for these questionnaires

to overcome the perceived challenges of managing young patients in a busy clinic setting and have high acceptability by parents and health professionals (Sandberg, Gardner et al. 2017, Ernst, Gardner et al. 2018). The development and utilisation of such tools will pave the way for the development of clinical benchmarks for psychosocial outcomes in DSD/ CAH with the overall aim of optimising patient care.

1.6 Conclusions

The assessment of outcomes and the development of clinical benchmarks for rare endocrine conditions such as DSD and CAH poses a challenge. This requires evaluation of high volume real-world data, with the overall aim of better informing the clinical and patient community and laying a foundation for which future studies can target interventions aimed at improving outcomes and quality of life for children with these conditions. Central to all rare conditions are disease registries, such as EuRRECa and the I-CAH registry, and the need for collaboration between international networks. Investigating the availability and participation in rare endocrine disease registries and the development of a virtual platform for evaluating the epidemiology of rare endocrine conditions in addition to signposting participants to high-quality, disease-specific registries will provide a better understanding of the occurrence of the rare conditions. Maximising the quality of registries by ensuring adherence to governance frameworks and incorporation of FAIR data principles will ensure best practice and long-term sustainability. Thus, the development of a quality evaluation tool for rare disease registries for self-assessment is a valuable objective.

There is a paucity of evidence on the occurrence of acute adrenal insufficiency related adverse events (sick day episodes and adrenal crises) in children with CAH from large multi-centre international cohort studies, thus, the development of international benchmarks to evaluate core outcomes at a global level is challenging. Evaluating real world epidemiological data from the I-CAH registry will enable a greater understanding of the factors influencing the risk of illness sequelae and the international variability of acute AI related adverse events and disease outcomes. The prevention and management of acute AI related adverse events is also challenging due to the rarity of CAH, varying presentations and a lack of consensus on definitions of sick day episodes and adrenal crises. A greater understanding of the current definitions and management of these events amongst international expert centres will facilitate the development of clinical benchmarks for CAH care.

Parents of young children with DSD are at risk of psychosocial morbidity, yet, there are a lack of tools available for the assessment of psychosocial outcomes in parents and young children for use in a routine clinic setting. Instruments that

can be used to perform routine screening would enable the assessment of psychosocial sequelae and the provision of psychosocial interventions in a timely manner. Longitudinal screening would also facilitate the development of international benchmarks for psychosocial outcomes in parents and children with this condition.

1.7 Key aims of the thesis

The overall objective of my studies was to improve the quality of care of individuals with rare conditions through the collection and use of real-world data. The focus of my PhD was on DSD and CAH as models of rare endocrine conditions and the methodology utilised in investigating the presentation and outcomes in these conditions are transferable to other rare conditions. By exploring a range of methods at a local, national and international level, the intention was to facilitate the development of clinical benchmarks for these conditions against which healthcare professionals can compare their own practice.

The aim of my studies will be:

1. To identify the availability of international registries for rare endocrine conditions and to understand the extent of engagement with these registries within a network of expert centres (Endo-ERN).

2. To ascertain the level of consensus amongst the rare disease community regarding the quality criteria that should be considered essential features of a rare disease registry and the development of a tool for the quality assessment of registries.

3. To explore web-based methods of capturing the presentation of rare endocrine conditions at an international level via the EuRRECa e-REC platform.

4. To investigate the occurrence of acute adrenal insufficiency related adverse events in children with CAH, evaluate factors which may influence these outcomes and determine inter-centre variability for sick day episodes and adrenal crises using data from the I-CAH registry.

5. To evaluate the level of consensus on criteria considered essential for defining and managing acute adrenal insufficiency related adverse events in children with CAH.

6. To study the presentation of DSD at a national level in Scotland.

7. To develop and validate health-related quality of life (HRQoL) tools for parents and young children with DSD.

CHAPTER 2

The current landscape of registries for rare endocrine conditions

The findings of this chapter have been published by **Ali SR**, Bryce J, Cools M, et al. The current landscape of European registries for rare endocrine conditions. *Eur J Endocrinol*. 2019;180:89-98.

2 The current landscape of registries for rare endocrine conditions

2.1 Abstract

Background: Registries are vital for centres of expertise. The European reference network for rare endocrine conditions (Endo-ERN) consists of 71 reference centres (RC) covering several groups of rare endocrine conditions within eight main thematic groups. It is unclear if awareness, participation and availability of registries is uniform for all Endo-ERN conditions.

Objective: To identify international registries that are led from Europe for rare endocrine conditions within Endo-ERN and understand the extent of engagement with these registries within the Endo-ERN expert network.

Methods: A database search of orphanet and RD-Connect for international registries, followed by a survey of all RC in Endo-ERN.

Results: Of the 42 conditions with orphacodes currently covered within Endo-ERN, international registries exist for 33 (78%). Of the 71 RC, 58 (82%) responded to the survey. Of 27 registries identified in the Orphanet and RD-Connect databases, Endo-ERN RC were aware of 11 (41%). Of 21 registries identified by the RC, RD-Connect and Orphanet did not have a record of 10 (48%). Of the 29 glucose RC, the awareness and participation rate in an international registry was highest for rare diabetes at 75% and 56% respectively. Of the 37 sex development RC, the corresponding rates were highest for disorders of sex development at 70% and 52%. Of the 33 adrenal RC, the rates were highest for adrenocortical tumours at 68% and 43%. Of the 43 pituitary RC, the rates were highest for pituitary adenomas at 43% and 29%. Of the 31 genetic tumour RC, the rates were highest for MEN1 at 26% and 9%. For the remaining conditions, awareness and participation in registries was less than 25%.

Conclusion: Although there is a need to develop new registries for rare endocrine conditions, there is a more immediate need to improve the awareness and participation in existing registries.

2.2 Introduction

A rare disease or rare condition is defined as one that affects less than 5 in 10,000 of the general population (European Commission (EC) Regulation # 141/2000). One in 17 people, or almost 6% of the population, will be affected by a rare condition at some point in their lifetime, equating to 3.5 million people in the UK and 30 million people across Europe (Baldovino, Moliner et al. 2016). Currently, there are 6000-8000 known rare conditions and around 5 new conditions are described in medical literature on a weekly basis. It is estimated that over 440 distinct rare diseases that affect the endocrine system exist (Reincke and Hokken-Koelega 2021). Rare endocrine conditions are often chronic and progressive requiring coalesced efforts over the lifetime of a patient to reduce morbidity and mortality. Rare endocrine conditions pose a challenge due to gaps in knowledge of long-term outcomes and prognosis, and a lack of expert, evidence based multidisciplinary care which results in variation in patient care.

Registries are important for centres of expertise and for multidisciplinary teams looking after patients with rare endocrine conditions (Kourime and Ahmed 2018). Registries enable pooling of data for quality improvement, research and the surveillance of conditions. They also enable multidisciplinary communication between healthcare staff, patients and other stakeholders, facilitatating the development of best practice guidelines and clinical benchmarks. Over 800 rare disease registries are reported to exist in Europe, some operating on regional, national or international levels (Taruscio, Vittozzi et al. 2015, Baldovino, Moliner et al. 2016). The use of cross border registries offers benefits for multicentre collaboration and standardised data collection for rare conditions, with the overall aim of improving patient care.

The international registration of patients with rare conditions is widely endorsed by the European Union International Rare Disease Research Consortium (http:/irdirc.org). Virtual database platforms such as Orphanet (orpha.net) and RD-Connect (rd-connect.eu/) have attempted to identify existing registries for rare conditions. Orphanet was established by the French National Institute for Health and Medical Research in 1997 and became a European endeavour from 2000, supported by the European Commission. It has grown to become a consortium of 40 countries within Europe and beyond. Orphanet provides

information on rare diseases including an inventory of registries and biobanks. It also provides a record of orphan drugs, a directory of patient organisations and expert centres and a list of ongoing research projects and clinical trials in rare diseases. Orphanet maintains the orphanet rare disease nomenclature (ORPHAcode), helping to improve the visibility of rare diseases in health and research information systems. RD-Connect was established in 2012 and funded by the European Commission (Gainotti, Torreri et al. 2018), it also provides a free inventory of rare disease registries and biobanks within an integrated platform that includes a clinical bioinformatics platform for data analysis and interpretation of DNA sequencing results.

European reference networks (ERNs) are clinical networks that aim to manage rare conditions requiring specialist input and a concentration of knowledge and resources (Azzopardi-Muscat and Brand 2015). The European reference network for rare endocrine conditions (Endo-ERN), developed in 2017, is the largest ERN and currently includes 111 reference centres (RC) from 27 member states. Endo-ERN includes 42 groups of rare endocrine conditions within 8 main thematic groups (MTGs) covering the spectrum of congenital and acquired endocrine conditions including disorders of sex development.

Registries are regarded as essential for networks such as Endo-ERN. However, the range of international registries that exist for these groups of rare endocrine conditions is unclear. In addition, the extent of awareness and participation with these registries amongst Endo-ERN expert centres is unclear. The development of databases such as Orphanet and RD Connect and the creation of Endo-ERN, provided a unique opportunity to study the existence of registries led from Europe and evaluate the extent of involvement with these registries of health professionals within an expert network such as Endo-ERN.

2.3 Aims

The aims of this study were:

- To identify international registries (led from Europe) for rare endocrine conditions
- Determine the extent of engagement with international registries for rare endocrine conditions within an expert network such as Endo-ERN
- Determine priorities for the future development and the need for registries for rare endocrine conditions

2.4 Methods

2.4.1 Ethics approval and consent

Ethics approval was not required as this project was performed as a health service evaluation based on information provided by the participating centres and did not require any information on patients or human participants. Participant consent was inferred from survey completion.

2.4.2 Database search

For the purpose of this mapping exercise, an international registry was defined as a patient registry that collected uniform information on individual patients, was used by more than one country within Europe and where the coordinating centre was based in Europe.

To identify the number of international registries that currently exist for the rare endocrine conditions covered within Endo-ERN, the outputs from Orphanet and RD-Connect databases were examined using Orphacodes for all conditions (Table 2-1).

2.4.3 Participants

Seventy-one Endo-ERN RC leads, from 19 countries, were invited to complete a survey documenting their awareness of international, national and local

registries and active participation in registries for rare endocrine conditions at an international, national and local level.

2.4.4 International survey

All Endo-ERN members were surveyed between October and November 2016. Endo-ERN RC leads were asked to complete their survey responses regarding their awareness and/or participation in international, national and local registries for each condition that they had been approved for, using preset answer categories (Yes/No). To understand future priorities, respondents were asked to denote 1–5 on a Likert scale to assess the level of priority for need of a registry for a given condition, where a score of 5 indicated the greatest priority.

2.4.5 Statistical analysis

Categorical data were analysed using descriptive statistics. Microsoft Excel 2016 (Microsoft Corp, Redmond, WA, USA) was used to collate and analyse numerical data. Median and range values were obtained for the dataset.

Table 2-1. Endo-ERN main thematic groups, specific conditions and corresponding Orphacodes.

Endo-ERN main thematic group (MTG)	Specific condition	Orphacode
MTG 1- Adrenal	Sporadic paraganglioma-phaechromocytoma	ORPHA276624
	Adrenocortical carcinomas	ORPHA1501
	Cortisol producing adenomas	ORPHA443287
	Primary adrenal insufficiency	ORPHA101959
	Congenital adrenal hyperplasia	ORPHA418
	Familial hyperaldosteronism	ORPHA235936
MTG 2- Calcium and phosphate	Hypoparathyroidism	ORPHA181405
	Pseudohypoparathyroidism (iPPSD)	ORPHA97593
	Hypocalcaemic vitamin D-dependent rickets	ORPHA289157
	Hypocalcaemic vitamin D-resistant rickets	ORPHA93160
	Hyperparathyroidism including parathyroid cancer	ORPHA181408
	Familial hypocalciuric hypercalcaemia	ORPHA405
	PTH-independent hypercalcaemia	ORPHA300547
	Hypophosphataemic rickets	ORPHA437
	X-linked hypophosphataemia	ORPHA89936
	Autosomal dominant hypophosphataemic rickets	ORPHA89937
	Autosomal recessive hypophosphataemic rickets	ORPHA289176
	Hereditary hypophosphataemic rickets with hypercalciuria	ORPHA157215
	Oncogenic osteomalacia	ORPHA352540
	Familial hyperphosphataemic tumoural calcinosis	ORPHA306661
MTG 3- Glucose and insulin	Rare diabetes	ORPHA101952
	Hyperinsulinism	ORPHA276525
	Insulin resistance syndrome	ORPHA181368
MTG 4- Genetic endocrine tumours	Multiple endocrine neoplasia type 1	ORPHA652
	Multiple endocrine neoplasia type 2	ORPHA653
	Carney complex	ORPHA1359
	Hereditary paraganglioma-phaechromocytoma	ORPHA29072
	Von Hippel-Lindau syndrome	ORPHA892
MTG 5- Growth and obesity	Silver russell syndrome	ORPHA813
	Beckwith-wiedemann syndrome	ORPHA116
	Prader willi syndrome and Prader willi-like Syndrome	ORPHA739
	Noonan syndrome	ORPHA648
	GH Resistance Syndromes	ORPHA633
MTG 6- Pituitary	Pituitary adenoma	ORPHA99408
	Congenital hypopituitarism	ORPHA95494
	Acquired hypopituitarism	ORPHA95502
MTG 7- Sex development	Chromosomal DSD	ORPHA325546
	XY DSD	ORPHA98085
	XX DSD	ORPHA2982
	Isolated congenital anosmic hypogonadotrophic hypogonadism	ORPHA478
	Isolated congenital normosmic hypogonadotrophic hypogonadism	ORPHA432
MTG 8- Thyroid	Thyroid hormone signalling disorders	ORPHA183631
	Congenital hypothyroidism	ORPHA442
	Congenital hyperthyroidism	ORPHA424
	Non-metastatic thyroid carcinoma	ORPHA100088

2.5 Results

2.5.1 Response rate

A response rate of 82% (58/71 RC) was obtained (Figure 2-1). Twenty-five (35%) RCs were involved in six or more MTGs and 26 (37%) RCs were involved in one MTG only. The average response rate across all eight themes was 80% (Figure 2-2).

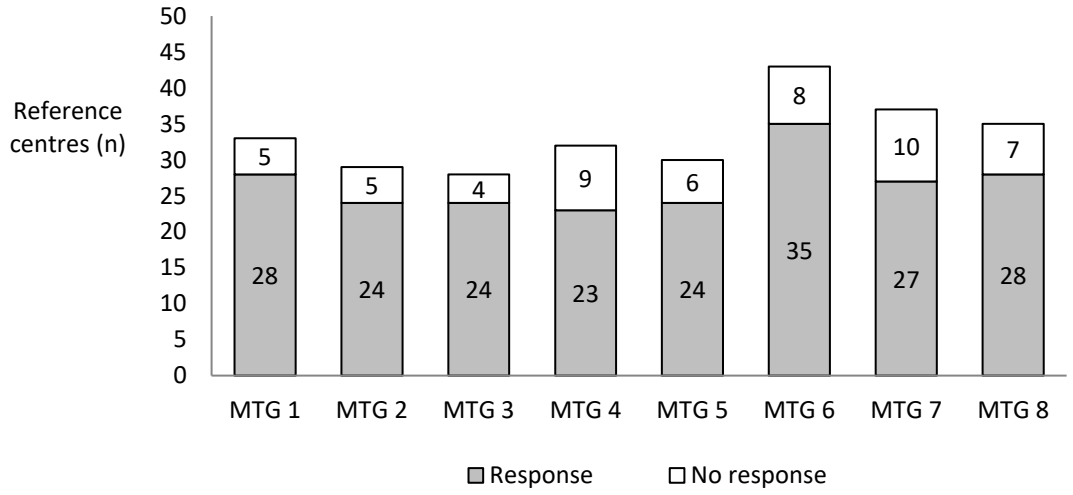


Figure 2-1. Endo-ERN reference centre lead survey response rates.
The numbers within each bar represent the number of reference centres that responded to the survey. MTG, main thematic group; MTG 1, adrenal disorders; MTG 2, disorders of calcium and phosphate homeostasis; MTG 3, genetic disorders of glucose and insulin homeostasis; MTG 4, genetic endocrine tumour syndromes; MTG 5, disorders of growth and genetic obesity; MTG 6, hypothalamic and pituitary disorders; MTG 7, disorders of sex development and maturation; MTG 8, thyroid disorders.

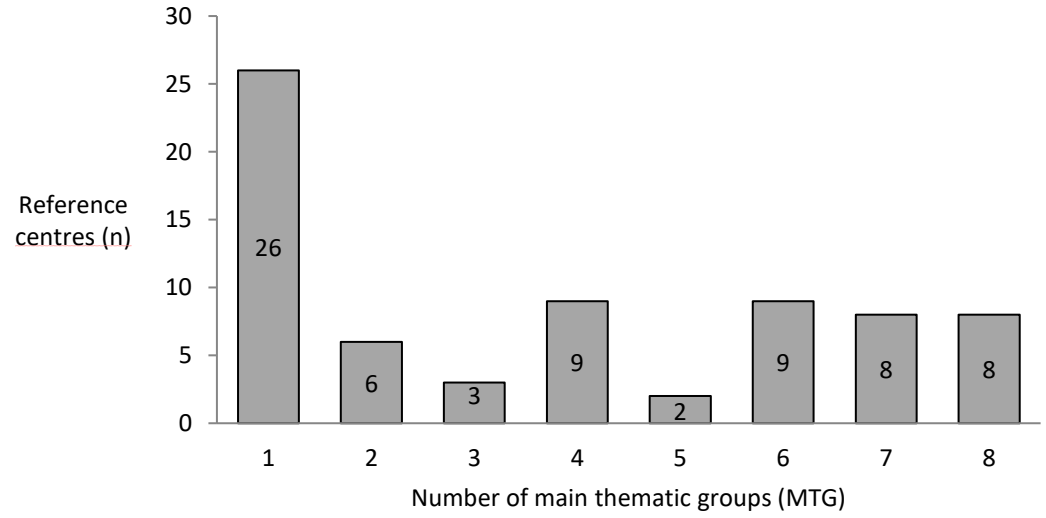


Figure 2-2. Reference centres participation in main thematic groups.
The numbers within each bar represent the number of reference centres that participated to the survey.

2.5.2 Current registries for rare endocrine conditions

Of the 42 rare endocrine conditions with orphacodes currently covered within the 8 main thematic groups of Endo-ERN, international rare disease registries exist for 33 (78%) conditions. A database search of Orphanet and RD-Connect identified 20 and 7 registries, respectively. The survey of Endo-ERN RC leads identified 21 registries. Of the 27 registries identified via Orphanet or RD-Connect, Endo-ERN members reported awareness of 11 (41%) registries (Figure 2-3).

Figure 2-3. International registries for rare endocrine conditions.
A total of 33 international registries were identified via Endo-ERN reference centres leads, Orphanet and RD-Connect.

Three international registries were identified by Endo-ERN, Orphanet and RD-Connect, and these included ERCUSYN (European Registry on Cushing's Syndrome, www.lb.de/ercusyn), EUROWABB (EU Rare Diseases Registry for Wolfram Syndrome, Alstrom Syndrome, Bardet–Biedl Syndrome and Other Rare Diabetes Syndromes, www.euro-wabb.org) and I-DSD (International Registry for Disorders of Sex Development, www.i-dsd.org). Amongst other international registries identified, several registries also existed for discrete groups of conditions including adrenal, genetic disorders of glucose and insulin homeostasis and growth and obesity syndromes. Six industry-led registries were identified by Endo-ERN RC and of these, none were identified in Orphanet and

RD-Connect; whereas, of the 27 non-commercial registries, all were identified through Orphanet, RD-Connect or both (Table 2-2).

In addition to the 21 international registries for rare endocrine conditions identified by RC leads, 61 national registries were identified by RC leads for conditions within the 8 MTGs, with the largest number of registries identified for conditions within the genetic endocrine tumours (n=15 registries), adrenal (n=10), calcium & phosphate (n=10) and thyroid (n=8) groups.

Table 2-2. International rare disease registries with a coordinating centre within Europe.
Endo-ERN conditions categorised according to the main thematic group (MTG) and their level of awareness within the Endo-ERN network, Orphanet and RD-Connect.

International Rare Disease Registry (Coordinating Centre Within Europe)	Endo ERN MTG (1-8)	Endo-ERN Conditions (Orphacode)	Orphanet	RD-Connect	Awareness-Endo-ERN
International Pheochromocytoma and Paraganglioma Registry (Freiburg, Germany)	1, 4	Sporadic phaeochromocytoma-paraganglioma (PCC/PGL) (ORPHA276624); Hereditary PCC/PGL (ORPHA29072); Von Hippel Lindau Syndrome (ORPHA892)	+	-	+
ENSAT: European Network for the Study of Adrenal Tumours (Brussels, Belgium)	1, 4	Sporadic phaeochromocytoma-paraganglioma (PCC/PGL) (ORPHA276624); Adrenocortical carcinoma (ORPHA1501); MEN type 1 (ORPHA652); MEN type 2 (ORPHA653); Carney complex (ORPHA1359); Hereditary PCC/PGL (ORPHA29072); Von Hippel Lindau Syndrome (ORPHA892)	+	-	+
EU-AIR: European Adrenal Insufficiency registry (Shire, Zug, Switzerland)	1	(Primary) Adrenal insufficiency (ORPHA101959)	-	-	+
EURADRENAL: European Patient Registry on Autoimmune Adrenal Failure (Bergen, Norway)	1	(Primary) Adrenal insufficiency (ORPHA101959)	+	-	+
I-CAH: International Registry for Congenital Adrenal Hyperplasia (Glasgow,UK)	1, 7	Congenital adrenal hyperplasia (ORPHA418); 46, XX DSD (ORPHA2982)	+	-	+
ERCUSYN: European Registry on Cushing's Syndrome (Barcelona, Spain)	1, 4, 6	Adrenocortical carcinoma (ORPHA1501); Cortisol producing adenomas (ORPHA443287); MEN type 1 (ORPHA652); MEN type 2 (ORPHA653); Carney complex (ORPHA1359); Pituitary adenoma (ORPHA99408)	+	+	+
ESPN/ERA-EDTA Registry: European Registry for Children on Renal Replacement Therapy (Amsterdam, Netherlands)	1, 4, 8	Adrenocortical carcinoma (ORPHA1501); Hereditary PCC/PGL (ORPHA29072); Von Hippel Lindau Syndrome (ORPHA892); Congenital hyperthyroidism (ORPHA424)	+	-	-
X-ALD: X-linked Adrenoleukodystrophy Database (Amsterdam, Netherlands)	1	(Primary) Adrenal insufficiency (ORPHA101959)	+	-	-
European LeukoDatabase (LeukoDB) (Paris, France)	1	(Primary) Adrenal insufficiency (ORPHA101959)	-	+	+
European Parathyroid Tumour Registry (Leiden, Netherlands)	2	Rare forms of hyperparathyroidism including parathyroid cancer and FHH (ORPHA181408)	+	-	+
EUROGLYCANET- International Patient Registry and Cohort for Congenital Disorders of Glycosylation (Leuven, Belgium)	2	Hyperphosphatemia (ORPHA306661)	+	-	-
XLH (X-linked Hypophosphataemia) Registry (Kyowa Kirin, Galashiels, UK)	2	Hypophosphatemia (ORPHA 89937)	-	-	+
UK10K_RARE_SIR- The Severe Insulin Resistance (SIR) Variant Database (HInxton, UK)	3, 5	Insulin-resistance syndrome (ORPHA181368); Rare diabetes mellitus (ORPHA101952); Rare genetic obesity (ORPHA77828)	+	-	-
EUROWABB: An EU Rare Diseases Registry for Wolfram Syndrome, Alstrom Syndrome, Bardet-Biedl Syndrome and Other Rare Diabetes Syndromes (Birmingham, UK)	3, 5	Rare diabetes mellitus (ORPHA101952); Rare genetic obesity (ORPHA77828)	+	+	+
SWEET: 'Better control in Pediatric and Adolescent diabetes: Working to create centers of reference' (Hannover, Germany)	3	Rare diabetes mellitus (ORPHA101952)	-	-	+
EcLip: European Consortium of Lipodystrophies (Ulm, Germany)	3	Rare diabetes mellitus (ORPHA101952)	-	-	+

ENETS: European Neuroendocrine Tumour Society (Athens, Greece)	4	Hereditary PCC/PGL (ORPHA29072)	-	+	+
Cooperative European Paediatric Renal Transplant Initiative registry (Heidelberg, Germany)	4, 6	Von Hippel Lindau Syndrome (ORPHA892); Congenital hyperthyroidism (ORPHA424)	+	-	-
MD-NET: Muscle Tissue Culture Collection (MTCC) (EuroBioBank partner) (Munchen, Germany)	5	Prader Willi and Prader Willi-like syndrome (ORPHA739); Rare genetic obesity (ORPHA77828)	+	-	-
European Prader-Willi Syndrome Database (Cambridge, UK)	5	Prader Willi and Prader Willi-like syndrome (ORPHA739); Rare genetic obesity (ORPHA77828)	+	-	-
RaDiCo-IDMet- French and European Cohort in Imprinting Disorders and Metabolism Future (Paris, France)	2, 3, 5	Hypoparathyroidism (ORPHA181405); Rare diabetes mellitus (ORPHA101952); Prader Willi and Prader Willi-like syndrome (ORPHA739); Silver Russell Syndrome (ORPHA813); Beckwith Wiedemann Syndrome (ORPHA116); Rare genetic obesity (ORPHA77828)	+	+	-
IGFD Registry: The Increlex Growth Forum Database (Ipsen, Paris, France)	5	GH resistance syndromes (ORPHA633)	-	-	+
Liège Acromegaly Survey (LAS) Database (Lèige, Belgium)	5, 6	Overgrowth syndrome (ORPHA93460); Pituitary adenoma (ORPHA99408)	-	-	+
KIMS (Pfizer International Metabolic Study) - Adults with GH Deficiency (Pfizer, Stockholm, Sweden)	5	GH resistance syndromes (ORPHA633); Congenital hypopituitarism (ORPHA95494); Acquired hypopituitarism (ORPHA95502)	-	-	+
KIGS (Pfizer International Growth Study) - (Pfizer, Stockholm, Sweden)	5, 6, 7	Prader Willi and Prader Willi-like syndrome (ORPHA739); Silver Russell syndrome (ORPHA813); Congenital hypopituitarism (ORPHA95494); Acquired hypopituitarism (ORPHA95502); Sex chromosome DSD (ORPHA325546)	-	-	+
ACROSTUDY (International Somavert Database) (Pfizer, Stockholm, Sweden)	5, 6	Overgrowth syndrome (ORPHA93460); Pituitary adenoma (ORPHA99408)	-	-	+
Nordinet International Outcome Study (Novo Nordisk, Bagsvaerd, Denmark)	5,7	Prader Willi and Prader Willi-like syndrome (ORPHA739); Noonan syndrome (ORPHA648); GH resistance syndromes (ORPHA633); Sex chromosome DSD (ORPHA325546)	-	-	+
DYSCERNE's Dysmorphology Diagnostic System (DDS) (Manchester, UK)	5	Silver Russell Syndrome (ORPHA813)	+	-	-
Global Familial Isolated Pituitary Adenoma (FIPA) consortium (London, UK)	6	Pituitary adenoma (ORPHA99408)	+	-	+
COST Action BM1105 Patient Registry- GnRH Network (Lausanne, Switzerland)	6 , 7	Congenital hypopituitarism (ORPHA95494); Isolated congenital anosmic hypogonadotrophic hypogonadism (ORPHA478); Isolated congenital normosmic hypogonadotrophic hypogonadism (ORPHA432)	+	+	-
I-DSD: International Registry for Disorders of Sex Development (Glasgow, UK)	7	Sex chromosome DSD (ORPHA325546); 46, XX DSD (ORPHA2982); 46, XY DSD (ORPHA98085)	+	+	+
UK10K_RARE_THYROID- Congenital Hypothyroidism Variant Database (Cambridge, UK)	8	Thyroid signalling disorders (ORPHA183631); Congenital hypothyroidism (ORPHA442)	+	-	-
MCT8 Registry. International registry of rare thyroid disorders (Rotterdam, the Netherlands)	8	Thyroid signalling disorders (ORPHA183631)	-	-	+

2.5.3 Awareness and participation in registries for rare endocrine conditions

The levels of awareness and participation in international, national and local registries amongst RC leads according to MTG are outlined in Table 2-3.

Adrenal registries

Of the 33 centres surveyed within the adrenal theme, awareness of an international registry was 68% for adrenocortical tumours, 57% for phaeochromocytoma, 54% for congenital adrenal hyperplasia (CAH), 46% for bilateral macro- and micro-nodular adrenal hyperplasia and 29% for adrenal insufficiency (Table 2-3). International registry participation rates were 39, 30, 18, 21 and 6% for these conditions, respectively.

Registries for disorders of calcium and phosphate homeostasis

Of the 29 centres within the calcium/phosphate theme, international registry awareness was 17% for disorders of phosphate disturbances, 13% for hypercalcaemia and 4% for hypocalcaemia; participation was 8, 8 and 0%, respectively (Table 2-3). Awareness and participation in local registries was higher for all conditions.

Registries for genetic disorders of glucose and insulin homeostasis

Of the 29 centres within the glucose theme, participants reported the highest rates of awareness and participation in an international registry for rare diabetes (75 and 56%, respectively) (Table 2-3).

Registries for genetic endocrine tumour syndromes

Of the 31 centres reporting on the rare genetic tumour theme, 26% reported an awareness of an international registry for MEN1 and 9% reported participation (Table 2-3). Seventy percent reported awareness and participation in local registries for MEN1.

Registries for growth and genetic obesity syndromes

Of the 30 centres within the growth theme, local and national registry awareness and participation for all conditions was greater than that for international registries. International registry awareness was highest for Prader Willi syndrome at 17% with a participation level of 10% (Table 2-3). Participation in international registries for Silver–Russell syndrome, Beckwith–Wiedemann syndrome and Noonan syndrome was 4% for each condition.

Pituitary registries

Of the 43 centres within the pituitary theme, awareness and participation in an international registry was greatest for pituitary adenomas, with 43% awareness and 29% participation, respectively (Table 2-3).

Registries for sex development and maturation

Of the 37 centres within the sex development theme, 70% reported an awareness and 52% reported participation in international registries for 46, XX and 46, XY DSD (Table 2-3). Despite greater awareness of international registries, rates of participation in local registries were higher than those for international registries for all DSD (49% versus 39%).

Thyroid registries

Of the 35 centres within the thyroid theme, international registry awareness was greatest for thyroid signalling disorders (21%), however, participation in an international registry was only 7% (Table 2-3).

Table 2-3. Survey of Endo-ERN reference centres (RC) showing extent of awareness and participation in registries for Endo-ERN conditions.

Endo-ERN MTGs and Conditions Surveyed	RC surveyed (n)	RC responded n (%)	Awareness of Registries n (%)			Participation in Registries n (%)		
			International	National	Local	International	National	Local
MTG1. Adrenal	33	28 (85%)						
Phaeochromocytoma			16 (57%)	7 (25%)	16 (57%)	10 (36%)	6 (21%)	14 (50%)
Adrenocortical carcinoma			20 (71%)	15 (54%)	15 (54%)	13 (46%)	6 (21%)	15 (54%)
Cortisol producing adenomas			19 (68%)	8 (29%)	12 (43%)	12 (43%)	8 (29%)	12 (43%)
Bilateral macronodular hyperplasia			13 (46%)	4 (14%)	11 (39%)	8 (29%)	4 (14%)	11 (39%)
Bilateral micronodular hyperplasia			13 (46%)	3 (10%)	10 (36%)	7 (25%)	3 (11%)	10 (36%)
(Primary) Adrenal insufficiency			8 (29%)	5 (18%)	13 (46%)	2 (7%)	5 (18%)	13 (46%)
Congenital adrenal hyperplasia			15 (54%)	15 (54%)	17 (61%)	6 (21%)	15 (54%)	17 (61%)
Familial hyperaldosteronism			6 (21%)	4 (14%)	8 (29%)	3 (11%)	4 (14%)	6 (21%)
MTG2. Calcium & Phosphate	29	24 (83%)						
Hypercalcaemia			3 (13%)	4 (17%)	11 (46%)	2 (8%)	4 (17%)	11 (46%)
Hypocalcaemia			1 (4%)	2 (8%)	13 (54%)	0 (0%)	2 (8%)	13 (54%)
Phosphate disturbances			4 (17%)	4 (17%)	15 (63%)	2 (8%)	2 (8%)	15 (63%)
MTG3. Glucose & Insulin	29	24 (83%)						
Hyperinsulinism			5 (21%)	9 (38%)	10 (42%)	3 (12%)	6 (24%)	9 (38%)
Insulin-resistance syndrome			12 (50%)	8 (33%)	6 (24%)	9 (38%)	8 (33%)	6 (24%)
Rare diabetes mellitus			18 (75%)	16 (67%)	12 (50%)	14 (56%)	16 (67%)	12 (50%)
MTG4. Endocrine Tumours	31	23 (74%)						
MEN type 1			6 (26%)	8 (35%)	16 (70%)	2 (9%)	8 (35%)	16 (70%)
MEN type 2			5 (22%)	4 (17%)	15 (65%)	1 (4%)	4 (17%)	15 (65%)
Carney complex			1 (4%)	1 (4%)	8 (35%)	0 (0%)	1 (4%)	7 (30%)
Hereditary phaeochromocytoma-paraganglioma			8 (35%)	7 (30%)	14 (61%)	4 (17%)	7 (30%)	14 (61%)
Von Hippel Lindau Syndrome			6 (26%)	4 (17%)	15 (65%)	3 (13%)	4 (17%)	15 65%)
MTG5. Growth & Obesity	30	24 (80%)						
Prader Willi and Prader Willi-like syndrome			5 (21%)	16 (67%)	19 (79%)	3 (13%)	14 (58%)	18 (75%)
Silver Russell Syndrome			3 (13%)	9 (38%)	10 (42%)	1 (4%)	7 (29%)	9 (38%)
Beckwith Wiedemann Syndrome			1 (4%)	3 (13%)	6 (24%)	1 (4%)	3 (12%)	5 (21%)
Noonan Syndrome			2 8%)	9 (38%)	10 (42%)	1 (4%)	9 (38%)	9 (38%)
GH resistance syndromes			3 (13%)	5 (21%)	9 (38%)	1 (4%)	5 (21%)	9 (38%)
MTG6. Pituitary	43	35 (81%)						

Pituitary adenoma			14 (43%)	17 (49%)	24 (69%)	10 (29%)	17 (49%)	24 (69%)
Congenital hypopituitarism			7 (20%)	12 (34%)	19 (54%)	5 (14%)	11 (31%)	19 (54%)
Acquired hypopituitarism			9 (25%)	13 (37%)	20 (57%)	6 (17%)	13 (37%)	20 (57%)
MTG7. Sex Development	37	27 (73%)						
Sex chromosome DSD			18 (67%)	12 (44%)	18 (67%)	13 (48%)	10 (37%)	18 (67%)
46, XX DSD			19 (70%)	12 (44%)	17 (63%)	14 (52%)	10 (37%)	17 (63%)
46, XY DSD			19 (70%)	13 (48%)	18 (67%)	14 (52%)	11 (41%)	18 (67%)
Congenital hypogonadotrophic hypogonadism			15 (56%)	10 (37%)	16 (59%)	9 (33%)	10 (37%)	16 (59%)
MTG8. Thyroid	35	28 (80%)						
Thyroid signalling disorders			6 (21%)	4 (14%)	8 (29%)	2 (7%)	4 (14%)	7 (25%)
Congenital hypothyroidism			2 (7%)	18 (64%)	12 (43%)	0 (0%)	15 (54%)	11 (39%)
Congenital hyperthyroidism			1 (4%)	1 (4%)	4 (14%)	0 (0%)	1 (4%)	3 (11%)
Non-metastatic thyroid macro-carcinoma			5 (18%)	15 (54%)	16 (57%)	0 (0%)	15 (54%)	16 (57%)
Radioiodine sensitive differentiated thyroid cancer			3 (11%)	8 (29%)	12 (43%)	0 (0%)	8 29%)	12 (43%)
Non-metastatic medullary thyroid carcinoma			4 (14%)	11 (39%)	14 (50%)	0 (0%)	11 (39%)	14 (50%)

2.5.4 Priorities for the development of registries for rare endocrine conditions

Regarding RC views on future priorities for the need for registries for rare endocrine conditions within the 8 MTGs, a median priority score of 5, indicating highest priority, was attributed to the following conditions within each MTG: Adrenal disorders- adrenocortical tumours, phaeochromocytoma and CAH; Disorders of calcium and phosphate homestasis- hypocalcaemia and hypophosphataemia; Genetic disorders of glucose and insulin homeostasis- rare diabetes and congenital hyperinsulinism; Genetic endocrine tumour syndromes- all conditions; Growth and genetic obesity syndromes- all conditions; pituitary disorders- pituitary adenoma; Sex development and maturation disorders- all conditions; Thyroid disorders- thyroid signalling disorders, thyroid carcinoma, radioiodine sensitive differentiated thyroid carcinoma (RI sensitive DTC), non-metastatic medullary thyroid disease (Figure 2-4).

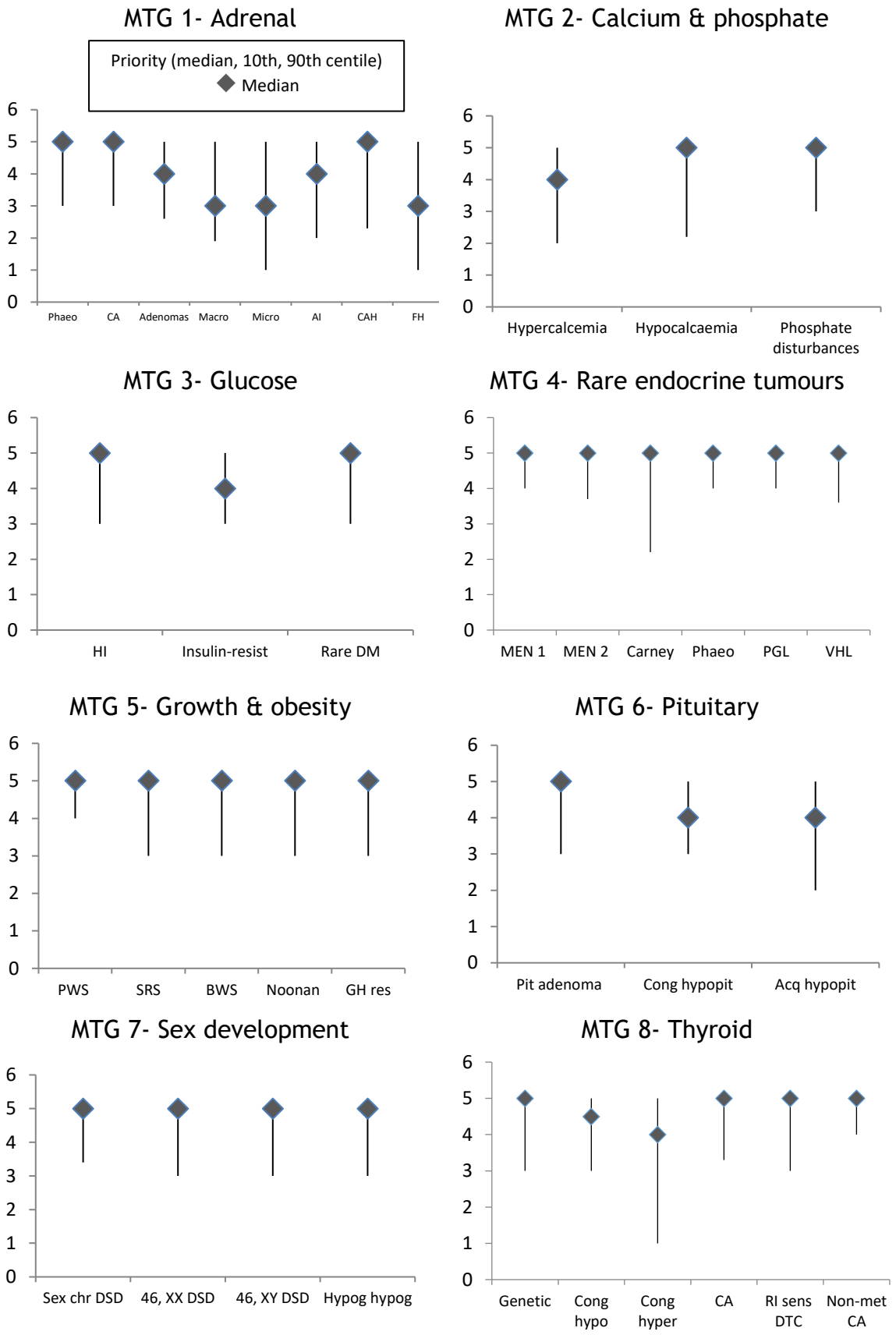


Figure 2-4. Views on future priorities categorised according to the main thematic groups (MTGs 1-8).
A score of 5 (highest priority for need of a registry) was attributed to all conditions within MTG 4 (rare endocrine tumours), MTG 5 (growth and obesity) and MTG 7 (sex development). Phaeo, phaechromocytoma; CA, adrenocortical carcinoma; Adenomas, cortisol producing adenomas; Macro, bilateral macronodular hyperplasia; Micro, bilateral micronodular hyperplasia; AI, primary adrenal insufficiency; CAH, congenital adrenal hyperplasia; FH, familial hyperaldosteronism; HI,

hyperinsulinism; Insulin-resist, insulin-resistance syndrome; Rare DM; rare diabetes mellitus; Phaeo, hereditary phaeochromocytoma; PGL, hereditary paraganglioma; VHL, Von Hippel Lindau syndrome; PWS, prader-willi syndrome; SRS, Silver Russell syndrome; BWS, Beckwith Wiedemann syndrome ; GH res, GH resistance syndromes; Pit adenoma, pituitary adenoma; Cong hypopit; congenital hypopituitarism; Acq hypopit, acquired hypopituitarism; Sex chr DSD, sex chromosome DSD; Hypog hypog; congenital hypogonadotrophic hypogonadism; Genetic, thyroid signalling disorders; Cong hypo; congenital hypothyroidism; Cong hyper, congenital hyperthyroidism; CA, non-metastatic thyroid macrocarcinoma; RI sens DTC, Radioiodine sensitive differentiated thyroid cancer; Non-met CA, non-metastatic medullary thyroid carcinoma.

2.6 Discussion

This contemporary survey of registries has revealed that there are several registries for a range of rare endocrine conditions, with international rare disease registries existing for 78% of conditions covered within Endo-ERN MTGs. Nevertheless, there are gaps in the coverage of conditions and gaps in the level of awareness and use as well as the international profile of existing international registries for rare endocrine conditions.

For conditions including disorders of calcium and phosphate, endocrine tumour syndromes, growth syndromes and pituitary and thyroid disease, there was greater awareness of local or national registries rather than international registries. On the other hand, for other groups of conditions such as adrenal disorders, insulin resistance syndrome, rare diabetes mellitus and DSD, there was a high level of awareness and participation in international registries.

The increased awareness of international registries amongst the Endo-ERN expert centres for particular subgroups of conditions may be attributed to the presence of already established secure web-based registries such as those listed within Orphanet and RD-Connect and/ or to existing international collaboration of RC within a given theme prior to the establishment of Endo-ERN, for example, the glucose, adrenal and DSD themes. The SWEET registry is an example of a registry that was initially developed to cover type 1 diabetes mellitus; however, in doing so, it has also become a powerful resource for rare forms of diabetes (Pacaud, Schwandt et al. 2016).

Although the use of international, cross-border registries may be primarily linked to the availability and awareness of registries, many RC leads did not use these registries despite being aware of them. The reasons for not participating in registries require further exploration, however, previous studies have reported that these may include failure to obtain consent and lack of time or personnel (Kyriakou, Dessens et al. 2016). It is also possible that an absence of transparent quality indicators that can be used to assess registries may play a role (Kodra, Posada de la Paz et al. 2017). Interestingly, this study reported that Endo-ERN RC were aware of only 41% of international registries identified via the database search of Orphanet and RD-Connect, suggesting that lack of awareness of a

registry may be very important factor. Conditions for which a registry was considered a high priority were often those for which international registries already existed. There may be several explanations for this finding. Firstly, it may simply reflect the respondent's lack of awareness of the existing registries. Alternatively, it may reflect the respondent's belief that the existing registry needs to remain high priority or the respondent's view that another new registry needs to be developed.

Virtual database platforms such as Orphanet and RD-Connect have been developed to facilitate greater awareness of registries for rare conditions and may also pave the way towards improving the quality of registries. However, it is important to note that Orphanet and RD-Connect did not have a record of several international registries that are currently led from Europe. This was noted particularly for rare disease registries led by industry. Given that rare disease registries have to enter their details on these databases, the discordance suggests a mutual lack of awareness between these databases and the rare disease registries of the respective platforms. It is possible that registries led by industry have been designed specifically for post-marketing surveillance of specific drugs for a fixed period with limited applicability to the wider community and long-term sustainability may not be a priority, and this may explain their lack of visibility on Orphanet and RD-Connect. On the other hand, these registries are generally well resourced with a clear objective, and it is possible that the data within them are of high quality. In the field of rare conditions, greater partnership with industry is generally supported by all stakeholders (European Medicines Agency Report on the Patient Registries Workshop (28 October 2016)) and is necessary for effective use of limited resources.

2.6.1 Summary

In summary, whilst there is a clear need to develop new detailed disease registries, there is also a need to improve the awareness and signposting of existing registries. A common platform such as the European Registries for Rare Endocrine Conditions (EuRRECa) that can be used by the whole endocrine community and which directs the user to high-quality detailed disease registries has the potential to achieve this objective.

The I-DSD/I-CAH registries are international registries that are commonly identified and well known amongst the international endocrine community, thus these registries also provide an ideal platform for the study of core clinical outcomes at a global level.

CHAPTER 3

The quality evaluation of disease registries for rare endocrine conditions

The findings of this chapter have been published by **Ali SR**, Bryce J, Kodra Y, et al. The quality evaluation of rare disease registries- an assessment of the essential features of a disease registry. *Int J Environ Res Public Health*. 2021;18:11968.

3 The quality evaluation of disease registries for rare endocrine conditions

3.1 Abstract

Background: Rare disease (RD) registries aim to promote data collection, data sharing and facilitate multidisciplinary collaboration with the overall aim of improving patient care. Recommendations relating to the minimum standards necessary to develop and maintain high quality registries are essential to ensure high quality data and sustainability of registries.

Objective: The aim of this international study was to survey RD registry leaders to ascertain the level of consensus amongst the RD community regarding the quality criteria that should be considered essential features of a disease registry.

Methods: An online survey of RD registry leaders including former participants of the International Summer School on Rare Diseases, RD-Connect registry contacts and coordinators of international registries for rare endocrine conditions.

Results: Of 35 respondents representing 40 RD registries, over 95% indicated that essential quality criteria should include establishment of a good governance system (ethics approval, registry management team, standard operating protocol and long-term sustainability plan), data quality (personnel responsible for data entry and procedures for checking data quality) and construction of an IT infrastructure complying with Findable, Accessible, Interoperable and Reusable (FAIR) principles to maintain registries of high quality, with procedures for authorised user access, erasing personal data, data breach procedures and a web interface. Of the 22 rare endocrine registries that performed a self-assessment, over 80% demonstrated adherence to proposed quality criteria and stated that their registry had a leader, project management group, steering committee, active funding stream, website, and user access policies.

Conclusion: There are high levels of consensus for the proposed quality criteria outlined in this survey amongst the RD community and the survey has acceptability for the self-evaluation of RD registries.

3.2 Introduction

Currently, over 800 disease registries exist for rare conditions in Europe alone, with this number likely to continue to increase in the future (Taruscio, Gainotti et al. 2013, Taruscio, Vittozzi et al. 2015, Groft, Posada et al. 2021). The emphasis on rare disease (RD) registries has been further strengthened with the inclusion of participation in RD registries as a quality indicator of a reference centre for European reference networks such as Endo-ERN. Detailed disease registries that are of high quality are more likely to be sustained long-term, with greater utility. By prioritising ethical and legal standards, high quality registries can provide access to data on a platform that ensures data security and patient confidentiality. Thus, the continued expansion and development of disease registries for rare conditions places greater emphasis on the need for robust criteria for ensuring the high quality of a registry and for these to be publicised for new and existing registries (Kodra, Posada de la Paz et al. 2017, Kodra, Weinbach et al. 2018).

Recently, quality criteria for rare disease registries was outlined, with recommendations for improving the quality of registries (Kodra, Weinbach et al. 2018) (Figure 3-1). This quality framework highlights the importance of the establishment of clear governance structures, identification of correct data sources, development of data elements and standardisation with construction of a suitable IT infrastructure complying with FAIR (findable, accessible, interoperable, reusable) principles to make data available for wider use (Wilkinson, Dumontier et al. 2016). Moreover, as highlighted in Figure 3-1, this quality framework should encompass the development of adequate documentation, provision of staff training and data quality audit. Adherence to these recommendations would ensure that registry data can be pooled for meaningful clinical research and public health purposes, with wider involvement of healthcare professionals, patients and other stakeholders to also ensure sustainability of registries (Pinto, Martin et al. 2016, Jonker, de Vries et al. 2021).

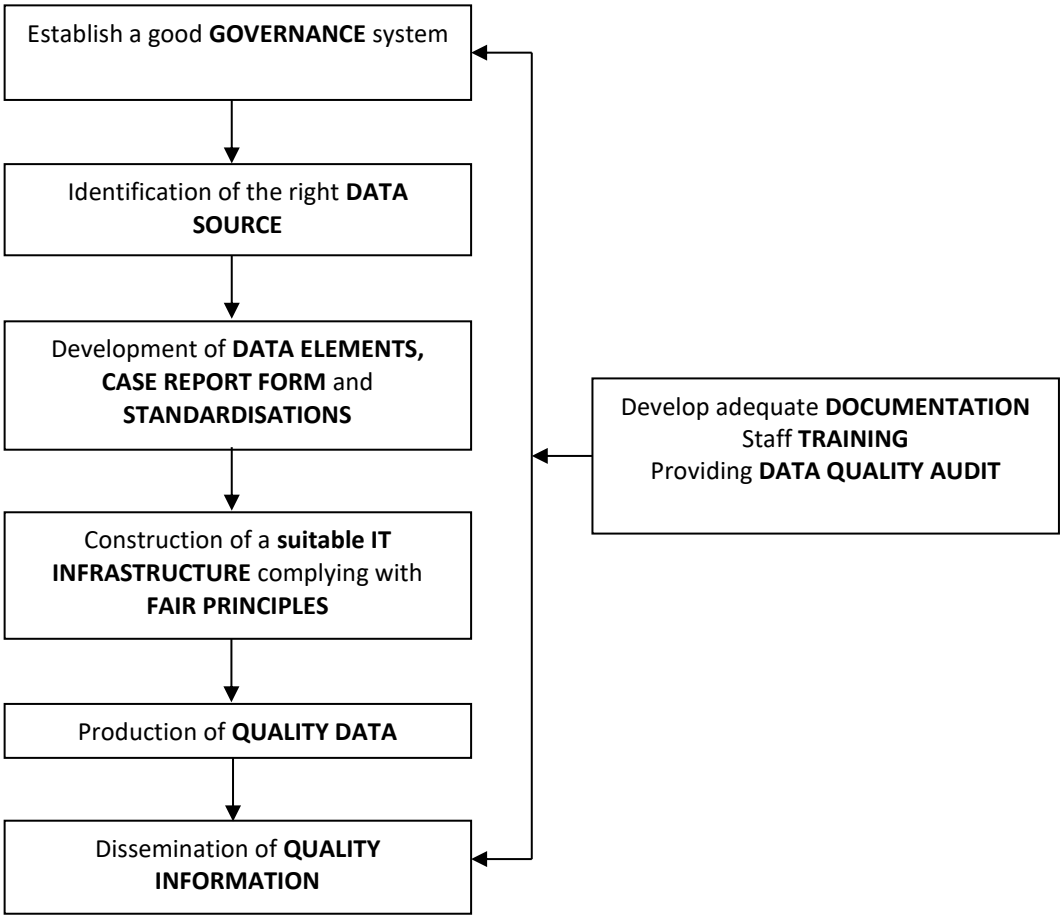


Figure 3-1. A framework for the quality management of a rare disease registry (adapted from Kodra et al. 2018).

A recent study that reported the results of a survey amongst Endo-ERN expert centres and a search of Orphanet and RD-Connect found that international registries, led from Europe, exist for almost 80% of rare endocrine conditions covered within Endo-ERN (Ali, Bryce et al. 2019). Thus, it is vital to understand whether these existing registries comply with quality recommendations. Moreover, an understanding of the level of consensus and the use of a standardised set of quality criteria will enable RD registries such as the European Registries for Rare Endocrine Conditions (EuRRECa; eurreca.net) to develop a pathway of vetting high quality registries with whom data can be shared (Ali, Bryce et al. 2020, Ali, Bryce et al. 2021).

3.3 Aims

The aims of this study were to:

- Identify the criteria for the quality assessment of rare disease registries
- Understand the level of consensus in the rare disease community regarding the quality criteria that should be considered as essential features of a disease registry, and therefore considered as inclusion criteria to the EuRRECa platform
- Evaluate the extent to which existing international rare endocrine disease registries meet the proposed quality criteria and understand the extent of variation that may exist

3.4 Methods

3.4.1 Ethics approval and consent

Ethics approval was not required, as per the UK's Policy Framework for Health and Social Care Research (2021), as this study was a service evaluation project and did not require any information on patients or human participants. Participant consent was inferred from survey completion.

3.4.2 Participants

In order to understand the level of consensus in the rare disease community on the quality criteria that should be considered as essential features of a disease registry, online survey invitations were circulated to former participants of the International Summer School on Rare Disease Registries (n=16) and RD-Connect registry contacts (n=296).

To evaluate existing rare endocrine disease registries using the list of essential quality criteria and understand the extent of variation that may exist amongst registries, an online survey was circulated to registry leads of 31 international registries for rare endocrine conditions identified in a previous mapping exercise (Ali, Bryce et al. 2019).

3.4.3 International survey

A EuRRECa project group consisting of Work Package 3 (Quality Assurance and Evaluation), in close collaboration with Work Package 5 (Patients, Parents and Ethics), identified a small number of quality criteria from the quality management framework outlined in a previous study (Kodra, Weinbach et al. 2018), that could be regarded as essential for the assessment of quality of a RD registry. These criteria were incorporated into a simple online survey that could also be used for self-assessment by RD registries. Webropol, a secure online platform endorsed and supported by NHS Greater Glasgow and Clyde and NHS Scotland was used to host the survey. All information within Webropol is kept in compliance with the UK Data Protection Act (2018) and General Data Protection Regulation (GDPR 2016/679). The survey was performed in the last quarter of 2020.

The survey contained 17 items divided into 3 domains (Table 3-1). The items in the first section related to registry governance (e.g. ‘registry should have a named lead’), with items in subsequent sections enquiring regarding data quality (e.g. ‘core data elements in the registry should have a clear definition and coded values’) and IT infrastructure criteria (e.g. ‘registry should have a web interface’) for RD registries. Respondents were asked to indicate their level of agreement with each item by selecting ‘Agree’ or ‘Disagree’ responses. If disagreeing with an item, respondents were provided with a free text option for further comment. An additional section at the end of the survey sought to obtain feedback from the respondent regarding acceptability of the length of the survey, clarity of questions, any other criteria that should be considered as essential for the quality assessment of a RD registry and any other issues that the respondent may wish to comment on regarding quality criteria for RD registries.

Table 3-1. Quality criteria for a rare disease registry survey items (abbreviated version).

Survey Domain	Item	Response Type
Respondent contact details	Name Email Institution Registry/Registries[a]	
Governance	The registry should have: Named lead Management team Patient involvement in registry governance Long-term sustainability plan Ethics approval Publicly accessible consent forms and participant information sheets Standard operating protocol Report or newsletter to disseminate activity If you disagree with any of the above criteria, please comment:	Select one option for each item (Agree or Disagree)
Data quality	The registry should have: Core data elements with clear definition and coded values Specified who is responsible for entering clinical data Procedures for checking data quality Training for all users If you disagree with any of the above criteria, please comment:	
IT infrastructure	The registry should have: Web interface Web interface allowing uploading and downloading of data Data breach procedures Procedures for erasing personal data when requested Only authorised user access to registry data If you disagree with any of the above criteria, please comment:	
Feedback	Was the length of the survey acceptable? (Please specify time taken for completion) Could any of the questions be clearer? Are there other criteria that should be considered as essential? Are there any other issues that you would like to comment on?	Select one option (Yes or No) and please specify (free text)

[a]Mandatory field

3.4.4 Statistical analysis

Categorical data were analysed using descriptive statistics. Numerical data were collated and analysed using Minitab version 18 statistical software (Minitab LLC, State College, PA, USA).

3.5 Results

3.5.1 Survey response

Thirty-five registry leaders representing 40 RD registries responded to the survey regarding the quality criteria that should be considered essential features of a disease registry (Table 3-2). Of the 40 RD registries, 10 (25%), 8 (20%), and 1 (3%) were coordinated from the USA, UK, and Canada, respectively. The remaining 21 (53%) registries were coordinated from a total of seven other European countries.

Of the 31 international registries for rare endocrine conditions that were identified in a previous mapping exercise (Ali, Bryce et al. 2019), 22 registries (71%) performed the current self-assessment survey, reporting the extent to which their disease registry met the proposed quality criteria for a rare disease registry (Table 3-2).

Table 3-2. Rare disease registries represented by survey respondents.

Registries reporting on essential quality features of a rare disease registry, n=40
3q29 Registry
Amyotrophic Lateral Sclerosis (ALS) Registry
Barth Syndrome Registry
Behcet Disease Registry
Canadian Neuromuscular Disease Registry
Clinical Registry investigating Bardet-Biedl Syndrome (CRIBBS)
Congenital Muscular Disease International Registry
Cystinuria: Rare Kidney Stone Consortium
EU Rare Diseases Registry for Wolfram Syndrome, Alstrom Syndrome, Bardet-Biedl Syndrome and other rare diabetes syndromes (EURO-WABB)*
European Alport Registry
European Consortium of Lipodystrophies (EcLip)*
European Network and Registry for Homocystinurias and Methylation Defects (E-HOD)
European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)
European Registry for Children on Renal Replacement Therapy (ESPN/ ERA-EDTA Registry)*
European Registry for Rare Bone and Mineral Conditions (ERN BOND: EuRR-Bone)
European Registry on Cushing's Syndrome (ERCUSYN)*
FAP Registry (Belgium)
Friedreich's Ataxia Registry
GLUT1 deficiency
Inherited Retinal Dystrophies
International Cholangiocarcinoma Patient Registry
International Disorders of Congenital Adrenal Hyperplasia (I-CAH) Registry*
International Disorders of Sex Development (I-DSD) Registry*
International Working Group on Neurotransmitter Related Disorders (iNTD)
LGMD2A/R1 Global Registry
Leige Acromegaly (LAS) Database*
Mitochondrial Registry
Myotubular and Centronuclear Myopathy Patient Registry (MTM and CNM)
National Alpha-1 Antitrypsin Deficiency Registry
Nordinet International Outcome Study*
Poland Syndrome Registry
RenalTube Registry
Ring14 Syndrome Registry
Sarcoidosis Advanced Registry for Cures (FSR-SARC)
Spinal Muscular Atrophy (CSMA) Registry
Spinal Muscular Atrophy (SMA) Global Registry
UK Duchenne Muscular Dystrophy (DMD) Registry
Unified Registry for Inherited Metabolic Disorders (U-IMD)
X-linked Hypophosphataemia (XLH) Registry
Registries undertaking self-assessment of essential quality criteria for rare disease registries, n=22
ACROSTUDY (International Somavert Database)
Congenital Hypothyroidism Variant Database (UK10K_RARE_THYROID)
Cooperative European Paediatric Renal Transplant Initiative registry
COST Action BM1105 Patient Registry- GnRH Network
European LeukoDatabase (LeukoDB)

European Network for the Study of Adrenal Tumours (ENSAT)
European Neuroendocrine Tumour Society (ENETS)
International network for paediatric diabetes centers (SWEET)
International Patient Registry and Cohort for Congenital Disorders of Glycosylation (EUROGLYCANET)
National and European cohort on Imprinting Disorders and their Metabolic Consequences (RaDiCo-IDMet)
Pfizer International Growth Database (KIGS)
Pfizer International Metabolic Database (KIMS)
X-linked Adrenoleukodystrophy Database (X-ALD)
X-linked Hypophosphataemia (XLH) Registry

*Registries also involved in the self-assessment of essential quality criteria.

3.5.2 Consensus on essential quality criteria for rare disease registries

Regarding governance quality criteria that should be considered essential features of a disease registry, all registry leads agreed that a registry should have ethics approval (Figure 3-2). Of the 35 registry leads, 34 (97%) agreed that a registry should have a long-term sustainability plan, management team and a document outlining its standard operating protocol. A named lead, publicly accessible consent forms and participant information sheets were deemed essential by 33 (94%) respondents; 32 (91%) agreed that a registry should disseminate its activity through a report or newsletter. Of the 35 registry leads, 25 (71%) agreed that patients should be involved in the governance of a registry. Some respondents indicated that while best practice may suggest patient involvement in the governance of a registry, there are some scenarios where this may not be applicable, for example, the role of a patient in a physician driven registry may be minimal.

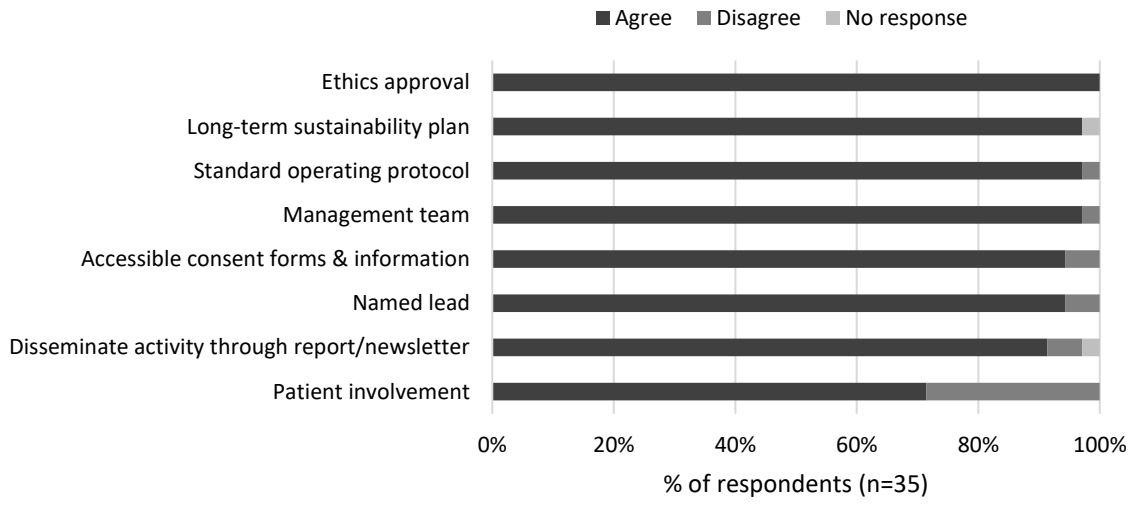


Figure 3-2. Level of consensus on quality criteria for governance of a registry.

Regarding data quality criteria that should be considered essential features of a disease registry, almost all registry leads (n, 34; 97%) agreed that a registry should specify who is responsible for entering the clinical data and a registry should have procedures for checking data quality (Figure 3-3). Of the 35 registry leads, 32 (91%) agreed that the core data elements in a registry should have a clear definition and coded values and 30 (86%) agreed that training should be provided to all registry users. Some respondents commented that clinical users of the registry may not require training if data input is clear and intuitive. However, researchers or other stakeholders may require formal training.

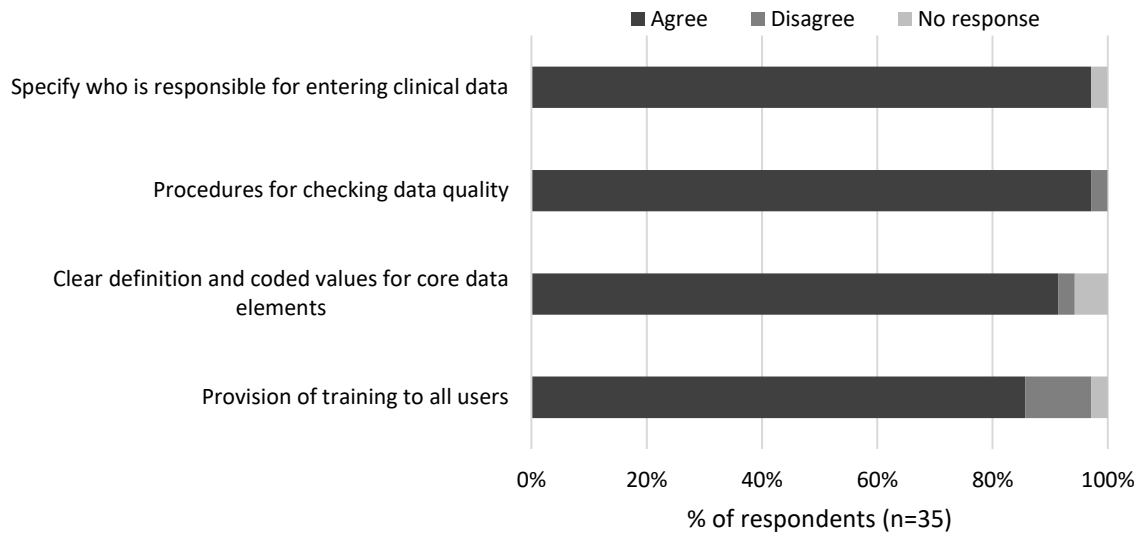


Figure 3-3. Levels of consensus on data quality criteria for a registry

Regarding IT infrastructure criteria that should be considered essential features of a disease registry, all registry leads agreed that a registry should have clear procedures that only allow authorised users to have access to registry data (Figure 3-4). Of the 35 respondents, 33 (94%) agreed that a registry should have clear procedures for erasing personal data when requested; 32 (91%) agreed that a registry should have a web interface and data breach procedures in place, and 28 (80%) agreed that the web interface should allow uploading and downloading of data. Respondents commented that whilst it may be useful to have the facility to upload and download data, uploading may only be feasible and less time constraining if the same data field structures were present within databases.

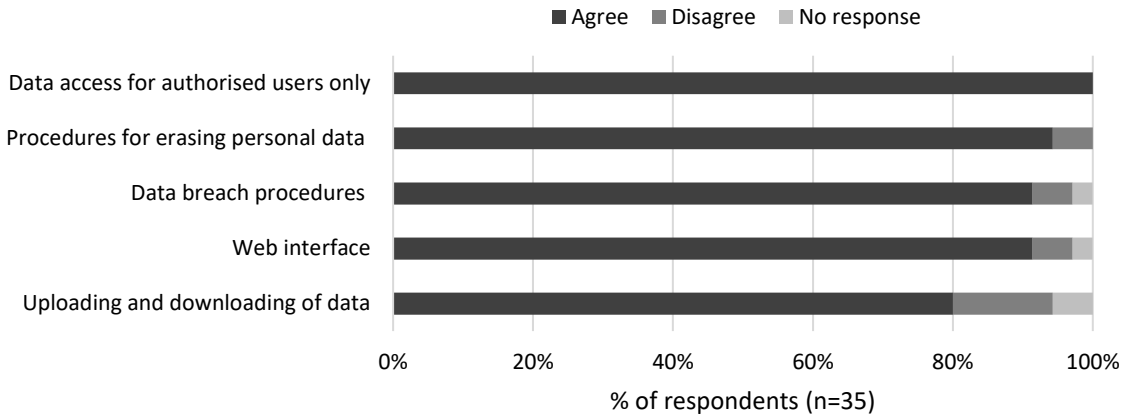


Figure 3-4. Levels of consensus on quality criteria for the IT infrastructure of a registry

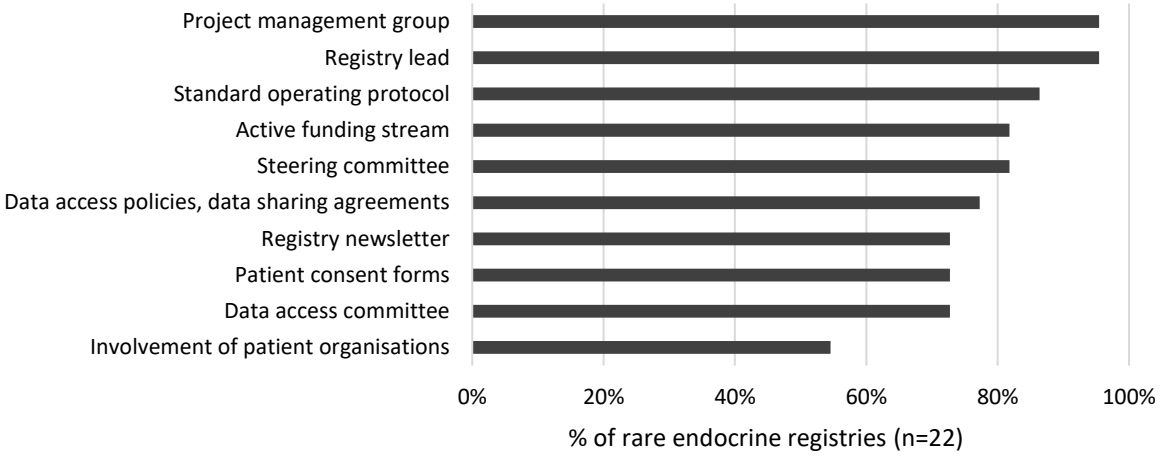
3.5.3 Self-assessment and quality evaluation of disease registries for rare endocrine conditions

Of the 31 endocrine registry leads that were approached to perform a self-assessment, information was available for 22 (71%) international rare endocrine registries (Table 3-2). Regarding governance of a registry, of the 22 registries, 21 (95%) had a registry lead and project management group; 19 (86%) had a document available outlining the standard operating protocol for the registry. The majority of registries (n, 18; 82%) had a steering committee and an active funding stream. Moreover, 17 (77%) registries had data access policies and data sharing agreements, with 16 (73%) also specifying that they had a data access committee, patient consent forms and a registry newsletter. Around half (n, 12; 55%) reported involvement of patient organisations (Figure 3-5 A).

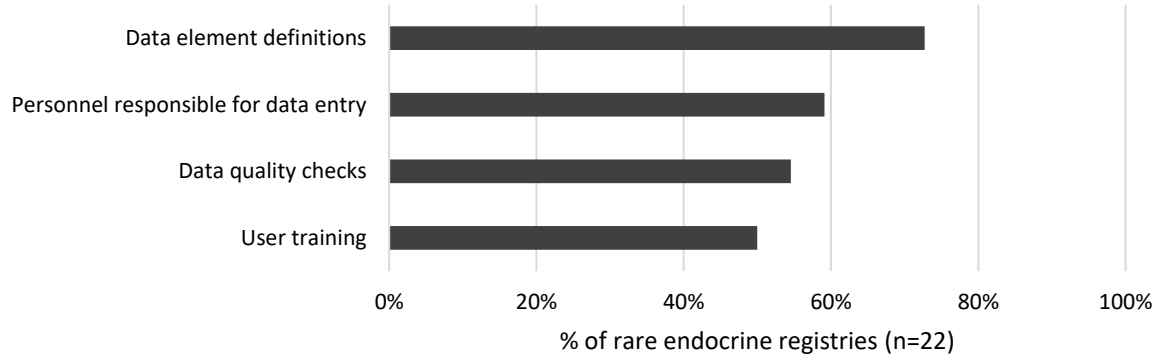
In terms of data quality aspects, of the 22 registries for international rare endocrine registries, 16 (73%) reported that their registry had data element definitions, with 13 (59%) specifying the availability of personnel responsible for data entry. Around half of registries (n, 12; 55%) performed data quality checks, and 11 (50%) embarked on user training for clinical users of the registry (Figure 3-5 B).

The majority of registries had a registry website and authorised user access policies, as reported by 21 (95%) and 20 (91%) of registries, respectively. Data erasure procedures and data breach procedures were reported to be in place for 16 (73%) and 14 (64%) of registries. Less than half of registries had data available for upload and download (n, 9; 41% (Figure 3-5 C).

A. Data governance



B. Data quality



C. IT infrastructure

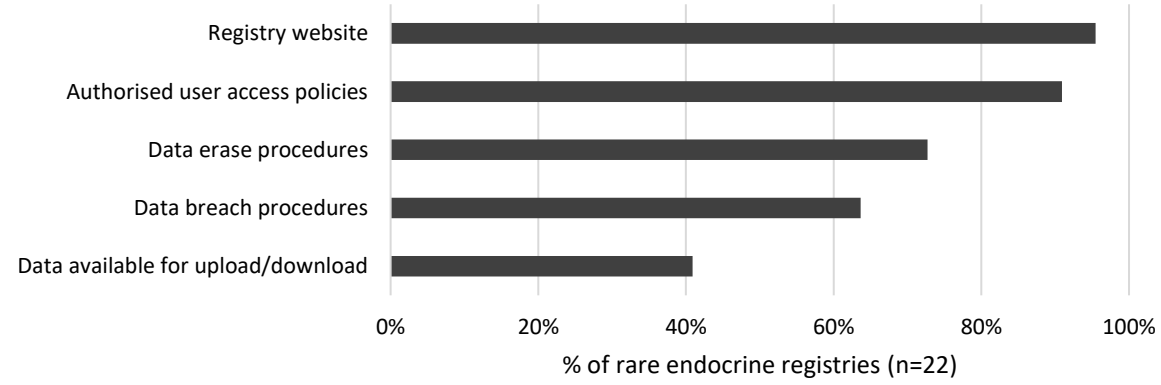


Figure 3-5. Self-evaluation of rare endocrine disease registries using the essential quality criteria.
Essential quality criteria included aspects of data governance (A), data quality (B) and IT infrastructure (C) of the registries.

3.5.4 Implementation of the quality criteria as tool for EuRRECa

The simple self-assessment quality evaluation survey developed from this work will be incorporated into the EuRRECa project and freely available on the EuRRECa website (https://eurreca.net/affiliate-registries/) to be completed by registries seeking affiliate status. The use of these standardised set of quality criteria will enable rare disease registries such as EuRRECa to develop a pathway of vetting high quality registries with whom data can be shared and may be used to highlight areas of a registry that need improvement in order to maximise the quality of its data.

3.6 Discussion

3.6.1 Key findings

This study reports the results of an international survey of registry leaders representing 54 RD registries, providing objective insight into quality criteria considered essential for RD registries. It also reports the results of a self-assessment exercise in which registry leaders representing 22 rare endocrine registries evaluated aspects of registry governance, data quality and IT infrastructure.

Our results showed that there was a high level of consensus amongst respondents on the majority of quality criteria that should be considered as essential features of a RD registry. Regarding registry governance, all respondents agreed that ethics approval should be mandatory, with almost all indicating that a registry management team and long-term sustainability plan would be preferable for a high-quality registry. Ensuring sustainability through clear policies that are acceptable to patients, health care providers, researchers and industry for data provision and data access coupled with widespread dissemination and knowledge exchange through closely affiliated professional societies and patient support groups is vital. Interestingly, our results showed that almost one third of registry leaders indicated that patient involvement would not be an essential quality criterion for a RD registry. However, the involvement of patients and patient organisations may be advantageous, with previous studies showing that patient involvement complements the research emphasis of registries, and most RD patient organisations have goals to promote or support research of rare conditions (Pinto, Martin et al. 2016, Groft, Posada et al. 2021).

Regarding data quality criteria, almost all respondents (97%) agreed that personnel responsible for data entry and procedures for checking data quality should be specified, with the majority (91%) also agreeing that core data elements should have clear definitions and coded values. These opinions regarding data quality and governance appear to be well-aligned across the RD community and other stakeholders including industry (Jonker, de Vries et al. 2021). High quality data is an important element in the maintenance of a

registry. Data quality can be assessed via a number of dimensions including: data completeness, validity, coherence and comparability, accessibility, usefulness, timeliness, and prevention of duplicate entries (Kodra, Posada de la Paz et al. 2017, Kourime, Bryce et al. 2017, Lazem, Sheikhtaheri et al. 2021). The European Platform on Rare Diseases Registration (EU RD Platform) developed via the European Commission through its Directorates-General Joint Research Centre (DG JRC) and Health and Food Safety (DG SANTE) also aims to set European-level standards for data collection and data sharing, enabling interoperability and sustainability for existing RD registries in Europe, facilitating the production of high quality data from these registries (Kinsner-Ovaskainen, Lanzoni et al. 2018). Regarding the IT infrastructure of a high-quality registry, all respondents stated that registries should have clear procedures for allowing only authorised user access to data, with the majority also specifying that registries should have clear procedures for erasing personal data and data breach procedures in place.

The survey showed that there does appear to be some variation in the governance of existing endocrine registries within Europe. Nevertheless, over 80% of rare endocrine disease registries that performed self-assessment using the survey tool stated that their registry had leadership, a project management group, a steering committee, an active funding stream, a web interface and user access policies. More than 70% of these registries also reported to have data element definitions within their platform.

3.6.2 Strengths

RD registries are vital to enable research and to improve healthcare planning and delivery. The vast expansion of RD registries that has been noted over recent years necessitates the need for a simple survey that can be used to assess the quality of RD registries against recommendations outlined by expert groups, patient organisations and other stakeholders (Kodra, Weinbach et al. 2018). All respondents stated that the overall length of the survey was acceptable.

Through this study, an international perspective was obtained regarding levels of agreement for the quality criteria considered essential for an RD registry, with responses from registry leaders representing over 50 RD registries across a range of medical disciplines. Former participants of the annual International Summer

School on Rare Disease Registries were amongst the survey respondents. This event plays an important role in the education and training of those involved in RD registries and forms part of a series of training activities that have been proposed by the European Joint Programme on Rare Diseases (EJP RD). Thus, inclusion of this group of respondents was beneficial. Going forward, there is a need for such training courses to engage with a greater number of RD registries from a wider range of geographical and resource settings.

3.6.3 Limitations

Obtaining more detailed information through provision of further quality selection criteria would have perhaps been advantageous, however, a balance needed to be struck between maximising the information available for collection and reducing respondent burden. There was a preponderance of responses from registry leaders in developed countries, thus, it must also be acknowledged that whilst the criteria outlined in this survey may be considered essential quality criteria for a RD registry, fulfilling these recommendations may be challenging in resource limited settings where funding is restricted.

Of the 353 registries that were approached to participate in the current survey, 54 responded, providing an overall response rate of 15%. It is possible that there may have been an element of response bias with those registries that had a greater level of adherence to the proposed quality standards responding to the survey. Interestingly, a survey of 272 registries performed by the European Platform For Rare Disease Registries (EPIRARE), a European Union (EU)-funded project ('Building Consensus and Synergies for the EU Registration of Rare Disease Patients') reported that 48% did not have a clear strategy for long-term sustainability, 34% did not have a specific management group, 30% did not share data, and 21% were established without any clear funding (Taruscio, Gainotti et al. 2013). Despite the heterogeneity of the European registries, a survey performed by EPIRARE amongst European RD registries identified the following requisites for registries: financial support, motivation of data providers, data quality assessment, improvement of communication and visibility and extension of collaborations. Moreover, the registry leaders were supportive of a common EU platform for RD registries (Taruscio, Gainotti et al. 2013, Taruscio, Vittozzi et al. 2015).

3.6.4 Summary

The online quality assessment survey described in this exercise demonstrates acceptability amongst the RD community, with a high level of consensus on the quality criteria that should be considered as essential features of a disease registry. It may be used for the quality evaluation of RD registries and enables assessment and improvement of organisational aspects of RD registries to ensure their sustainability. A survey like this may be used by networks such as EuRRECa to develop objective criteria that allows them to collaborate and engage with registries of an optimal quality.

CHAPTER 4

Electronic reporting of rare endocrine conditions within a clinical network- Results from the EuRRECa project

4 Electronic reporting of rare endocrine conditions within a clinical network- Results from the EuRRECa project

4.1 Abstract

Background: EuRRECa (eurreca.net) is a web-based project that includes an e-reporting registry (e-REC) which can be used to perform regular surveillance of specific conditions within networks such as the European Reference Network (ERN) for rare endocrine conditions (Endo-ERN).

Objective: To report the experience of e-REC over the three and a half years since its launch in 2018.

Methods: Electronic reporting of new cases of any of the conditions included within Endo-ERN was performed through a bespoke platform on a monthly basis by clinicians registered to participate in e-REC from July 2018 to December 2021.

Results: The number of centres reporting on e-REC increased over the 3.5 year period to a total of 61 centres from 22 countries. A median of 29 (range 11, 45) paediatric and 32 (14, 51) adult centres reported cases on a monthly basis. A total of 9,715 and 4,243 new cases were reported in adults (age ≥18 years) and children, respectively. In children, conditions within the sex development group comprised 40% of all reported conditions and amongst them, cases of transgender were most commonly reported, comprising 58% of cases. The median number of sex development cases reported per centre per month was 0.6 (0, 38). Amongst adults, pituitary conditions comprised 44% of all reported conditions and pituitary adenomas (69% of cases) were the most commonly reported condition. The median number of pituitary cases reported per centre per month was 4 (0.4, 33).

Conclusion: The e-REC platform has gained increasing acceptability over the last 3.5 years for capturing brief information on new encounters of rare conditions and shows wide variations in the rate of presentation of these conditions to centres within a reference network.

4.2 Introduction

The field of clinical endocrinology covers a very wide range of rare conditions. However, clear information on the occurrence of these conditions is lacking. By pooling standardised information from several sources, registries have the potential to facilitate surveillance, audit and research. Generally, rare disease registries tend to focus on the collection of detailed natural history data and are usually not equipped to support epidemiological research. On the other hand, linked datasets and population registries often do not cover rare endocrine conditions at a sufficiently granular level to provide data on occurrence of specific diagnoses that can be compared at an international level and that are relevant to stakeholders such as patients, healthcare professionals and researchers (Crafa, Calogero et al. 2021).

Many clinical and scientific networks for rare conditions operate an electronic reporting system to capture activity as well as to understand the incidence and prevalence of conditions (Elliott, Nicoll et al. 2001, Lynn, Pebody et al. 2006, El-Fakhri, Williams et al. 2013, Rodie, Ali et al. 2022). The European Registries for Rare Endocrine Conditions (EuRRECa) project, that was launched in 2018 (http://eurreca.net/) aimed to provide its users with a wide range of registry solutions that would maximise the opportunity for patients, healthcare professionals and researchers to participate in registries for rare endocrine conditions. Amongst these solutions, EuRRECa developed an electronic reporting system called e-reporting of rare endocrine conditions (e-REC, https://eurreca.net/e-rec/), a simple registry that can facilitate voluntary electronic surveillance of any activity within a network of centres such as the European Reference Network for rare endocrine conditions (Endo-ERN). These networks have a mission of objectively mapping conditions and related activity, thus, having a better understanding of the occurrence of the rare conditions covered within the network is critical. Given that reference networks such as Endo-ERN can have several centres, with several clinical users at each centre who may encounter a wide range of rare endocrine conditions, some that are more easily diagnosed than others, the e-REC platform was designed to capture with greatest ease as many conditions as possible.

4.3 Aim

The aim of the current study was to report the experience of e-REC over the three and a half years since its launch in 2018.

4.4 Methods

4.4.1 Ethics approval and consent

The EuRRECa project complied with EU General Data Protection Regulation (GDPR) and was approved by the Information Governance authorities at the NHS Greater Glasgow & Clyde Health Board and the National Research Ethics Service in the UK. Reporter consent was inferred from completion of the electronic case reporting forms. No personally identifiable information was collected for the reported cases and the process of case-reporting did not require informed patient consent.

4.4.2 The e-REC platform

All centre leads of Endo-ERN were invited to register and use the e-REC platform. In addition, information about the platform was disseminated through allied professional societies including the European Society of Endocrinology (ESE) and the European Society for Paediatric Endocrinology (ESPE). Between July 2018 and September 2019, data were collected and managed using the REDCap (Research Electronic Data Capture) tool hosted at the University of Glasgow (Harris, Taylor et al. 2019). From October 2019, registered users were able to create a reporting set-up via a new bespoke web-based platform, also hosted at the University of Glasgow, in which the reporters could specify the rare endocrine conditions and the patient age group (patients under 18 years old and/or patients over 18 years old) that they would like to report on. Upon reporting a case, a unique ID was generated instantaneously for each case and provided electronically to users to be stored locally at the reporting centre. Multiple reporters could be selected within each reporting centre, however, a reporter from that centre was not able to sign up to report on the same condition within the same age group over the same reporting period as another reporter at the centre.

From the last quarter of 2019, users were also able to specify whether a clinical diagnosis was suspected or confirmed for each reported case and the platform also enabled updating of previously reported suspected cases to either a confirmed or excluded diagnosis. Reporters were invited to report any new case of any of the conditions included within Endo-ERN on a monthly basis and the 'reporting month' remained open for a period of three months. The reported data were stored on a secure server in the University of Glasgow and could be downloaded from the e-REC platform in MS Excel CSV file format with details of the reporter, centre and information on the reported number of cases of each rare endocrine condition included within Endo-ERN.

4.4.3 Statistical analysis

Categorical data were analysed using descriptive statistics. Results are reported as frequencies and percentages and median (with ranges) values. Numerical data were collated and analysed using Minitab version 18 statistical software (Minitab LLC, State College, PA, USA).

4.5 Results

4.5.1 Reporting centres

Over the 3.5 year period, from July 2018 to December 2021, 61 centres from 22 countries had reported cases on e-REC. Of these 61 centres, 44 (72%) were Endo-ERN reference centres, 3 (5%) were affiliated with another ERN (e.g. ERN on rare bone diseases, ERN-BOND) and 14 (23%) were not in any ERN. Of the 61 centres, 58 (95%) were from countries within the European Union. To date, 45 centres from 18 countries have reported paediatric cases (<18 years of age), 51 centres from 19 countries have reported adult cases (≥18 years of age) and 29 centres have reported on both children and adults. The cumulative number of centres (total centres that have submitted a case on e-REC) that had reported paediatric and adult cases increased over the 3.5 year period (Figure 4-1). In December 2021, a median of 29 centres (range 11, 45) were reporting paediatric cases and 32 (14, 51) were reporting adult cases from 15 (10, 19) countries, on a monthly basis.

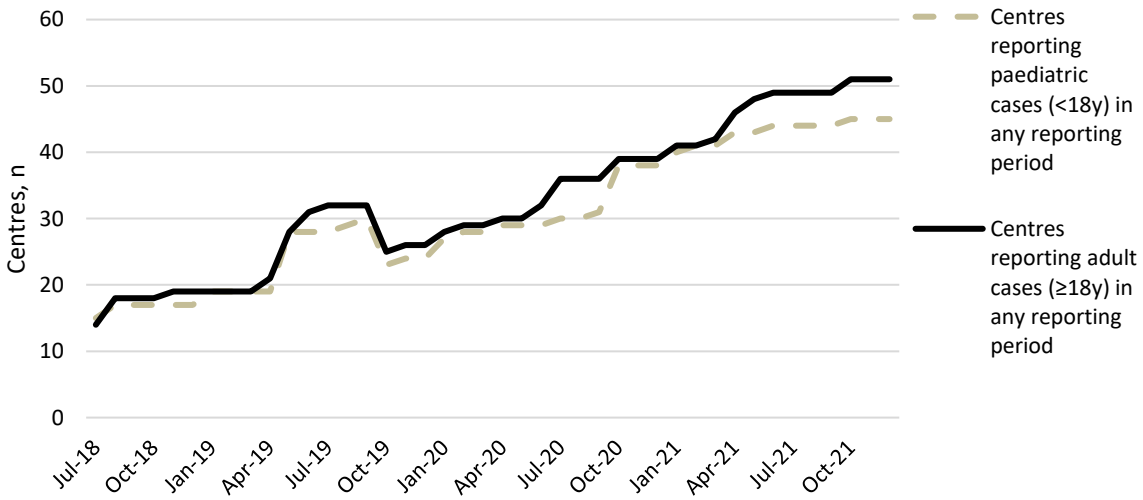


Figure 4-1 The change in the number of paediatric and adult centres reporting on the e-reporting platform (e-REC) between July 2018 and December 2021.

Of the 61 centres that had reported cases on e-REC, there were 33 centres (54%) who had reported in over 80% of the months since they joined the e-REC platform. Of these 33 centres, 23 were reporting adult cases and 25 were reporting paediatric cases (Table 4-1). The reporting pattern of these centres

who were in the top quintile was also studied separately to reduce the bias of intermittent reporting when studying overall annual case occurrence rate.

4.5.2 Reported cases

Over the 3.5 year period, a total of 9,715 and 4,243 new cases were reported in adults and children (Table 4-2), respectively, with annual increases in the number of reported cases in both adults and children (Figure 4-2). Overall, in adults and children, 8,668 (89%) and 3,562 (84%) cases were reported as confirmed, respectively, and 1,047 (11%) and 681 (16%) cases were reported as having a suspected diagnosis, respectively (Figure 4-2). In adults, an increase in the number of suspected diagnoses over time was also apparent. Moreover, there was a trend towards an increasing number of cases being reported on an annual basis for the majority of Endo-ERN condition groups (Figure 4-3). The number of cases reported per condition group per centre also increased over the 3.5 year period (Figure 4-4).

In the 33 frequently reporting centres, a total of 5,389 cases were reported in adults and 2,821 cases were reported in children. Of the 5,389 cases in adults, 4,662 (87%) were confirmed and 727 (14%) were suspected cases and of the 2,821 cases in children, 2,289 (81%) were confirmed and 532 (19%) were suspected (Table 4-1). Amongst the frequently reporting centres, the percentage of suspected cases varied from one condition group to another and amongst children, pituitary and calcium disorders comprised the greatest number of suspected cases; whilst in adults, disorders of glucose and insulin homeostasis comprised the highest percentage of suspected cases (Table 4-1).

Table 4-1 The number of cases reported from centres with 80% or more monthly submission rates from October 2019 to December 2021.

Endo-ERN MTG	Centres, n	Suspected cases reported, n (%)	Confirmed cases reported, n (%)	Total cases reported, n	Duration of reporting in months, median (range)	Cases reported per centre per month, median (range)	Estimated annual case occurrence rate for a centre
Children (<18y)							
Adrenal	17	42 (23%)	138 (77%)	180	21 (10, 27)	0.3 (0.1, 2)	3.6
Calcium & phosphate	18	30 (31%)	67 (69%)	97	19 (5, 27)	0.2 (0, 1.6)	2.4
Glucose & insulin	17	24 (15%)	141 (85%)	165	21 (1, 27)	0.1 (0, 3.1)	1.2
Endocrine tumours	13	6 (9%)	60 (91%)	66	21 (2, 27)	0.1 (0, 1.3)	1.2
Growth & obesity	16	32 (12%)	225 (88%)	257	19 (5, 27)	0.4 (0, 5.6)	4.8
Pituitary	17	176 (51%)	168 (49%)	344	22 (4, 27)	0.4 (0, 8.7)	4.8
Sex development	20	133 (10%)	1230 (90%)	1363	22 (5, 27)	0.6 (0, 38)	7.2
Thyroid	17	89 (25%)	260 (75%)	349	22 (2, 27)	0.2 (0, 6.3)	2.4
Adults (≥18y)							
Adrenal	17	230 (23%)	751 (77%)	981	24 (5, 27)	1.2 (0.3, 11.8)	14.4
Calcium & phosphate	16	12 (7%)	164 (93%)	176	21 (3, 27)	0.5 (0, 9.3)	6.0
Glucose & insulin	14	14 (36%)	25 (64%)	39	19 (5, 27)	0.02 (0, 0.8)	<1
Endocrine tumours	16	61 (22%)	213 (77%)	274	25 (8, 27)	0.5 (0, 3.1)	6.0
Growth & obesity	9	1 (3%)	31 (97%)	32	21 (5, 27)	(0, 0, 1.5)	<1
Pituitary	17	295 (14%)	1789 (86%)	2084	24 (6, 27)	3.5 (0.4, 32.8)	42
Sex development	13	42 (5%)	772 (95%)	814	24 (8, 27)	1.8 (0, 8.6)	21.6
Thyroid	16	72 (7%)	917 (93%)	989	25 (5, 27)	2 (0, 9)	24

Table 4-2 Total number of cases reported within the eight Endo-ERN broad main thematic groups (MTG).

Endo-ERN MTGs (1-8)	Total number of cases reported, n (%)			
	<18y		≥18y	
MTG 1. Adrenal	268	6%	1470	15%
Congenital adrenal hyperplasia	181	68%	267	18%
Primary adrenal insufficiency	57	21%	287	20%
Cortisol producing adenomas	12	4%	222	15%
Sporadic phaeochromocytoma-paraganglioma	12	4%	518	35%
Adrenocortical carcinomas	6	2%	164	11%
Familial hyperaldosteronism	0	0%	12	1%
MTG 2. Calcium & phosphate	262	6%	294	3%
X-linked hypophosphataemia	82	31%	31	11%
Pseudohypoparathyroidism	68	26%	10	3%
Hypoparathyroidism	43	16%	117	40%
Hyperparathyroidism incl parathyroid cancer	16	6%	82	28%
Hypophosphataemic rickets	12	5%	6	2%
Hypocalcaemic vitamin D dependent rickets	12	5%	5	2%
Familial hypocalciuric hypercalcaemia	9	3%	15	5%
PTH independent hypercalcaemia	8	3%	12	4%
Hypocalcaemic vitamin D resistant rickets	5	2%	2	1%
AD hypophosphataemic rickets	2	1%	3	1%
Familial hyperphosphataemic tumoural calcinosis	2	1%	4	1%
AR hypophosphataemic rickets	1	0%	0	0%
Hereditary hypophosphataemic rickets with hypercalciuria	1	0%	1	0%
Oncogenic osteomalacia	1	0%	6	2%
MTG 3. Glucose & insulin	274	6%	106	1%
Hyperinsulinism	176	64%	16	15%
Rare diabetes	89	32%	42	40%
Insulin resistance syndrome	9	3%	48	45%
MTG 4. Endocrine Tumours	134	3%	538	6%
MEN Type 1	47	35%	159	30%
MEN Type 2	41	31%	69	13%
Von Hippel Lindau Syndrome	24	18%	65	12%
Hereditary phaeochromocytoma-paraganglioma	14	10%	223	41%
Carney complex	8	6%	11	2%
Other neuroendocrine tumours	0	0%	11	2%
MTG 5. Growth & Obesity	412	10%	61	1%
Rare genetic obesity	109	26%	2	3%
Prader-Willi syndrome & Prader-Willi-like syndrome	94	23%	49	80%
Noonan Syndrome	87	21%	0	0%
Overgrowth syndrome	54	13%	1	2%
Silver-Russell syndrome	44	11%	6	10%
GH Resistance syndromes	14	3%	0	0%
Beckwith-Wiedemann syndrome	10	2%	3	5%
ROHHAD syndrome	0	0%	0	0%
MTG 6. Pituitary	568	13%	4,265	44%
Congenital hypopituitarism	324	57%	96	2%
Acquired hypopituitarism	179	32%	1,199	28%
Pituitary adenoma	65	11%	2,970	70%
MTG 7. Sex Development	1,713	40%	1,106	11%
Transgender	988	58%	320	29%
XY DSD	294	12%	34	3%
Chromosomal DSD	259	11%	213	19%
XX DSD	90	4%	47	4%
Congenital normosmic hypogonadotrophic hypogonadism	52	2%	70	6%
Congenital anosmic hypogonadotrophic hypogonadism	30	1%	48	4%
MTG 8. Thyroid	612	14%	1,875	19%
Congenital hypothyroidism	486	79%	18	1%
Non-metastatic thyroid carcinoma	64	10%	1,821	97%
Congenital hyperthyroidism	37	6%	0	0%
Thyroid hormone signalling disorders	25	4%	36	2%

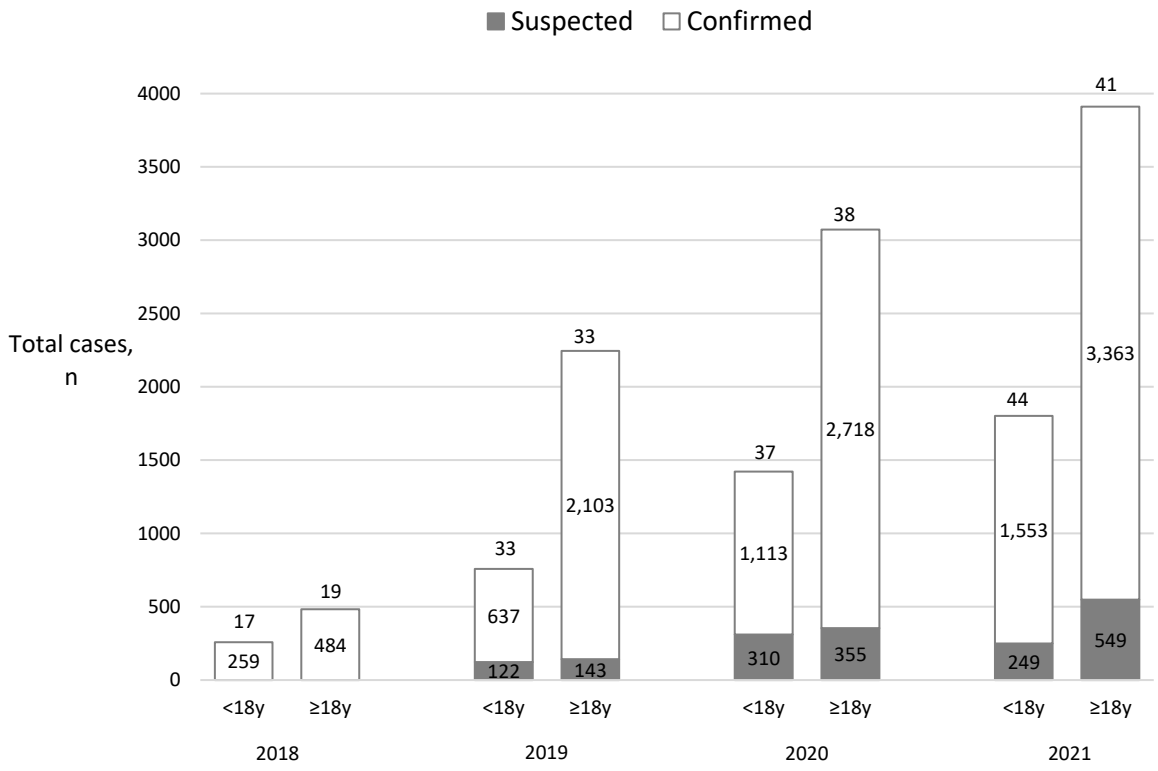


Figure 4-2. The change in the total number of cases reported on the e-reporting platform between July 2018 and December 2021 in children and adults.
The number at the top of each bar represents the number of centres that reported cases. The white and grey sections of each bar represent the number of confirmed and suspected cases, respectively.

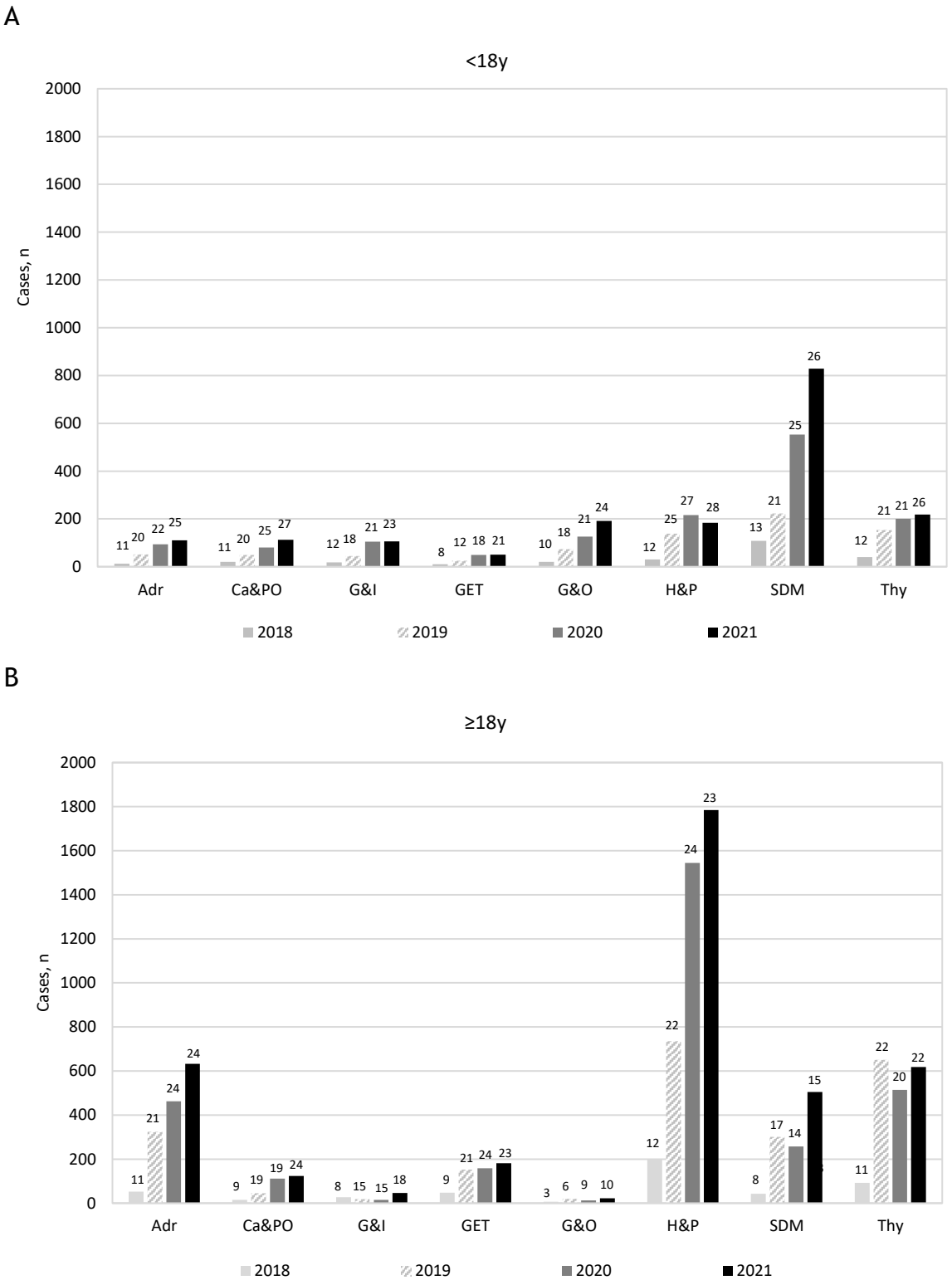


Figure 4-3 The total number of cases reported per main thematic group (MTG) in children and adults between July 2018 and December 2021.
The number at the top of each bar represents the number of centres that reported cases. Adr; adrenal, Ca & PO; calcium and phosphate, G&I; glucose and insulin, GET; genetic endocrine tumours, G&O; growth and obesity, H&P; hypothalamic and pituitary, SDM; sex development and maturation, Thy; thyroid.

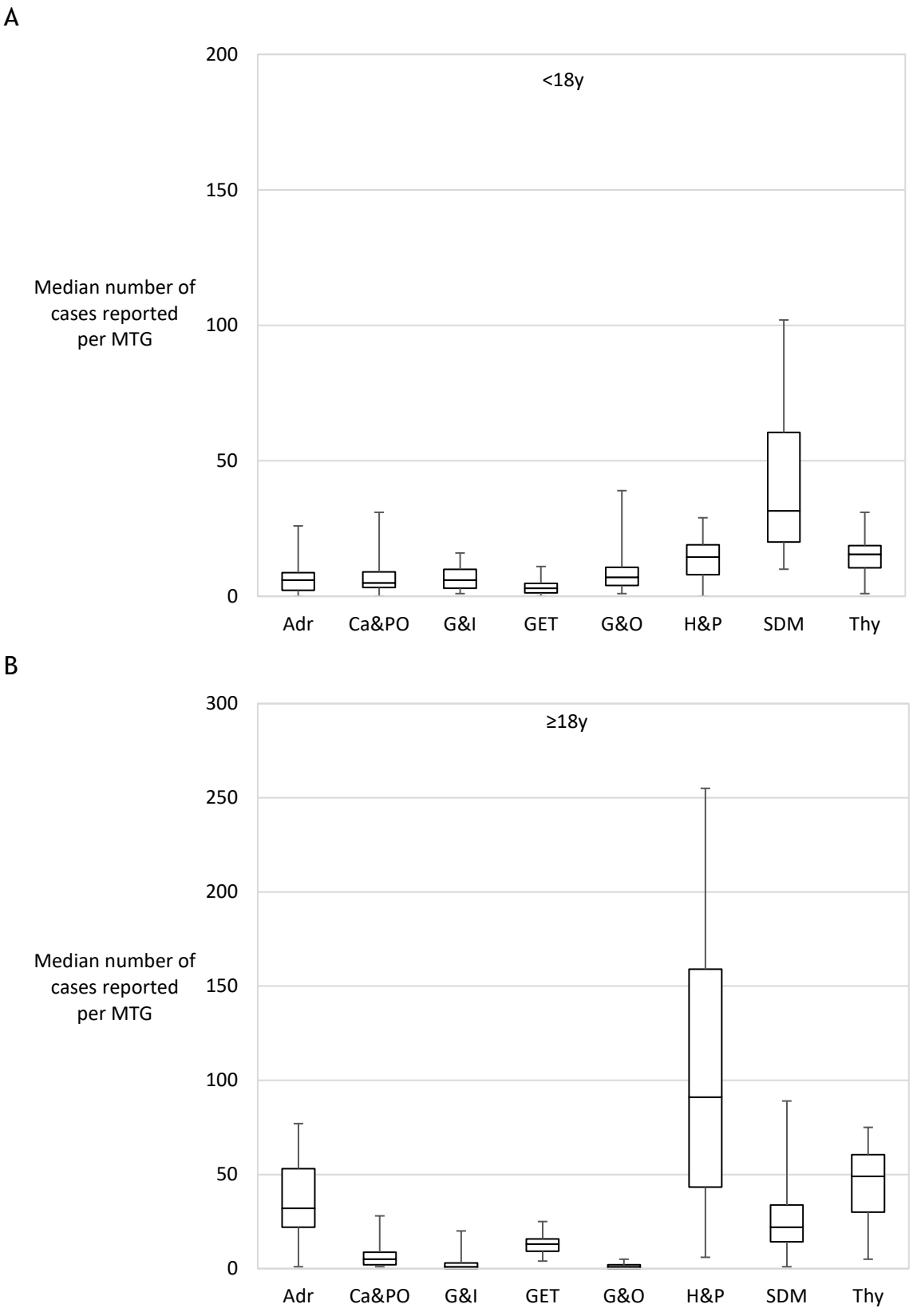


Figure 4-4 The median number of cases reported per main thematic group (MTG) per month between July 2018 and December 2021.
Adr; adrenal, Ca & PO; calcium and phosphate, G&I; glucose and insulin, GET; genetic endocrine tumours, G&O; growth and obesity, H&P; hypothalamic and pituitary, SDM; sex development and maturation, Thy; thyroid.

4.5.3 Adrenal disorders

Of the 4,243 new cases in children, 268 (6%) had an adrenal disorder. Of these 268, 181 (68%) were cases of congenital adrenal hyperplasia and 57 (21%) were primary adrenal insufficiency (Table 4-2). Of the 9,715 cases in adults, adrenal disorders were reported in 1,470 (15%) with 518 (35%) cases of sporadic phaeochromocytoma-paraganglioma. The overall median (range) number of paediatric and adult cases encountered by centres for adrenal conditions was 6 (0, 26) and 32 (1, 77), respectively (Figure 4-4). In children, despite an initial increase over the first year and half of reporting, the total number of adrenal cases reported remained constant over the latter 2 year period, whilst the number of adrenal cases reported in adults continued to increase (Figure 4-3). The estimated annual case occurrence rate amongst the 33 frequently reporting centres for children and adults was 3.6 per centre and 14.4 per centre, respectively (Table 4-1).

4.5.4 Disorders of calcium and phosphate homeostasis

In children, of the 4,243 new cases, 262 (5%) calcium and phosphate conditions were reported; 82 (31%) were specified as X-linked hypophosphataemia, 68 (26%) were pseudohypoparathyroidism and 43 (16%) were hypoparathyroidism; these conditions comprised more than 70% of reported cases in this condition group (Table 4-2). Of the 9,715 cases in adults, 294 (3%) had calcium and phosphate conditions, with 117 (40%) cases of hypoparathyroidism and 82 (28%) cases of hyperparathyroidism. The overall median number of paediatric and adult cases encountered by centres for this group of conditions was 5 (range 0, 31 and 1, 28, respectively), respectively and the total number of cases encountered over the past 2 years in both groups remained constant (Figures 4-3 and 4-4). The estimated annual case occurrence rate amongst the frequently reporting centres for children and adults was 2.4 per centre and 6.0 per centre, respectively (Table 4-1).

4.5.5 Genetic disorders of glucose and insulin homeostasis

Of the 4,243 new cases in children, 274 (6%) were glucose disorders, with 176 (64%) cases of hyperinsulinism (HI) and 89 (32%) of rare diabetes (Table 4-2). These conditions were less frequently reported in adults and of 9,715 cases, 16

(0.2%) cases of HI and 42 (0.4%) of rare diabetes were specified. Almost half of all reported cases of glucose and insulin disorders in adults were insulin resistance syndrome, comprising 48 (45%) cases. The overall median (range) number of paediatric and adult cases encountered by centres for glucose and insulin disorders was 6 (1, 16) and 1 (0, 20), respectively (Figure 4-4). The estimated annual case occurrence rate amongst the 33 frequently reporting centres for children and adults was 1.2 per centre and <1 per centre, respectively (Table 4-1).

4.5.6 Genetic endocrine tumour syndromes

In children, of the 4,243 cases, genetic endocrine tumour syndromes were reported in 134 (3%) cases and comprised the smallest number of reported conditions of all Endo-ERN condition groups (Table 4-2). Multiple endocrine neoplasias (MEN) accounted for more than 75% of reported cases, with 47 (35%) cases of MEN type 1 and 41 (31%) cases of MEN type 2 specified. In adults, of the 9,715 cases, there were 538 (6%) cases of genetic tumour syndromes; hereditary phaeochromocytoma-paraganglioma and MEN type 1 were the most commonly reported conditions, comprising 223 (41%)) and 159 (30%) conditions, respectively. The overall median (range) number of paediatric and adult cases encountered by centres for genetic endocrine syndrome was 3 (0, 11) and 13 (4, 25), respectively (Figure 4-4). The estimated annual case occurrence rate amongst the 33 frequently reporting centres for children and adults was 1.2 per centre and 6.0 per centre, respectively (Table 4-1).

4.5.7 Growth and genetic obesity syndromes

In children, of the 4,243 cases, 412 (10%) growth and rare genetic obesity conditions were reported. Rare genetic obesity, Prader-Willi syndrome and Noonan syndrome, were reported in 109 (26%), 94 (23%) and 87 (21%) cases, respectively, comprising 70% of reported growth conditions (Table 4-2). In adults disorders of growth and obesity were the least commonly reported condition group and of the 9,715 conditions reported in adults, only 61(1%) cases of this group were reported, with 49 (80%) cases attributed to Prader-Willi syndrome. The overall median (range) number of paediatric and adult cases encountered by centres for growth conditions was 7 (1, 39) and 1 (0, 5), respectively (Figure 4-

4). The estimated annual case occurrence rate amongst the 33 frequently reporting centres for children and adults was 4.8 per centre and <1 per centre, respectively (Table 4-1).

4.5.8 Hypothalamic and pituitary disorders

In children, of the 4,243 cases, 568 (13%) pituitary conditions were reported, with 324 (57%) cases of congenital hypopituitarism and 179 (32%) cases of acquired hypopituitarism reported (Table 4-2). In adults, conditions within the pituitary group were most commonly reported. Of the 9,715 cases in adults, 4265 (44%) pituitary cases were reported. with an increasing number of cases reported over time (Figure 4-3). The most common pituitary condition reported in adults was pituitary adenoma, with 2970 (70%) cases reported over a 3.5 year period. The median (range) number of cases encountered by centres for pituitary conditions in children was 15 (0, 29) and 91 (6, 255) in adults (Figure 4-4). The estimated annual case occurrence rate amongst the 33 frequently reporting centres for children and adults was 4.8 per centre and 42 per centre, respectively (Table 4-1).

4.5.9 Sex development and maturation disorders

In children, conditions within the sex development group were most commonly reported, comprising 1,713 (40%) cases of a total of 4,243 reported cases (Table 4-2). Cases of transgender were reported in 988, comprising 58% of reported cases in this condition group. In adults, of the 9,715 reported cases, 1106 (11%) of all reported cases were sex development disorders, with 320 (29%) cases of transgender. The median (range) number of paediatric and adult cases encountered by centres for conditions within the sex development were 32 (10, 102) and 22 (1, 89) (Figure 4-4). A trend towards an increasing number of cases being reported over time was apparent in both age groups (Figure 4-3). The estimated annual case occurrence rate amongst the 33 frequently reporting centres for children and adults was 7.2 per centre and 21.6 per centre, respectively (Table 4-1).

4.5.10 Thyroid disorders

In children, of the 4,243 reported conditions, 612 cases of thyroid conditions were reported, comprising 14% of all reported cases in children (Table 4-2). Congenital hypothyroidism was the most commonly reported condition in this group with 486 (79%) cases reported. In adults, of the 9,715 conditions reported, 1,875 (19%) thyroid cases were reported. Non-metastatic carcinoma was the commonest condition and reported in 1,821 (97%) adult cases. The median (range) number of cases encountered by paediatric and adults centres for thyroid conditions were 16 (1, 31) and 49 (5, 75), respectively, with the overall number of reported cases remaining constant over time (Figures 4-3 and 4-4). The estimated annual case occurrence rate amongst the 33 frequently reporting centres for children and adults was 2.4 per centre and 24 per centre, respectively (Table 5-1).

4.6 Discussion

4.6.1 Key findings

Since launching in 2018, the e-REC platform, an electronic reporting platform within the European Registries for Rare Endocrine Conditions (EuRRECa) project has enabled monthly reporting of new clinical cases by 61 centres from 22 countries, clearly showing that the platform can function as a simple registry which can perform epidemiological activities. The results show a steady increase in the total number of centres actively reporting cases via e-REC over the past 3.5 years. Around 30% of the reporting centres were also out-with the Endo-ERN network, demonstrating the wider scope for multicentre international collaboration within the endocrine community.

This initial phase in the use of e-REC also showed an increase in the total number of cases of rare endocrine conditions reported across most broad groups of conditions, in both adults and children. This may reflect widening participation, with a greater number of centres actively reporting cases over time and increasing awareness of the e-REC platform and Endo-ERN activities amongst the wider endocrine community. Despite comparable numbers of centres reporting paediatric and adult cases, a higher number of total cases were reported in adults compared with children (9,715 versus 4,243 cases). It is possible that this may be due to a higher incidence and prevalence of these conditions in adults or perhaps due to a small number of rare conditions which are more common. Previous studies examining the epidemiology of more common endocrine conditions in an industrialised nation estimated a prevalence of about 5% for some conditions including disorders of glucose homeostasis, calcium and phosphate conditions and thyroid disorders in adults, with a much lower incidence for other conditions including adrenocortical carcinoma, pheochromocytoma, and pituitary adenomas (Golden, Robinson et al. 2009). Although the epidemiology of more common conditions such as diabetes has been well-defined in large population-based studies (Ford, Li et al. 2008), there are a lack of comprehensive data regarding population-based estimates of the prevalence of many rarer endocrine conditions. Further studies evaluating the prevalence and presentation of these conditions to health care providers are

vital due to implications for planning of health service delivery models and allocation of public health and research resources (Golden, Brown et al. 2012).

The current bespoke e-REC platform enables reporting of confirmed and/or suspected cases which is particularly useful in cases where genetic or biochemical diagnostic confirmation is pending. Overall, in children and adults, a greater proportion of reported cases were defined as having a confirmed diagnosis rather than a suspected diagnosis. Interestingly, our results show that a greater proportion of cases were reported as suspected in children compared with adults and this may reflect the groups of conditions that are more often reported in these two age groups. However, there was a temporal increase in the proportion of cases reported as suspected over the 3.5 year period in adults. It is likely that by improving diagnostic ability, the number of cases that are reported as suspected may decrease and the prospective use of e-REC will allow networks such as Endo-ERN to monitor this metric of care.

Our results show that some rare endocrine conditions were more commonly reported than others. Overall, in children, almost half of all reported cases were sex development conditions, with transgender cases comprising 58% of reported cases. Recent studies have also highlighted increasing rates of transgender cases amongst both age groups (de Graaf, Carmichael et al. 2018, Indremo, White et al. 2021). In adults, almost half of all reported cases were pituitary conditions and pituitary adenomas were reported in 70% of these cases. Recent data from the continuous monitoring programme for ERNs regarding the median number of new pituitary patients seen in 2018 are comparable (de Vries, Bruin et al. 2020). However, challenges exist with regards to estimating the prevalence of pituitary adenomas and wide prevalence rates have been reported (Molitch 2017, Melmed 2020). By examining the centres that reported regularly and frequently, we have estimated the annual occurrence rates of rare endocrine conditions presenting to centres within a network such as Endo-ERN. These figures can, therefore, be reliably used as a clinical benchmark.

4.6.2 Limitations

Limitations that should be acknowledged include potential response bias amongst reporting centres and the preponderance of participating centres from

Europe, with 95% of centres from within Europe. In addition, differences in the definition of a confirmed and suspected condition and the collection of a small core dataset with information only collected on details of the reporter, reporting centre and the number of cases of each rare endocrine condition encountered are limitations. However, it was imperative to reduce respondent burden as respondents would be completing case returns on a monthly basis. Going forward, it would also be helpful to compare reported data to actual hospital activity data to ascertain the level of reporting accuracy.

4.6.3 Summary

In summary, the e-REC platform is a simple online platform that can be used to capture information on new encounters of patients with rare endocrine conditions. The platform is designed to minimise the reporting burden on healthcare professionals and promote a greater understanding of the number of people affected by a particular rare condition presenting to a clinical centre. The platform can be adapted to serve the needs of other reference networks that are interested in understanding the occurrence of rare conditions.

CHAPTER 5

A nationwide study of the prevalence and initial management of atypical genitalia in the newborn

The findings of this chapter have been published by Rodie ME, **Ali SR**, Jayasena A, et al. A nationwide study of the prevalence & initial management of atypical genitalia in the newborn in Scotland. *Sex Dev*. 2021;5:1-8.

5 A nationwide study of the prevalence and initial management of atypical genitalia in the newborn

5.1 Abstract

Background: There are a lack of data regarding the prevalence of atypical genitalia and the time taken to assign sex remains unclear. The provision of optimum healthcare for infants with atypical genitalia requires a clear understanding of the occurrence of this condition.

Objective: To determine the prevalence and initial managment of atypical genitalia and its initial management.

Methods: A prospective, electronic survey of clinicians within managed clinical networks in Scotland was undertaken between 2013 and 2019. Notification was sought for term neonates requiring specialist input for atypical genitalia. In addition, information was obtained from four regional genetics laboratories on neonates who had an urgent karyotype performed for atypical genitalia or sex determination.

Results: Overall, 171 term infants required investigation for atypical genitalia in the neonatal period providing a birth prevalence of 1 in 1,881 term births. Of the 171, 97 (57%) had specialist input over the first 3 months of life, providing a birth prevalence of 1 in 3,318 term births that received specialist input. Of the 97 cases, 92 had complete 3 month follow-up data. Of the 92, 62 (67%) presented within 24 hours of birth and age at presentation ranged from birth to 28 days. Assignment of sex occurred at birth in 63 (68%) and age range at sex assignment was birth to 14 days. Thus, the birth prevalence of a case of atypical genitalia where sex assignment was reported to be delayed beyond birth was estimated at 1 in 11,097 births.

Conclusion: Atypical genitalia requiring specialist input within the first month of life are rare in term newborns. Sex assignment is delayed beyond birth in only one third of cases. This study provides new clinical benchmarks for centres that manage these conditions.

5.2 Introduction

Sex assignment most often occurs immediately after birth. In circumstances where the child is born with atypical genitalia and immediate assignment is not possible, it is recommended that assignment should be delayed (Ahmed, Achermann et al. 2021). This is an extremely stressful situation for parents of a newborn (Sandberg, Gardner et al. 2012) and current guidelines highlight the need for expert communication, emotional support, and thorough clinical evaluation during this period of potential uncertainty (Ahmed, Achermann et al. 2021).

There are a paucity of studies investigating the prevalence and presentation of atypical genitalia in newborn infants. A greater understanding of the epidemiology of these conditions would have implications for planning of health care delivery and allocation of public health and research resources. Previous studies using linked hospital datasets estimate that atypical genitalia may occur in 1 in 300 births (Ahmed, Dobbie et al. 2004), whilst other data have suggested that complex forms of atypical genitalia may occur in 1 in 1,000 births (Aydin, Saka et al. 2019). Another study reported a similar birth prevalence in the immediate neonatal period in the tertiary hospital setting (Rodie, McGowan et al. 2011). Ambiguous genitalia where sex assignment on expert examination is difficult is reported to occur in about 1 in 5,000 births (Thyen, Lanz et al. 2006). However, the extent of variation in the genitalia is a continuum and it is possible that delayed sex assignment may occur more frequently.

A possible marker of delayed sex assignment is the infant with atypical genitalia who requires chromosome analysis, traditionally by karyotype, in the immediate neonatal period. Karyotype is a recommended first-line investigation in cases presenting with a suspected disorder or difference of sex development (DSD) (Ahmed, Achermann et al. 2021), thus, an assessment of its performance may also allow an understanding of the cases of atypical genitalia requiring expert evaluation. A previous registry-based study suggested that a karyotype may be performed within the first 10 days in about 1 in 1,300 infants (Rodie, McGowan et al. 2011). Thus, the occurrence of atypical genitalia is very variable and depends primarily on the definition of this condition.

In Scotland, managed clinical networks (MCN) such as the multidisciplinary Scottish DSD Network (SDSD; www.sdsd.scot.nhs.uk) and the Scottish Paediatric Endocrine Group (SPEG; www.speg.scot.nhs.uk) form the entire group of specialist clinicians who would become involved in any case of an infant with atypical genitalia that required expert input. Utilising these networks to evaluate the epidemiology of atypical genitalia in newborns would provide clarity of evidence to improve service delivery and would also allow the development of benchmarks of clinical practice.

5.3 Aims

The aim of this study was to:

- Analyse the prevalence and understand the presentation of atypical genitalia in the newborn period in Scotland, focusing primarily on delayed sex assignment and its management

5.4 Methods

5.4.1 Ethics approval and consent

The study was approved by the National Research Ethics Service in Scotland and the Caldicott Guardian as a health care evaluation survey. Participant consent was inferred from survey completion.

5.4.2 Case notification

Monthly emails were sent to all clinicians (consultant paediatricians, paediatric surgeons, paediatric urologists and paediatric endocrinologists) who were members of the SDSD network and SPEG between July 2013 and December 2019. Clinicians were asked to report any cases of atypical genitalia. Case notification was restricted to infants who were born at term, defined as ≥37 weeks gestation, with any form of atypical genitalia that required specialist pediatric surgical or endocrine input at under 4 weeks of age. Preterm infants were not included as assessment of their genitalia is often complicated by the effects of prematurity on the genitalia.

Upon notification of a case, a questionnaire was issued that enquired about the care received at the centre where the child was born as well as the specialist centre where the child may have been referred or transferred to for further care over the first 3 months of life (Table 5-1). Along with the case notification questionnaire, information was also provided regarding categorising the site of the urinary meatus (Figure 5-1) and DSD diagnostic categories (Table 5-2), to facilitate succinct completion of the case notification questionnaire. The extent of virilisation of the external genitalia was described as the external masculinisation score (EMS) (Ahmed et al., 2000). Clinicians who did not respond

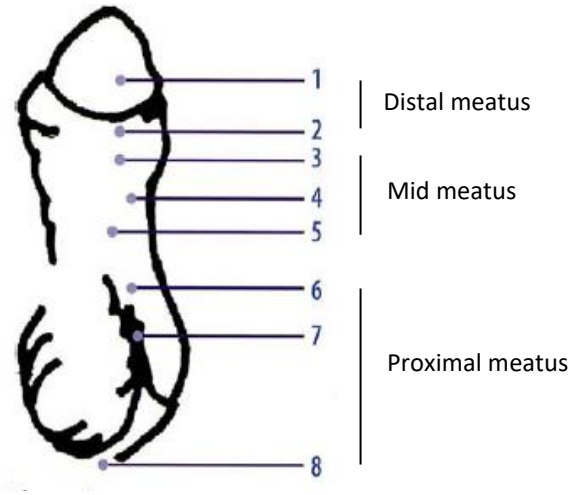
to the monthly email for 3 consecutive months were removed from the email circulation list. Birth prevalence was calculated by using annual live birth rates in Scotland as the denominator (https://www.nrscotland.gov.uk). Term birth rate was calculated using a figure of 8% preterm births in Scotland (www.europeristat.com).

All four regional NHS genetics laboratories that cover Scotland were contacted every 6 months from July 2013 to December 2019 to obtain information on all newborns that had an urgent karyotype within the first 4 weeks of life for atypical genitalia or sex assignment using the codes ‘sex’ or ‘genitalia’. The requesting clinician was then sent the case notification questionnaire to complete (Table 5-1).

Table 5-1. Items in case notification questionnaire.

Case Details			
Infant hospital number	**Maternal hospital number or Surname**	**Postal code**	**Date of birth** dd/mm/yyyy
Gestational age, weeks	**Ethnicity**	**Referral to or from another centre** Yes/ No/ Not known If Yes: Centre name, Consultant	
Sex Assignment			
Date of presentation to health care staff dd/mm/yyyy	**Age (hours) at presentation if less than 24 hours old**	**Date of sex assignment** dd/mm/yyyy	**Age (hours) at sex assignment if less than 24 hours old**
Sex at assignment Male/ Female/ Unclear	**Sex at 3 months after initial presentation** Male/ Female/ Unclear		
If sex re-assignment:			
Date of sex re-assignment dd/mm/yyyy	**Age (hours) at sex re-assignment if less than 24 hours old**	**Sex at re-assignment** Male/ Female/ Unclear	
Clinical Features			
Birth weight, grams	**Level of care over first 4 weeks of life** Normal/ Special care/ High dependency/ Intensive care		
Genital examination at sex assignment			
Phallus length Normal for boy/ Normal for girl/ Small for boy/ Large for girl	**Site of urinary meatus** (see Figure 5-1) Normal for boy/ Distal/ Mid shaft/ Proximal/ Not known/ Normal for girl	**Labioscrotal fusion** Yes/ No/ Not known	**Right Gonad** Labioscrotal/ Inguinal/ Impalpable/ Not known **Left Gonad** Labioscrotal/ Inguinal/ Impalpable/ Not known
Genital re-examination in cases of sex re-assignment			
As above/ Different from above	If different, please describe: Phallus, Urinary meatus, Labioscrotal fusion, Right gonad, Left gonad		
Parental Involvement with Senior Clinical Specialists (date, centre name)			
Neonatologist/ Paediatrician	**Paediatric Endocrinologist**	**Paediatric Urologist**	**Paediatric Surgeon**

Clinical Psychologist	Nurse Specialist	Clinical Geneticist	Other
Investigations (date performed)			
Karyotype Yes/ No/ Not known	**X and Y specific probes by FISH/PCR** Yes/ No/ Not known	**Other DNA based test- specify** Yes/ No/ Not known	
Sodium and potassium Yes/ No/ Not known	**Fasting glucose** Yes/ No/ Not known	**Anti-Müllerian Hormone** Yes/ No/ Not known	**17 OH-progesterone** Yes/ No/ Not known
Cortisol Yes/ No/ Not known	**Cortisol following synacthen stimulation** Yes/ No/ Not known	**Androstendione** Yes/ No/ Not known	**Androstendione following hCG stimulation** Yes/ No/ Not known
Testosterone Yes/ No/ Not known	**Testosterone following hcG stimulation** Yes/ No/ Not known	**Urinary steroid profile** Yes/ No/ Not known	
Ultrasound pelvis/abdomen Yes/ No/ Not known	**MRI pelvis/abdomen** Yes/ No/ Not known	**Genitoscopy** Yes/ No/ Not known	**Laparoscopy** Yes/ No/ Not known
Contrast genitogram Yes/ No/ Not known	**Gonadal biopsy** Yes/ No/ Not known	**Other** Yes/ No/ Not known	
Provisional Diagnosis			
Sex chromosome complement			
Presumed XY	**Presumed XX**	**XY**	**XX**
X	**XY/X**	**XX/XY/XXY**	**Other**
Other chromosomal variations Yes/No/Not known	**Provisional diagnosis** (see Table 5-2)	**Approximate date of reaching provisional diagnosis**	
Communication and Provision of Information (select multiple)			
Face to face discussion	**Audio records of interviews**	**Telephone discussion**	**Typed summary of case**
Information leaflets Specify source	**Directing to websites** Specify website/s	**Directing to support groups** Specify group/s	



1. Glanular
2. Coronal
3. Distal Penile
4. Midshaft
5. Proximal Penile
6. Penoscrotal
7. Scrotal
8. Perineal

Figure 5-1. Categorising the site of the urinary meatus.

Table 5-2. Coding for DSD diagnosis

A	**Disorder of gonadal development**	**1**	Complete gonadal dysgenesis
		2	Partial gonadal dysgenesis
		3	Gonadal regression
		4	Ovotesticular DSD
		5	Testicular DSD
		6	Other, *please write in section I3*
B	**Disorder of androgen synthesis**	**1**	Lipoid congenital adrenal hyperplasia due to StAR deficiency
		2	3β-hydroxysteroid dehydrogenase type 2 deficiency
		3	P450 side chain cleavage deficiency
		4	17β-hydroxysteroid dehydrogenase type 3 deficiency
		5	5α-reductase-type 2 deficiency
		6	Other, *please write in section I3*
C	**Disorder of androgen action**	**1**	Complete androgen insensitivity syndrome with suspected mutation in AR gene
		2	Partial androgen insensitivity syndrome with mutation in AR gene
		3	Other, *please write in section I3*
D	**Disorder of androgen excess**	**1**	21α-hydroxylase deficiency
		2	11β-hydroxylase deficiency
		3	Aromatase deficiency
		4	P450oxidoreductase deficiency
		5	Other, *please write in section I3*
E	**Disorder of Müllerian Development**	**1**	Persistent Müllerian duct syndrome with low AMH
		2	Persistent Müllerian duct syndrome with normal AMH
		3	Other, *please write in section H3*
F	**Non-specific disorder of masculinisation**	**1**	Isolated hypospadias
		2	Isolated micropenis
		3	Isolated bilateral undescended testes
		4	Combined genital anomalies including F.1, F.2 and/or F.3
		5	Other, *please write in section I3*
G	**Other**	**1**	Leydig cell hypoplasia
		2	LH deficiency
		3	Cloacal anomaly
		4	Other, *please write in section H3*

5.4.3 Statistical analysis

Intergroup comparison of categorical and continuous variables was performed using the Chi-squared test and the Mann Whitney U test, respectively, and $p<0.05$ was considered to statistically significant.

5.5 Results

5.5.1 Survey response

Between July 2013 and December 2019, the number of monthly responses ranged from 16 to 22 and the median (range) monthly response rate to the survey was 78% (55, 91). Over this period, 94 infants were reported by clinicians via case notification surveys. Of these 94 infants, 67 (71%) fulfilled the inclusion criteria. Of the remaining 27 infants, 16 cases were excluded because of prematurity and the remaining 11 cases were excluded as they were duplicate notifications. An additional 30 cases were identified through the 4 regional genetic laboratories, contributing to a total of 97 cases (Figure 5-2). In Scotland over the duration of the survey, the total live term birth rate was 321,811 births. Thus, the birth prevalence of atypical genitalia in term newborns requiring specialist input within the first month of birth, was calculated as 1 in 3,318.

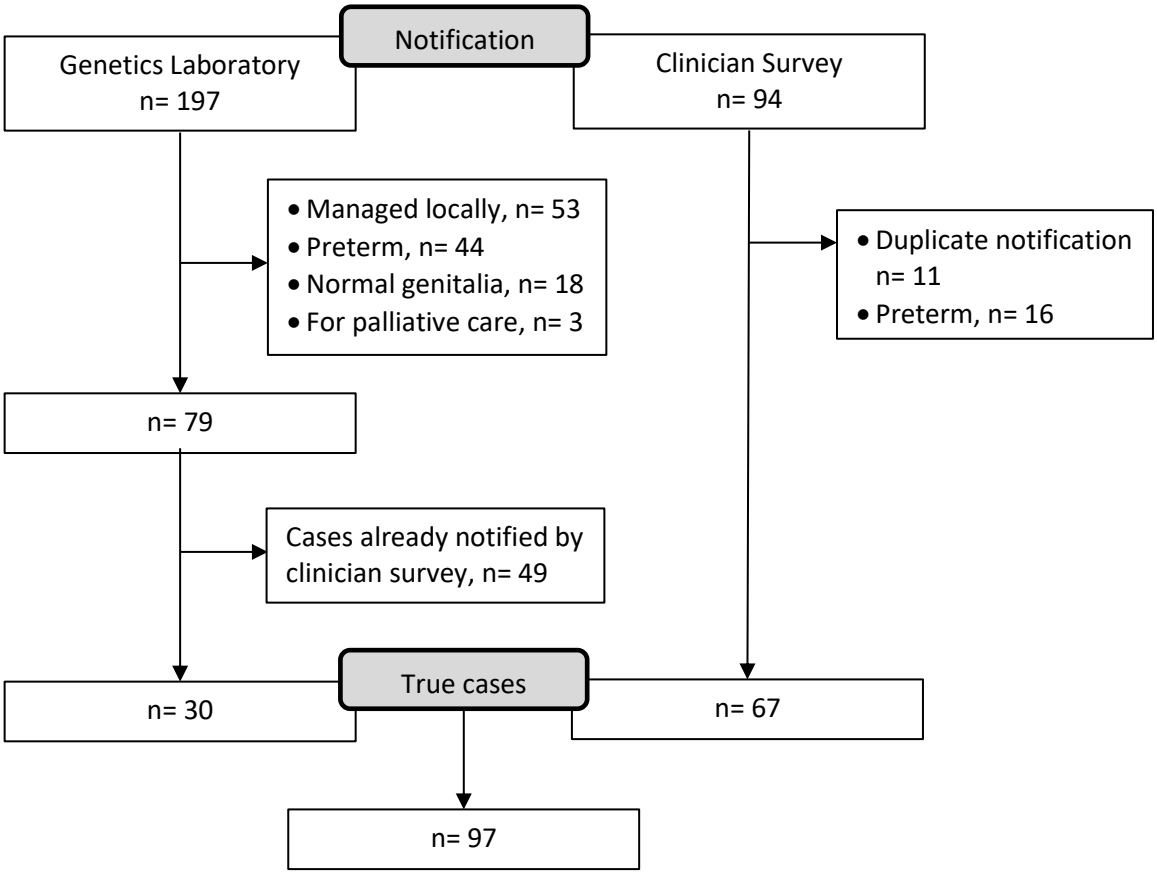


Figure 5-2. Total number of cases notified by the survey and identified through the genetics laboratories.

5.5.2 Cases not fulfilling all notification criteria

Of the 197 infants who had a karyotype performed by the genetics laboratories, 44 were excluded due to prematurity, 49 had already been notified through the clinician survey and 30 were identified as true cases which had not been notified (Figure 5-2). This left a group of 74 infants, of which 18 had normal genitalia, 3 died and 53 were managed in their local centres without specialist input within the first 4 weeks of life. Of the 53 infants managed locally, the clinical presentation included cases of: Bilateral undescended testes (n,34; 64%), hypospadias (n,6; 11%), suspected clitoromegaly (n,7; 13%), concerns regarding a prenatal sex chromosome variation (n,2; 4%), micropenis (n,2; 4%) and non-specific atypical genitalia (n,2; 4%). Of these 53 cases, 29 (55%) were referred for a specialist endocrine or surgical opinion after the age of 4 weeks. Diagnoses in these 29 cases included: Bilateral undescended testes (n,22), hypospadias (n,6) and sex chromosome variation- 47, XXY (n,1). Inclusion of the 74 term infants who had an urgent karyotype performed but did not have specialist input into the calculation of the birth prevalence of atypical genitalia resulted in a figure of 1 in 1,881 births.

5.5.3 Description of presentation

Of the 97 cases, 92 (95%) term infants had complete 3 month data. Of the 92 cases, 43 (47%) presented at birth, 20 (22%) presented within 24 hours of birth, and the remaining 29 cases presented after 24 hrs. Of the 92 infants, 64 (70%) and 20 (22%) were 46, XY and 46, XX, respectively whilst the remaining 8 (8%) had a range of sex chromosome variations with a Y-chromosome complement. Of the 92 infants, 40 (43%) had required a period of stay in the neonatal unit. Of the 64 XY cases, diagnoses included non-specific XY DSD (n,55), complete androgen insensitivity syndrome (CAIS) (n,3), bladder exstrophy (n,2), partial gonadal dysgenesis (n,2), CAH (n,1) and persistent Müllerian duct syndrome (n,1). Amongst the 20 XX cases, diagnoses included CAH (n,8), non-specific clitoromegaly (n,5), atypical genitalia (n,4), cloacal anomalies (n,2) and disorder of Müllerian development (n,1).

5.5.4 Sex assignment

Of the 92 term infants with complete 3 month data, 66 (72%) were initially assigned a male sex and 26 (28%) were assigned female sex. Of the 72 infants who were 46 XY or had a Y chromosomal complement, 66 (92%) were assigned a male and the remainder female. Of the 20 infants assigned 46,XX, 19 (95%) were assigned female, and one infant was assigned male but re-assigned to female when she was diagnosed with CAH at 28 days of life. Thus, 6 out of 26 (23%) assigned a female sex were 46,XY or had a Y chromosomal complement. The age at sex assignment ranged from birth to 14 days. Of the 92 infants, 63 (68%) had sex assignment at birth, 4 (4%) by Day 1 but not at birth, 24 (26%) by Day 7 and 1 (1%) by Day 14 (Figure 5-3). Thus, the birth prevalence of a case of atypical genitalia where the sex assignment was reported to be delayed beyond birth was estimated at 1 in 11,097 term infants. The 13 cases who were 46 XY or had a Y chromosomal complement, and in whom sex was assigned on Day 3 or later, included non-specific XY DSD (n,10) and partial gonadal dysgenesis (n,3). The median (range) EMS in this group who were assigned sex on Day 3 or later was 5 (2, 9) compared to 8 (0, 12) for those assigned sex at an earlier age (p=0.047).

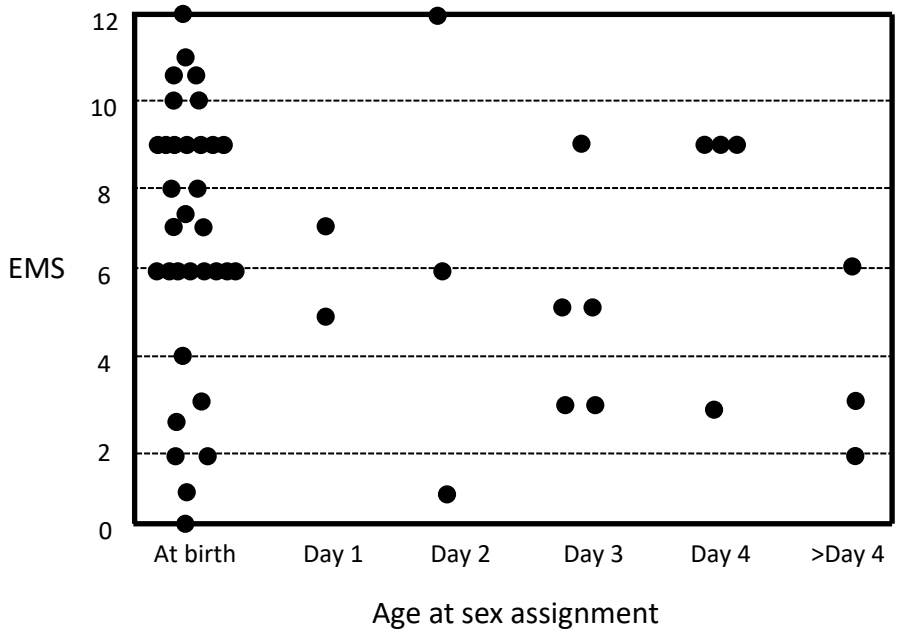


Figure 5-3. Age at sex assignment and External Masculinisation Score (EMS) in the infant with a XY karyotype or with a karyotype containing a Y chromosome.

5.5.5 Multidisciplinary team involvement

Of the 92 cases with complete 3 month data, 86 (93%) families met a neonatologist or general paediatrician within the first 3 months, 68 (74%) met a paediatric endocrinologist and 59 (64%) met a paediatric surgeon or urologist. Of the 92 cases, 21 (23%) families met a clinical geneticist, 20 (22%) met an endocrine nurse specialist and 12 (13%) had input from a clinical psychologist (Figure 5-4). In the 72 infants who had an XY karyotype or a Y chromosome complement, the median (range) number of health professionals encountered by those cases with an EMS <6, EMS 6-9 and EMS >9 was 4 (2, 6), 2 (2, 5) and 3 (2, 5), respectively (Figure 5-4). Information on provision of psychology input was available for 69 infants and the median (range) EMS of the infants whose parents met a psychologist (n,12) and did not meet a psychologist (n,57) was 3 (0, 9) and 8 (0, 12), respectively (p=0.01). Of the 18 infants with an XY karyotype or who had a Y chromosome complement who had delayed sex assignment after birth, the parents of 4 infants (22%) met a psychologist. Of the 18 infants with an XY karyotype or who had a Y chromosome complement and an EMS <6, 7 (39%) had involvement with a psychologist and of these, 4 (57%) had delayed sex assignment.

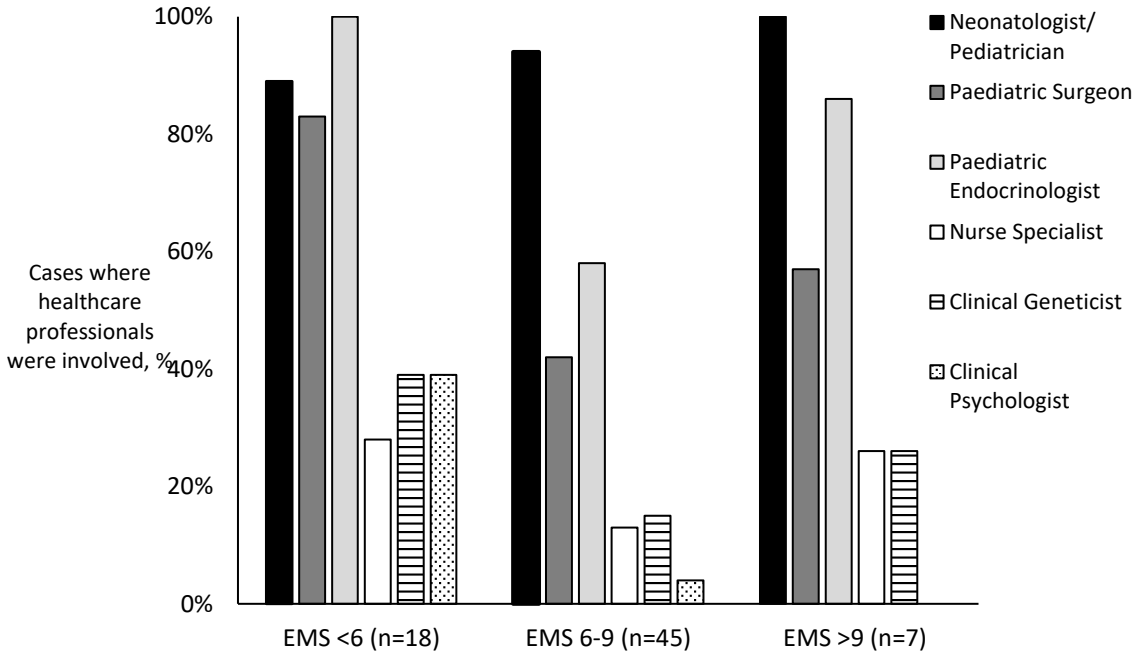


Figure 5-4. Healthcare professionals involved in the care of XY DSD infants by EMS category.
EMS, external masculinisation score.

5.5.6 Investigations

Other than the karyotype, the most common investigations performed in cases of 46 XX DSD were serum urea and electrolytes, pelvic ultrasound scan and serum glucose levels within the first 3 months of life. In the 72 infants with an XY karyotype or a Y chromosome complement, the most common investigations, other than the karyotype, within the first 3 months were serum urea and electrolytes, serum testosterone and pelvic ultrasound scan (Table 5-3). Apart from the hCG stimulation test and serum dihydrotestosterone, all investigations, including analysis of urinary steroid excretion, were usually performed within the first week of birth.

Table 5-3. Investigations performed within the first 3 months of life in the 72 infants with atypical genitalia at birth and a Y chromosome complement.

	Number of infants, n (%)	Median age at test in days (range)	Median EMS (range)
Urea & electrolytes	57 (79%)	2 (1, 24)	8 (0, 12)
Pelvic ultrasound scan	52 (72%)	3 (1, 58)	7 (0, 12)
Testosterone	51 (71%)	3 (1, 86)	7 (0, 12)
Anti-Müllerian hormone	43 (60%)	3 (1, 30)	7 (0, 10)
Androstenedione	39 (54%)	3 (1, 86)	8 (1, 12)
Glucose	28 (39%)	2 (1, 7)	7 (1, 12)
Cortisol	28 (39%)	3 (1, 11)	6 (1, 9)
Urinary steroid analysis	24 (33%)	5 (1, 46)	6 (1, 12)
Luteinizing hormone	20 (28%)	3 (1, 77)	6 (1, 9)
Follicle stimulating hormone	19 (26%)	3 (1, 77)	6 (1, 9)
Dihydrotestosterone	11 (15%)	5 (3, 86)	6 (2, 9)
ACTH level	10 (14%)	6 (3, 27)	9 (4, 9)
hCG stimulation	8 (11%)	33 (1, 89)	9 (0, 10)

5.6 Discussion

5.6.1 Key findings

This study provides a new clinical benchmark for the birth prevalence of atypical genitalia requiring specialist input in term newborns which was calculated as 1 in 3,318 in Scotland. This is more common than previously reported and perhaps reflects the differences in definition (Thyen, Lanz et al. 2006). Delayed sex assignment defined as sex assignment at any time point beyond birth was only reported to occur in 1 in 11,097 term newborns. There were no cases where sex was assigned after two weeks of age and there was only one case of sex reassignment within the first 3 months of life. Thus, a delay in assigning sex beyond birth was a rare occurrence and although this was more likely in those infants who were XY and had less virilised genitalia, this was not always the case.

In routine clinical practice, urgent query for X and Y specific probes may take up to two working days. This study suggests that sex assignment was performed at a very early stage in cases of atypical genitalia and often well before seeking expert opinion or undertaking specialist investigations. Current expert guidance recommends that sex assignment should be delayed until completion of a thorough expert evaluation (Ahmed, Achermann et al. 2021). Interestingly, recent studies of temporal trends in sex assignment in DSD suggest that affected infants with an XY karyotype are more likely to be raised as male, irrespective of the extent of virilisation of the external genitalia (Kolesinska, Acierno et al. 2018). This change in practice may be another explanation for the relatively short time taken to assign sex in the current study.

Our results show that almost all infants that satisfied the reporting criteria were seen by a neonatologist or a paediatrician and the majority by a paediatric endocrinologist or a paediatric surgeon/urologist within the first 3 months of life. However, less families received psychology input and this was not dependent on whether there was any reported delay in sex assignment. Psychological support had not been provided in the first 3 months in over 78% of cases where sex assignment was reported to have been delayed. In addition, there was some evidence of targeting psychology resources to those cases that

were severely undermasculinised and had delayed sex assignment. Previous studies have highlighted that many expert centres have psychology support available at an early stage following neonatal presentation (Pasterski, Prentice et al. 2010, Kyriakou, Dessens et al. 2016, Dessens, Guaragna-Filho et al. 2017, Rolston, Gardner et al. 2017). Moreover, the appearance of the external genitalia may not be a good indicator of the extent of distress experienced by parents (Duguid, Morrison et al. 2007). This study is the first to provide objective data that quantifies the proportion of cases that were actually provided psychological support.

Karyotype and pelvic ultrasound are the first line investigations for an infant presenting with a suspected DSD. In this study, along with pelvic imaging, more than half of the patients had biochemical investigations including urea and electrolytes, testosterone, AMH and androstenedione within the first few days of life. Other studies have reported similar findings, with testosterone being the most frequently performed biochemical investigation (Kyriakou, Dessens et al. 2016). Second line investigations such as hCG and ACTH stimulation tests are less frequently carried out, only being performed if concerns have been raised from the initial work-up (Kyriakou, Dessens et al. 2016), in accordance with current UK guidance on the initial management of infants with atypical genitalia (Ahmed, Achermann et al. 2021). Our data also suggests that AMH and urinary steroid analysis are assessed more often whilst the hCG stimulation test is performed less often within the first 3 months of life, compared with recent data evaluating worldwide practice at expert centres (Kyriakou, Dessens et al. 2016).

Interestingly, over the 7.5 year study period, nine term infants with atypical genitalia were diagnosed with CAH within the neonatal period. Based on the total study term birth rate of 321,811 infants, this suggests a birth prevalence of CAH cases of 1 in 35,757, approximately half of what has been previously reported through a neonatal screening study performed in the same geographical region (Wallace, Beastall et al. 1986) as well as more widely in the UK (Khalid, Oerton et al. 2012). This may reflect the fact that boys with classic forms of CAH do not present with atypical genitalia in the neonatal period. The study also identified 3 infants with CAIS providing an occurrence of 1 in 107,270, similar to

that reported in a previous population based study (Berglund, Johannsen et al. 2016).

5.6.2 Strengths

This study did not include preterm infants as assessment of their genitalia is often complicated by the effects of prematurity on the genitalia. Cross referencing of the reported cases with the regional laboratories allowed the identification of cases that had not been notified by clinicians and cases who had a karyotype performed because of concern regarding sex development but in whom expert input was not sought during the neonatal period. Inclusion of this group for calculation of the birth prevalence of atypical genitalia where there is sufficient concern to perform a karyotype within the neonatal period provided a figure of 1 in 1,881, which is similar to that reported in a previous retrospective study (Rodie, McGowan et al. 2011).

The reported data represent a new clinical benchmark that requires further study and comparison to national and international practice.

5.6.3 Limitations

Parents and health care staff who were present at the delivery of the newborn were not interviewed directly. Thus, it is unclear whether there was any uncertainty amongst parents regarding sex assignment in those cases who were reported by health care staff to have been assigned sex at birth. Previous studies have reported that parents of newborns with a wide range of genital atypicality do have concerns regarding long-term outcomes related to gender (Duguid, Morrison et al. 2007, Timmermans, Yang et al. 2019), thus, these outcomes require further evaluation in future studies.

5.6.4 Summary

This study has prospectively and systematically collected data over a period of 7.5 years and has found that although atypical genitalia that raise some concerns and require investigations in the neonatal period may occur in 1 in 1,881 term births, specialist input is sought in 1 in 3,318 term births and delayed sex assignment is reported to occur in 1 in 11,097 term births. The study provides

several indicators that can be used as clinical benchmarks for comparing and improving the delivery of care in centres that manage these complex conditions.

CHAPTER 6

Real world estimates of adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia

The findings of this chapter have been published by **Ali SR**, Bryce J, Haghpanahan H, et al. Real world estimates of adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2021;106:e192-203.

6 Real world estimates of adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia

6.1 Abstract

Background: Although congenital adrenal hyperplasia (CAH) is a rare condition, it is the commonest cause of early-onset primary adrenal insufficiency in children and places patients at a life-long risk of sick day episodes (SDE) and adrenal crises (AC).

Objective: To investigate the epidemiology of SDE and AC in an international cohort of patients under the age of 18 years old with classic 21-hydroxylase deficiency CAH.

Methods: Data on children from 34 centres in 18 countries, of which 7 were Low or Middle Income (LMIC) and 11 were High Income (HIC), were collected from the International CAH (I-CAH) registry and analysed to examine the clinical factors associated with SDE and AC.

Results: A total of 518 children with a median of 11 children (range 1, 53) per centre had 5,388 visits evaluated over a total of 2,300 patient years. The median number of AC and SDE per patient year per centre was 0 (0, 3) and 0.4 (0.0, 13.3), respectively. Of the 1,544 SDE, an AC was reported in 62 SDE (4%), with no fatalities. Infectious illness was the most frequent precipitating event, reported in 1,105 (72%) and 29 (47%) of SDE and AC, respectively. On comparing cases from LMIC and HIC, the median SDE per patient year was 0.11 (0, 12.0) vs 0.75 (0, 13.3) ($p<0.001$), respectively and the median AC per patient year was 0 (0, 2.2) vs 0 (0, 3.0) ($p=0.43$), respectively.

Conclusion: The real-world data that are collected within the I-CAH Registry show wide variability in the reported occurrence of adrenal insufficiency related adverse events. As these data become increasingly used as a clinical benchmark in CAH care, there is a need for further research to improve and standardise the definition of SDE.

6.2 Introduction

Congenital adrenal hyperplasia (CAH) are a group of autosomal recessive conditions that have an overall incidence of 1 in 15,000 (Speiser, Arlt et al. 2018). More than 95% of cases of CAH are due to 21-hydroxylase deficiency (White and Speiser 2000). In this form of CAH, abnormalities in steroidogenesis can result in varying levels of glucocorticoid (GC) and mineralocorticoid deficiency. CAH is the most common cause of primary adrenal insufficiency (AI) in childhood (Wijaya, Huamei et al. 2019). In its most severe form, classic CAH, which may be further categorised into salt-wasting and simple-virilising forms depending on the level of residual enzyme activity, patients may have severe primary AI (White and Speiser 2000).

Patients with CAH have a life-long requirement for GC replacement. Although GC treatment has improved survival in patients with AI (Johannsson, Falorni et al. 2015), the risk of acute AI, also known as an 'adrenal crisis' (AC), has not been eliminated and life expectancy remains below that of the general population (Shulman, Palmert et al. 2007, Falhammar, Frisén et al. 2014). AC are the leading cause of mortality in patients with CAH (Falhammar, Frisén et al. 2014) and cortisol dose escalation, also known as 'stress-dosing' or 'sick-day dosing' is the cornerstone of AC prevention. Currently, there is no universally accepted definition of AC and patients presenting with this life-threatening emergency often present with non-specific symptoms including abdominal pain, vomiting and somnolence, contributing to difficulties in the diagnosis of AC (Rushworth, Torpy et al. 2017, Rushworth, Torpy et al. 2019). Patients with AC are usually managed in a hospital setting and treatment involves the administration of intravenous GC and fluid resuscitation which is highly effective if delivered in a timely manner (Allolio 2015).

Reported rates of AC are very variable, with rates of between 5.2 and 10.9 per 100 person years reported in children with CAH (Odenwald, Nennstiel-Ratzel et al. 2016, Rushworth, Falhammar et al. 2016, El-Maouche, Hargreaves et al. 2018, Ishii, Adachi et al. 2018). It is possible that some of this variation is related to lack of a universally accepted definition of AC as well as its prodrome, often referred to as a 'sick day episode' (SDE). There may be other factors that influence variation in the rates of these adverse events, including differences in

healthcare delivery service models and access to emergency medication such as parenteral GC and patient/family dependent factors such as sick day dosing education (Dineen, Thompson et al. 2019). Nevertheless, there is increasing consensus that the avoidance of acute adverse events due to AI is one of the most important outcomes that can be routinely measured (Chrisp, Maguire et al. 2018, Regan, Vaidya et al. 2019).

Given the rarity of CAH as well as AC in children, knowledge on the epidemiology of acute AI related adverse events including SDE in children with CAH is limited, with a paucity of data in large, multi-centre, international cohorts. Patient registry data is increasingly recognised as a valuable source of information for evaluating outcomes in rare diseases such as CAH (Ali, Lucas-Herald et al. 2019). The development of the International Congenital Adrenal Hyperplasia Registry (I-CAH) in 2013 has provided a valuable resource for evaluating outcomes in this rare condition.

6.3 Aims

Using real world data from the I-CAH registry, the aims of this study were to:

- Investigate the occurrence of acute AI related adverse events (SDE and AC) in an international cohort of children aged less than 18 years old with 21-hydroxylase deficiency CAH

- Examine the association of SDE and AC with clinical variables including age, sex, CAH phenotype (salt-wasting and simple-virilising) and treatment (GC and mineralocorticoid doses)

6.4 Methods

6.4.1 Ethics approval and consent

The I-CAH registry is an international database of pseudonymised information on patients with CAH and is approved by the National Research Ethics Service in the United Kingdom as a research database of information that is collected as part of routine clinical care (Ali, Lucas-Herald et al. 2019). The data within the registry are deposited by clinicians following informed consent from patients or guardians.

6.4.2 Study population

All patients under the age of 18 years registered as having 21-hydroxylase deficiency CAH were identified from the I-CAH registry (https://home.i-cah.org/) in July 2019.

Only those cases of 21-hydroxylase deficiency on GC with or without mineralocorticoid (fludrocortisone, FC) were included. For the purpose of this study, the phenotypic classification into salt-wasting and simple-virilising CAH was based on concurrent treatment with FC.

6.4.3 Clinical data collection

The I-CAH registry collects data on acute AI related adverse events since a patient's last clinic visit and this information is collected within the adverse events section of the CAH longitudinal module within the registry. Clinicians with cases meeting the inclusion criteria were approached to enter data for a minimum of two clinic visits per patient per year. SDE and AC were based on the clinical judgment of the reporting clinician. For each SDE, data were available on: the duration of SDE (number of days); any predisposing condition at the time of SDE (infectious illness, surgery, other, not known); management of each SDE, including sick day management of oral steroids (doubled, more than doubled, not increased, not known) and the requirement for intramuscular hydrocortisone (HC) injection (yes, no, not known); the occurrence of AC (yes, no, not known); and the need for health professional input (self-managed at home, health professional only, emergency room, admission to hospital, intensive care unit).

Data were also gathered about GC and FC regimens (preparation, dose, frequency) at the time of clinic visits. HC equivalent dose (ED) was calculated by multiplying prednisolone dose by 5 or dexamethasone dose by 80 (Hindmarsh 2009, Finkielstain, Kim et al. 2012). Total GC dose (HC equivalent) was converted from mg to mg per m^2 using the Mosteller formula for calculation of body surface area (BSA) (Mosteller 1987), or using pre-defined BSA values for weight as outlined in the British National Formulary for Children (http://bnfc.nice.org). GC and FC doses were categorised as low, normal or high as follows: GC low <10 mg/m^2/day, normal 10-15 mg/m^2/day, high >15 mg/m^2/day; FC low <50 µg/day, normal 50-200 µg/day, high >200 µg/day, based on Endocrine Society clinical practice guidelines for 21-hydroxylase deficiency CAH (Speiser, Arlt et al. 2018).

6.4.4 Statistical analysis

A longitudinal analysis of repeated measures reported from multiple visits was performed. The main outcome measures were occurrence of SDE, an increase in sick day oral GC dose, HC injection, AC and hospitalisation, defined as attendance at the emergency room or admission to hospital. Multilevel logistic regressions were applied to examine the association of these outcome measures

with clinical data obtained at each visit including age, sex, phenotype, GC and FC dose. Accordingly, a two-level multilevel regression model was built with individual patients (level 1) nested within centres (level 2). Random (intercept) effects for both levels were included in the modelling to allow variations between individuals and centres to be accounted for. The observed frequency of SDE and AC was determined as incidence rate, calculated as the number of SDE and AC divided by person-years.

For the assessment of geographical differences in the occurrence of SDE and AC, participating countries were categorised as those from a low or middle income country (LMIC) or from a high income country (HIC) as defined by the 2019 World Bank classification (http://datahelpdesk.worldbank.org). Inter-group comparison for these variables was performed by the Mann Whitney U test. The Fisher Exact Test was performed to compare proportions in different groups. Results are reported as frequencies and percentages, median (with ranges) or odds ratios (ORs) and 95% confidence intervals (CI). Data analysis was performed using R statistical software version 3.5.3 and Minitab version 18 statistical software (Minitab LLC, State College, PA, USA).

6.5 Results

6.5.1 Case selection

At the time of the study, 1,426 cases of CAH were registered in the I-CAH registry (Figure 6-1). Data on clinic visits including adverse events were available for 518 children aged less than 18 years with 21-hydroxylase deficiency CAH (Figure 6-2). Of the 518 children, 275 (53%) were girls, 459 (89%) had salt wasting CAH and 59 (11%) had simple-virilising CAH. These children were reported from 34 centres in 18 countries with a median of 11 cases per centre (range 1, 53).

Of the 518 children, 316 (61%) were from a high income country (HIC) and 202 (39%) were from a low or middle income country (LMIC) (Table 6-1). There was no significant difference in the proportion of cases from HIC or LMIC countries, CAH type or sex assigned when comparing those with and without clinic visits data (Table 6-2).

A total of 5,388 clinic visits, that occurred between 1984 and 2019, were evaluated in the 518 children, comprising a total of 2,300 patient years (Table 6-3). The median duration of follow-up per patient was 3 years (0.1, 17.9), with a median of 2.9 visits (0.3, 25.7) per patient year. The median patient age at the time of the visits was 2 years (0, 17.9).

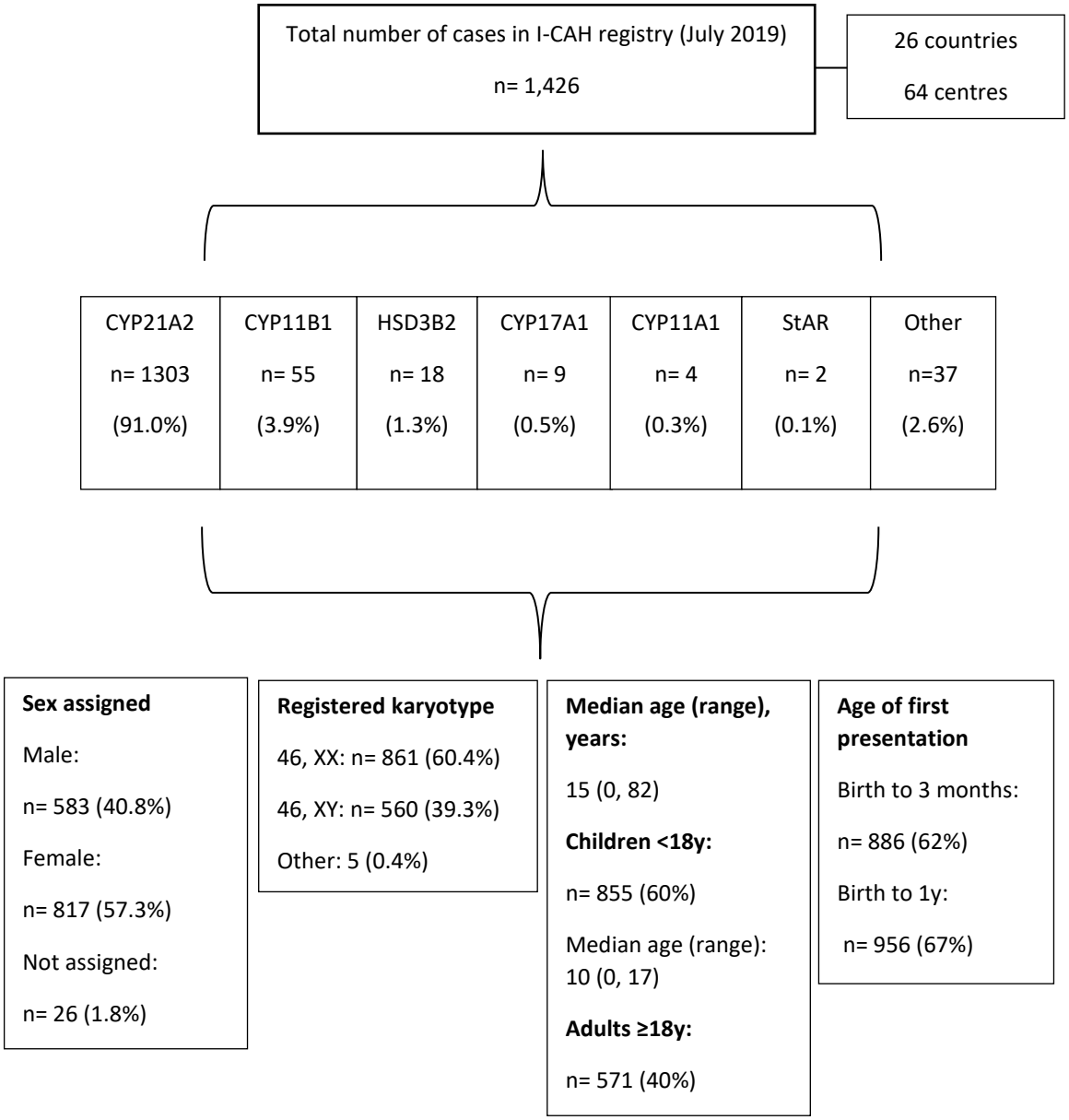


Figure 6-1. Cases in the I-CAH registry in July 2019.
CYP21A2, 21-hydroxylase; CYP11B1, 11 Beta-hydroxylase; HSD3B2, 3-beta-hydroxysteroid dehydrogenase; CYP17A1, 17 alpha-hydroxylase/17,20-lyase; CYP11A1, cholesterol side-chain cleavage enzyme (P450scc), StAR, steroidogenic acute regulatory protein deficiency.

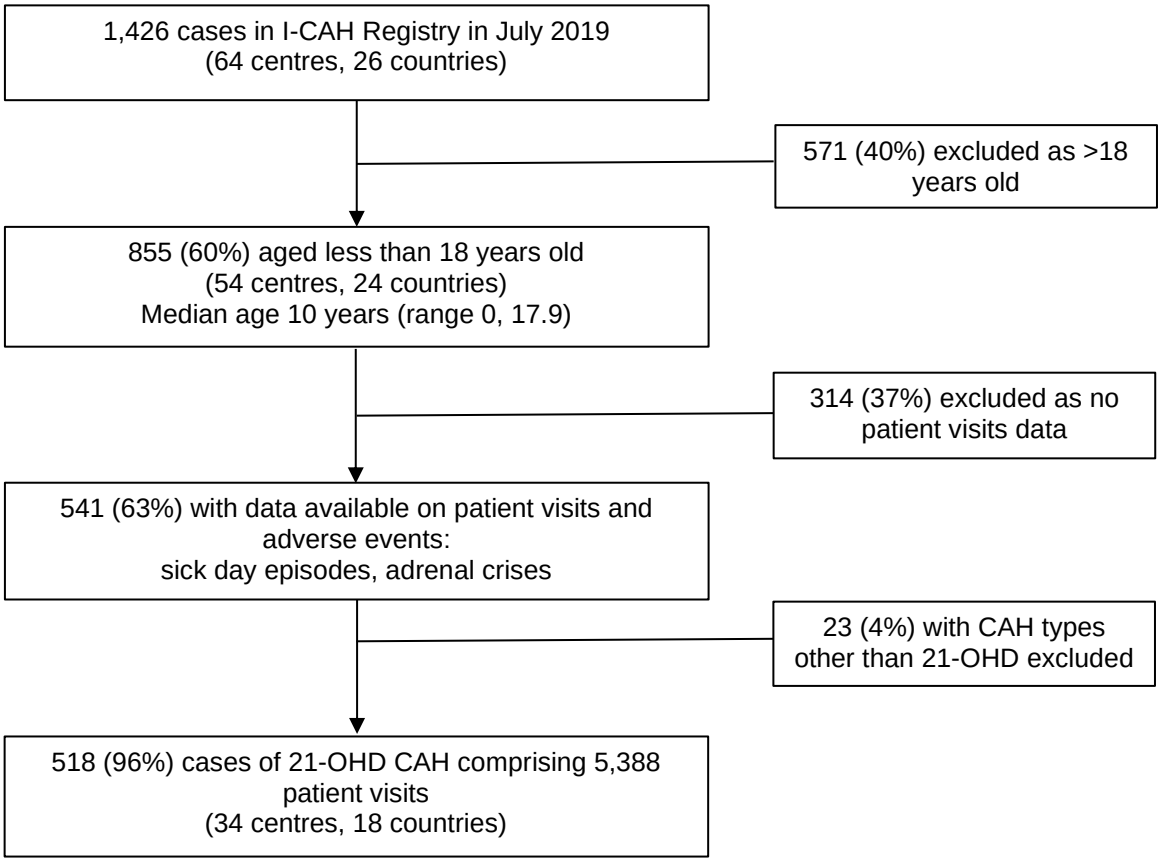


Figure 6-2. Participant selection from the I-CAH registry.
Abbreviations: 21-OHD, 21-hydroxylase deficiency; CAH, congenital adrenal hyperplasia; I-CAH, International Congenital Hyperplasia registry.

Table 6-1. Geographical distribution of the study cohort (n=518).

Region and total cases, n (%)	Country	Centres, n	Cases, n
Europe (n= 327, 63%)	Netherlands	4	99
	United Kingdom	7	63
	Germany	3	58
	Belgium	1	28
	Italy	2	27
	Denmark	1	17
	Serbia	1	13
	Switzerland	1	12
	Sweden	1	7
	Bulgaria	1	1
	Hungary	1	1
	Romania	1	1
Asia (n=95, 18%)	Turkey	3	84
	Sri Lanka	1	7
	Israel	1	4
South America (n=73, 14%)	Brazil	3	59
	Argentina	1	14
Africa (n=23, 4%)	Egypt	1	23

Table 6-2. Characteristics of children with CAH with and without clinic visit data in the I-CAH registry.

HIC, high income country; LMIC, low-middle income country; CYP21A2, 21-hydroxylase deficiency; CYP11B1, 11 beta-hydroxylase deficiency; HSD3B2, 3 beta-hydroxysteroid dehydrogenase deficiency; CYP11A1, cholesterol side-chain cleavage enzyme (P450scc) deficiency; StAR, steroidogenic acute regulatory protein. *Patients included in current study. Statistically significant p values are in bold type.

Core data information in I-CAH Registry	Patients with visits data (n=541)	Patients without visits data (n=314)	*p*-value
Total number of countries	18	18	
HIC, n (%)	11 (61.1%)	11 (61.0%)	1.00
LMIC, n (%)	7 (38.9%)	7 (38.9%)	1.00
Cases per country, Median (range)	17 (1, 101)	7 (1, 76)	
Age at first presentation, n (%)			
<1 month	402 (74.3%)	166 (52.9%)	**<0.001**
1– 3 months	75 (13.9%)	48 (15.3%)	0.61
4 – 12 months	6 (1.1%)	8 (2.5%)	0.16
>1 year	45 (8.3%)	40 (12.7%)	0.05
Not known	13 (2.4%)	52 (16.7%)	**<0.01**
CAH diagnosis, n (%)			
CYP21A2	518* (95.7%)	292 (93.0%)	0.11
CYP11B1	5 (0.9%)	8 (2.5%)	0.08
HSD3B2	7 (1.3%)	5 (1.6%)	0.77
CYP11A1	2 (0.4%)	1 (0.3%)	1.00
StAR	1 (0.2%)	1 (0.3%)	1.00
Other	8 (1.5%)	7 (2.2%)	0.43
Karyotype, n (%)			
46, XX	256 (47.3%)	182 (58.0%)	**<0.01**
46, XY	195 (36.0%)	98 (31.2%)	0.16
Presumed XX	37 (6.8%)	11 (3.5%)	0.05
Presumed XY	53 (9.8%)	23 (7.3%)	0.26
Sex Assigned, n (%)			
Female	283 (52.0%)	171 (54.4%)	0.57
Male	258 (48.0%)	133 (42.3%)	0.14
Not assigned	0	10 (3.2%)	**<0.01**

Table 6-3. Characteristics of children with 21-hydroxylase deficiency (21-OHD) CAH at all clinic visits (n=5,388).
CAH, congenital adrenal hyperplasia; SDE, sick day episodes; GC, glucocorticoid. HC ED, hydrocortisone equivalent dose (mg/m²/day); FC, fludrocortisone. GC and FC doses were categorised as low, normal or high, based on Endocrine Society clinical practice guidelines for 21-OHD CAH as follows: GC low <10 mg/m²/day, normal 10-15 mg/m²/day, high >15 mg/m²/day; FC low <50 µg/day, normal 50-200 µg/day, high >200 µg/day. *For GC and FC doses, the percentage of total visits was calculated based on 'known' (Normal/High/Low) values.

	Group	Patients, n	Total Visits, n (%)	Visits per patient, median (range)	Total follow-up duration (years)	Follow-up per patient (years), median (range)	Total visits per patient year	Visits per patient year, median (range)
Children, <18 years	All	518	5,388 (total)	9 (1, 42)	2,300	3.0 (0.1, 17.9)	1,744	2.9 (0.3, 25.7)
Sex	F	275	2,821 (52.4)	9 (1, 35)	1,277	3.0 (0.1, 17.9)	881	2.9 (0.3, 18.2)
	M	243	2,567 (47.6)	9 (1, 42)	1,003	3.0 (0.2, 17.9)	863	3.0 (0.4, 25.7)
CAH phenotype	SW	459	5,086 (94.4)	9 (1, 42)	1,984	3.0 (0.1, 17.9)	1,549	3.0 (0.3, 25.7)
	SV	59	302 (5.6)	9 (1, 35)	296	3.0 (0.2, 17.9)	195	2.5 (0.5, 14.7)
Age at visit, y	<1	418	1,621 (30.1)	3 (1,16)	234	0.7 (0.0,1.0)	2,770	5.9 (2.3, 51.4)
	1-4.9	422	2,427 (45.0)	5 (1,18)	893	2.0 (0.2, 4.6)	1,255	2.6 (0.6, 25.7)
	5-14.9	189	1,147 (21.3)	5 (1, 26)	606	2.2 (0.0, 9.7)	578	2.7 (0.9, 22.5)
	15-17.9	61	193 (3.6)	3 (1, 12)	85	1.5 (0.2, 2.6)	170	2.3 (1.3, 10.4)
Number of SDE	0	512	4,299 (79.8)	7 (1, 42)	2,142	2.9 (0.0, 17.9)	1,665	2.6 (0.3, 51.4)
	1	311	816 (15.1)	2 (1, 12)	667	0.9 (0.1, 17.6)	858	2.9 (0.2, 27.7)
	2-3	129	231 (4.3)	1 (1, 6)	165	0.3 (0.1, 14.0)	376	3.0 (0.1, 22.5)
	≥4	33	42 (0.8)	1 (1, 5)	17	0.3 (0.3, 2.7)	96	3.0 (0.8, 4.5)
Daily GC dose*	Normal	423	2,019 (47.8)	4 (1, 24)	1,224	1.8 (0.0, 17.2)	1,508	2.7 (0.2, 53.3)
(HC ED mg/m²/day)	High	341	1,201 (28.4)	3 (1, 17)	763	0.7 (0.0, 17.8)	1,762	3.0 (0.2, 65.5)
	Low	287	1,006 (23.8)	3 (1, 16)	496	0.9 (0.1, 17.2)	999	3.0 (0.3, 34.3)
	Not known	282	1,162	3 (1, 20)	700	1.2 (0.0, 17.6)	861	3.0 (0.1, 30.0)
Daily FC dose*	Normal	466	4,374 (90.2)	8 (1, 40)	1,925	3.0 (0.1, 17.8)	1,629	2.9 (0.2, 45.0)
(µg/day)	High	36	111 (2.3)	2 (1, 10)	23	0.3 (0.0, 2.7)	372	5.4 (1.2, 55.4)
	Low	95	359 (7.4)	2 (1, 16)	160	0.9 (0.2, 6.4)	283	3.0 (0.3, 8.7)
	Not known	143	544	2 (1, 25)	296	0.3 (0.0, 17.6)	695	3.0 (0.3, 65.5)

6.5.2 Steroid replacement

Of the 5,388 clinic visits, information on steroid replacement was available in 5,250 visits (97%). Of the 518 children, 435 (84%) were receiving HC, with 19 (3.5%) and 7 (1.5%) receiving prednisolone and dexamethasone, respectively; 16 children (3%) were taking a combination of different types of GC. The median steroid replacement dose, as HC ED, was 12.5mg/m^2/day (2.3, 71.4). The use of HC was documented in 4,733 visits (90%) and the doses of GC were known in 4,226 visits (82%). The GC doses were reported to be within the recommended HC ED of 10–15mg/m^2/day in 2,019 visits (48%) (Table 6-3).

Of the 518 children, 459 (89%) were receiving FC at the time of clinic visits, with a median dose of 93.8 µg/day (12.5, 500) and doses were reported to be within the recommended range of 50–200µg/day in 4,374 visits (90%) (Table 6-3).

6.5.3 Occurrence of sick day episodes and adrenal crises

Of the 5,388 visits in 518 children, a total of 1,544 SDE were reported in 1,089 visits (20%) from 334 children (64%), of whom 167 (50%) were female. Based on a total observation period of 2,300 patient years, the SDE incidence rate was calculated at 67 per 100 patient years and the median duration of a SDE was 3 days (1, 41). Of the 1,089 visits where a SDE was reported, in 989 (91%), the reported number of SDE since last clinic visit was ≤2. A median of 1 SDE (1, 8) was reported per patient per visit, and the overall median number of SDE per patient year per centre was 0.4 (0, 13.3) (Figure 6-3). When comparing SDE rates in HIC and LMIC countries, the median SDE per patient year was 0.75 (0, 13.3) vs 0.11 (0, 12.0); $p<0.001$, in HIC and LMIC countries, respectively.

Of the 1,544 SDE, 62 events (4%) were associated with an AC in 49 out of 334 children (15%), all had salt-wasting CAH and 22 (45%) were female. The overall median AC per patient year was 0 (0, 3), with no significant difference between HIC and LMIC countries, [0 (0, 2.2) vs 0 (0, 3.0); $p=0.43$], respectively (Figure 6-4). There was no AC related mortality reported amongst these children. The AC incidence rate in those children who had a SDE was 3.9 per 100 patient years, with an overall AC incidence rate of 2.7 per 100 patient years for all children.

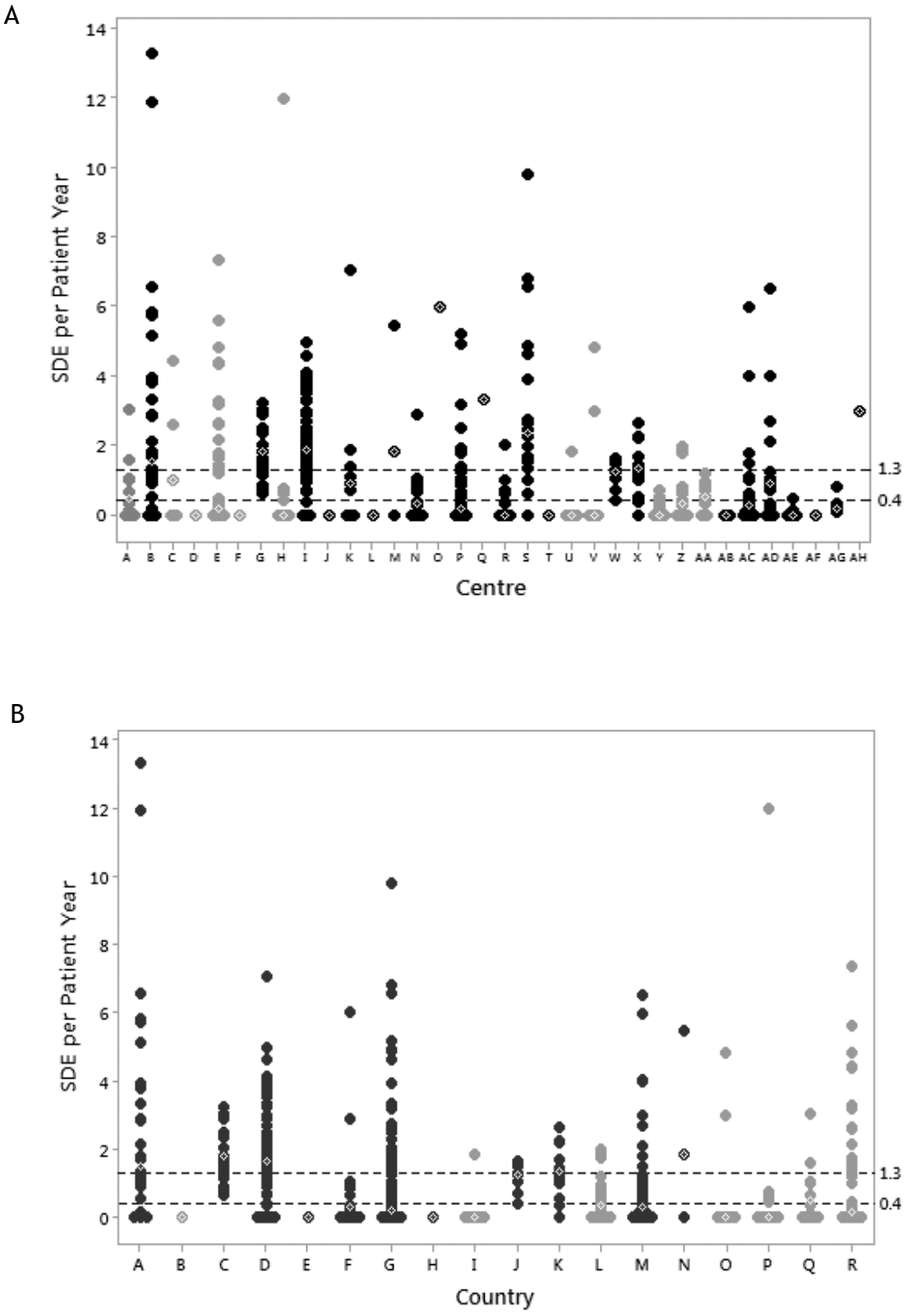


Figure 6-3. Sick day episodes (SDE) per patient-year per centre (A) and SDE per patient-year per country (B).
Centres are labelled “A” to “AH”. Countries are labelled “A” to “R”. Each point represents the median number of SDE per patient-year for each patient in that centre or country. The white diamond symbol indicates the median number of SDE per patient-year for all patients in that specific centre or country. The dashed horizontal black line indicates the overall median and 75th centile values for SDE per patient-year for all centres and countries. Black dots represent patients from a high income country (HIC). Grey dots represent patients from a low-middle income country (LMIC).

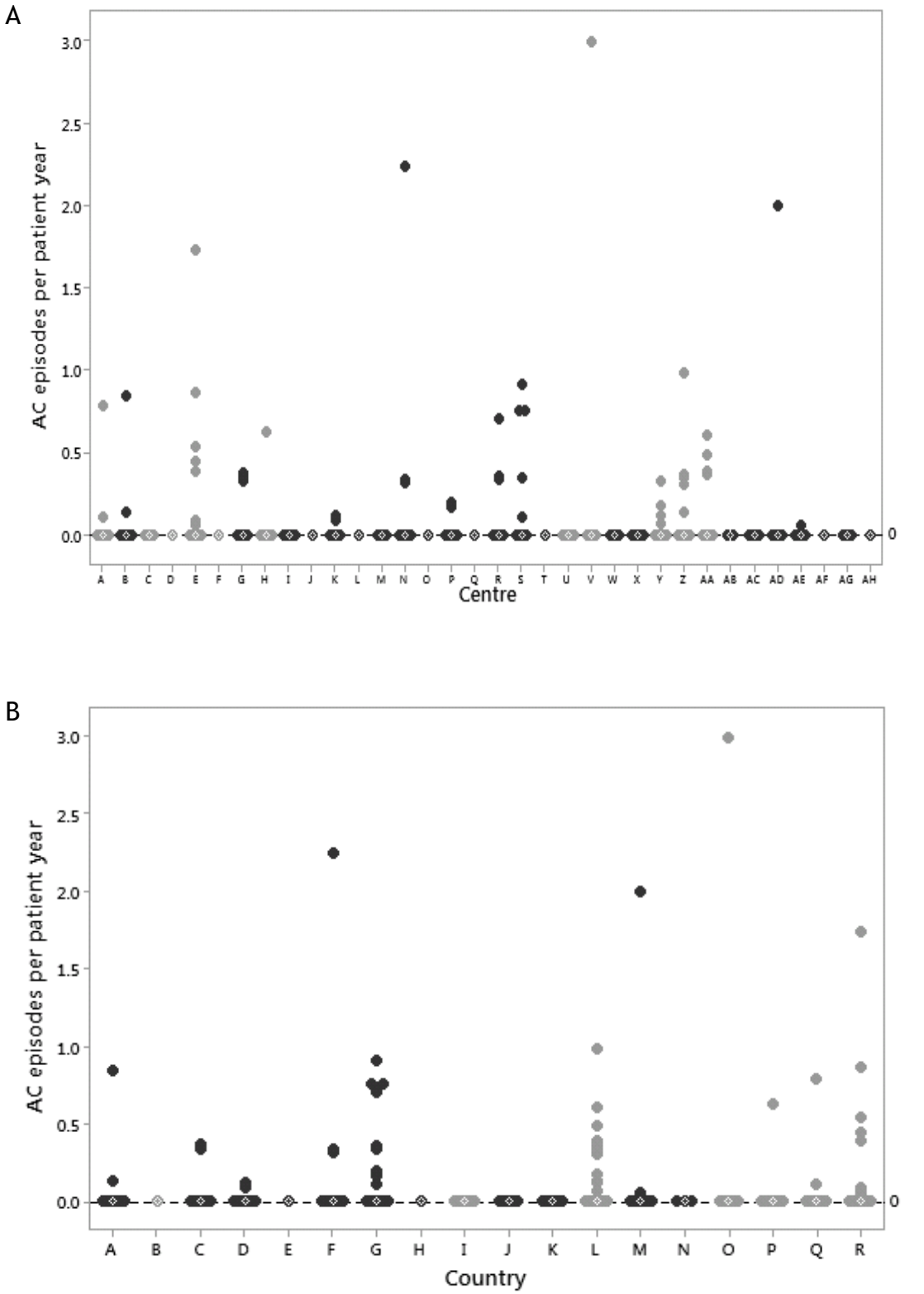


Figure 6-4. Adrenal crises (AC) per patient-year per centre (A) and AC per patient-year per country (B).
Centres labelled “A” to “AH”. Countries labelled “A” to “R”. Each point represents the median number of AC per patient-year for each patient in that centre or country. The white diamond symbol indicates the median number of AC per patient-year for all patients in that specific centre or country. The dashed horizontal black line indicates the overall median AC per patient-year for all centres and countries. Black dots represent patients from a high income country (HIC). Grey dots represent patients from a low-middle income country (LMIC).

6.5.4 Risk factors for sick day episodes and adrenal crises

Infectious illness was the most frequent event associated with SDE across all ages, reported in 1,105 of 1,544 SDE (72%). Surgery was reported as a factor predisposing to SDE in 58 (4%) episodes and no predisposing factor was specified in 381 SDE (24%) (Figure 6-5). Infection was also the most frequent event associated with AC, reported in 29 of 62 AC episodes (47%). No predisposing factor was specified in 33 (53%) AC episodes.

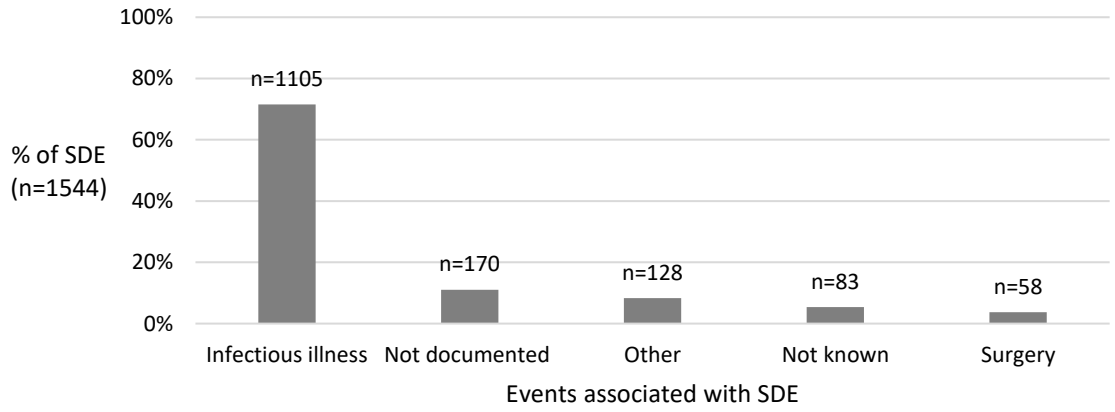


Figure 6-5. Events associated with the occurrence of a sick day episode (SDE).

Younger children (aged 1 to 4 years) and adolescents (15 to 18 years) had a greater likelihood of a SDE [OR 2.05 (95% CI 1.63–2.59) and OR 1.68 (95% CI 1.37–2.06); both p<0.001, respectively] and an increase in sick day oral GC [OR 2.11 (95% CI 1.63–2.73); p<0.001 and OR 1.98 (95% CI 1.57–2.49); p<0.01, respectively] compared to children <1 year of age (Figure 6-6). Compared to girls, boys were more likely to have SDE [OR 1.41 (95% CI 1.14–1.75); p<0.01] and an increase in sick day oral GC [OR 1.37 (95% CI 1.08–1.74), p<0.01]. Children receiving lower GC doses (HC ED <10mg/m^2/day) were more likely to have a SDE [OR 2.00 (95% CI 1.53–2.63), p<0.001] and an increase in sick day oral GC [OR 2.27 (95% CI 1.68–3.08); p<0.001] than those on higher GC doses (HC ED >15mg/m^2/day). Similarly, children receiving GC doses within the recommended range (HC ED of 10–15mg/m^2/day) were more likely to have SDE [OR 1.47 (95% CI 1.17–1.85); p<0.01] and an increase in sick day oral GC [OR 1.73 (95% CI 1.33–2.24); p<0.001], than children on higher GC doses (HC ED >15mg/m^2/day). Due to the small number of AC events overall, which decrease further when broken down over risk factor levels, the multilevel regression model parameters could not be reliably estimated and are not reported.

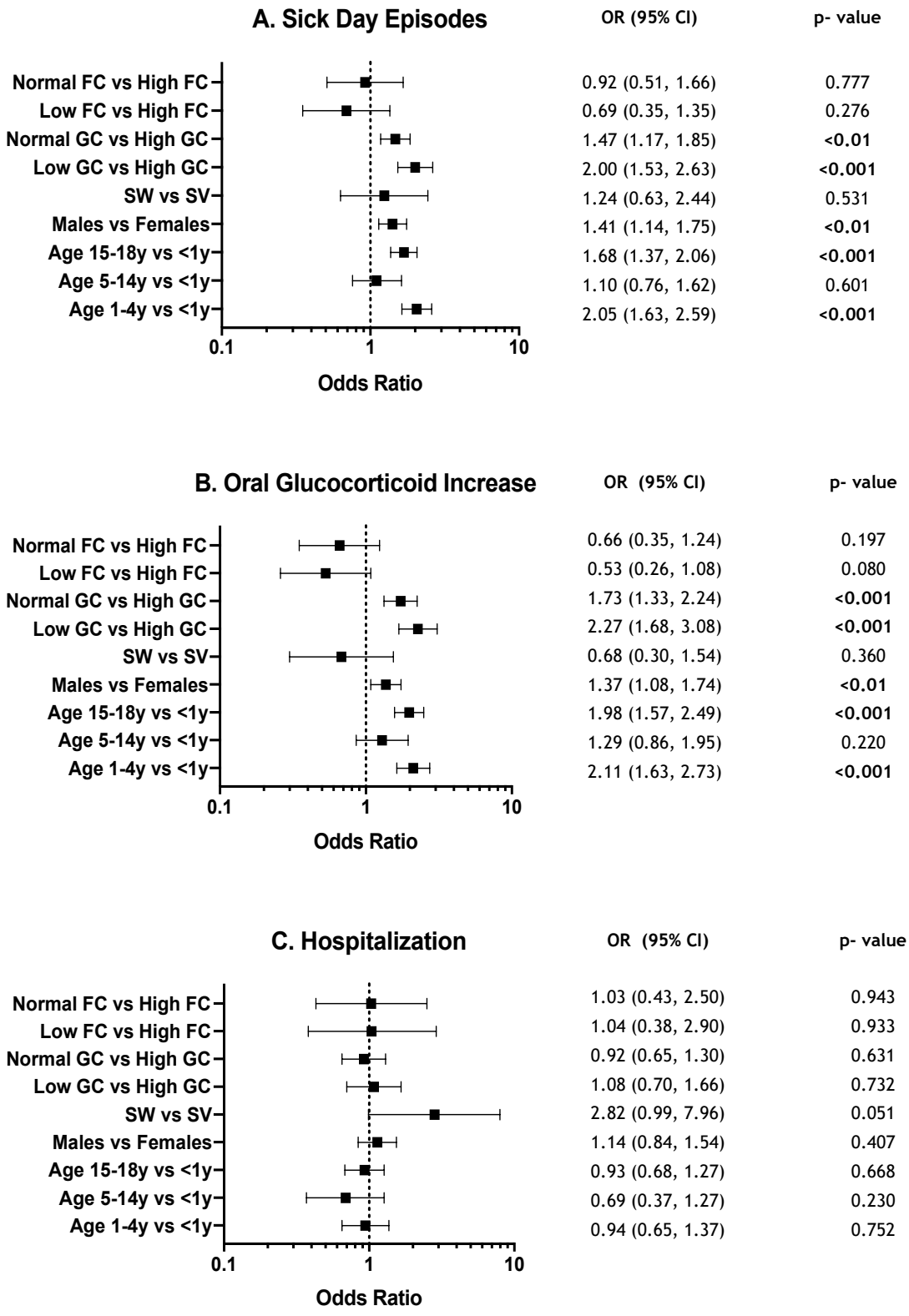


Figure 6-6. Association of age, sex, phenotype and medication dose with sick day episodes (A), an increase in sick day oral glucocorticoid (B) and hospitalisation (C).
FC, fludrocortisone (µg/day); GC, glucocorticoid (hydrocortisone equivalent dose, mg/m^2/day); SW, salt-wasting CAH; SV, simple-virilising CAH. Statistically significant p values are in bold type.

6.5.5 Management of sick day episodes and adrenal crises

Of the 1,544 reports of SDE, there was information on a change in the patients usual management documented in 1,451 SDE (94%). More specifically, an increase in oral GC dose was noted in 1,147 episodes (85%), HC injection was administered in 176 SDE (13%) and information on medical input was available in 1,419 SDE (92%) (Figure 6-7). Of the 1,451 SDE, 858 SDE (60%) were self-managed in the community and of these, 6 (1%) were associated with an AC. In 561 SDE (40%), medical input, including hospitalisation was sought and 55 (10%) of these were associated with an AC. In total, of the 62 episodes of AC that were reported, 55 (90%) were associated with hospitalisation. An increase in oral GC or HC injection administration was reported in 52 (84%) episodes of AC; in the remaining 10 (16%) episodes of AC, there was no information regarding an increase in oral GC dose or the administration of HC injection, however, all 10 of these episodes were associated with hospitalisation.

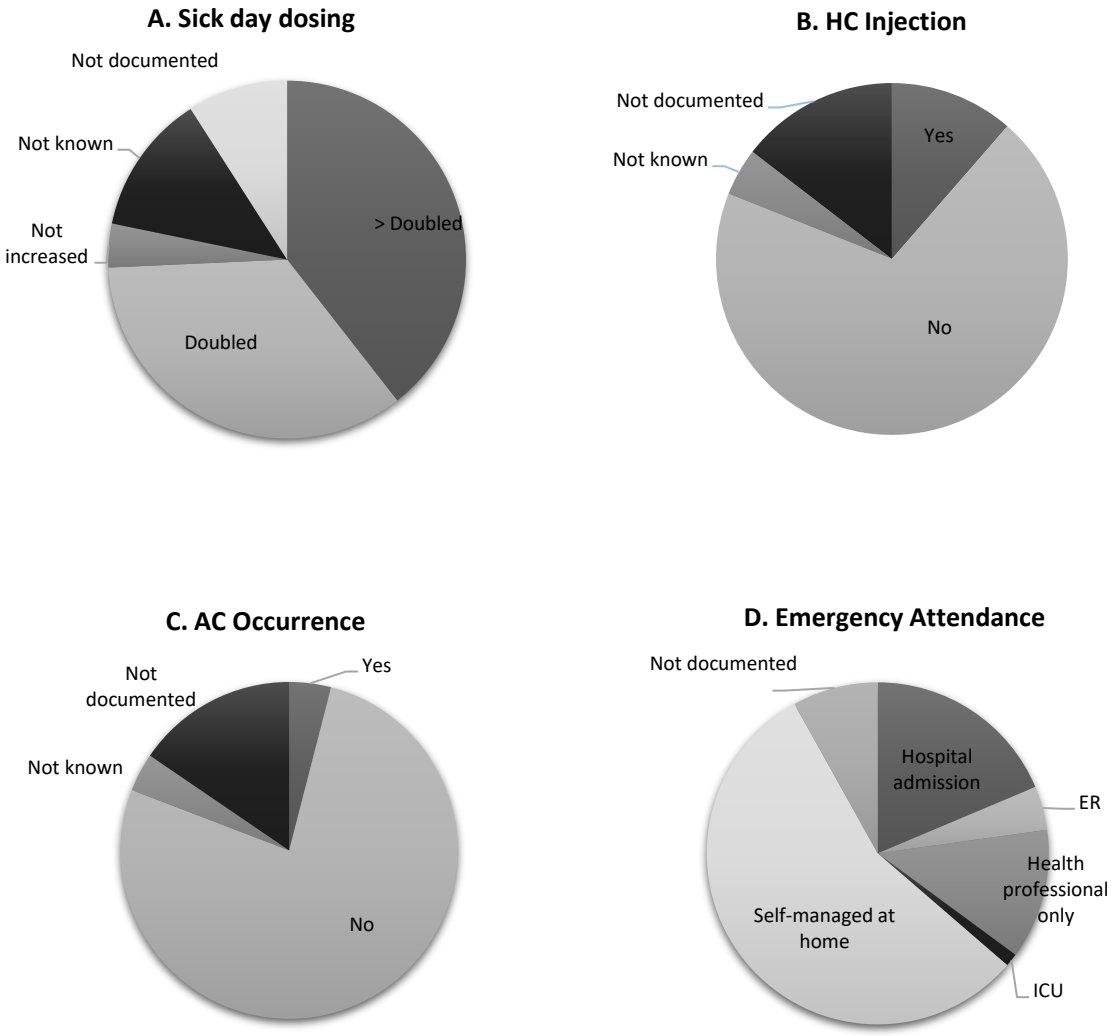


Figure 6-7. Management of sick day episodes (n=1544).
The proportion of SDE in which GC sick day dosing was administered (A), HC injection administration, (B), the occurrence of AC (C) and emergency attendance (D). AC, adrenal crisis; GC, glucocorticoid; ER, emergency room; HC, hydrocortisone; ICU, intensive care unit; SDE, sick day episode.

6.6 Utilisation of the I-CAH registry for facilitating quality improvement

This study provided valuable insight into the determinants and variation of reported AI related adverse events amongst specialist centres, demonstrating that the I-CAH registry may be used as a tool for quality improvement.

The clinical benchmarks for quality of care, as reflected by SDE and AC, were incorporated into an individualised report for each centre that participated in this study and issued to each centre (Figure 6-8).

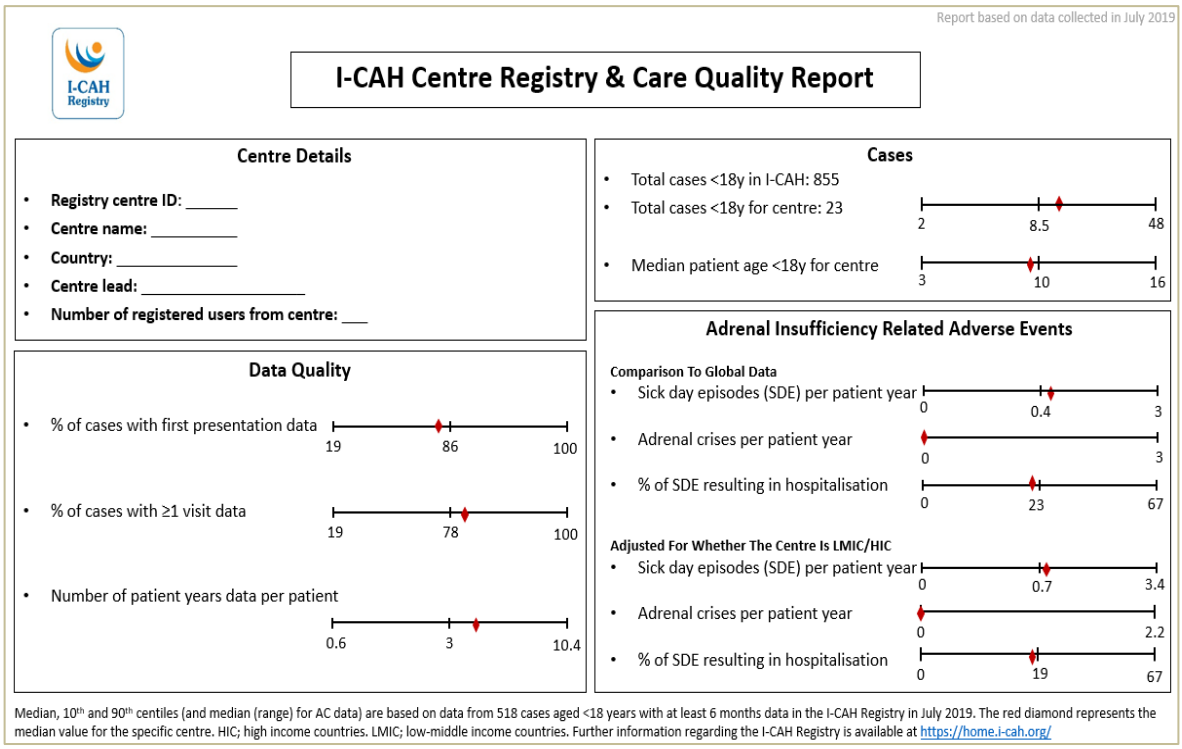


Figure 6-8. The I-CAH registry care quality report.

In addition, an online survey was circulated to the 32 I-CAH centre leads from participating centres in 18 countries to obtain feedback regarding the content and structure of the care quality reports. Of the 32 centres, 27 (84%) centres responded to the feedback survey. Overall, 22 (81%) respondents agreed that the I-CAH care quality report would lead to an improvement in their centre's record of entering data into the I-CAH registry; 19 (70%) agreed that the report would help to improve the care of children with CAH at their centre and 26 (96%) agreed that the report was useful to determine how their centre compares to other centres with regards to entering data into the registry. Moreover, 21 (70%) agreed that the report was useful to determine how their centre compares to

other centres in looking after children with CAH and 19 (70%) stated that the amount of information in the report was satisfactory.

Further work is required to determine whether the exercise of producing regular care quality reports for centres is associated with an improvement in these clinical benchmarks.

6.7 Discussion

6.7.1 Key findings

This study reports the findings of the largest, multicentre, international cohort study to date evaluating the epidemiology of acute AI related adverse events in children with 21-hydroxylase deficiency CAH. Whilst the majority of previous studies have investigated only adrenal crises, this is the first study to obtain a more complete perspective on adverse events by evaluating sick day episodes, adrenal crises and hospitalisation in a global cohort of children.

Interestingly, the incidence rate of AC of 2.7 to 3.9 per 100 patient-years is at the lower end of the range that has been reported in previous studies (Odenwald, Nennstiel-Ratzel et al. 2016, Rushworth, Falhammar et al. 2016, El-Maouche, Hargreaves et al. 2018, Ishii, Adachi et al. 2018, Notter, Jenni et al. 2018). This is perhaps a reflection of improvements in parent and patient education and increased awareness of AC amongst families and clinicians. It is also useful to note that overall, less than 5% of SDE were associated with an AC. Whilst it is possible that the management of SDE prevented an AC in these cases, confirmation of a causal link will require further study. Notably, all AC events occurred in children with the salt wasting phenotype and there were no fatalities. As regular data reporting is sustained over the longer-term by participating centres, there is also a need to look at temporal trends in future studies.

The SDE incidence rate of 67 per 100 patient-years also deserves further exploration. Whilst controversy remains about the definition of a SDE as well as its appropriate management (Riepe, Krone et al. 2002, Niranjan and Natarajan 2015, Chrisp, Maguire et al. 2018), a change in the patient's usual medical management, including an increase in oral GC, the administration of HC injection, hospitalisation or documentation of a predisposing factor was noted in 94% of SDE in this study. SDE incident rates have not been reported previously, thus, it is unclear whether the reported SDE rate is particularly high or low. Patients and parents, themselves, may have a different definition of a SDE compared to their clinician and this could be explored in the future by

comparing patient/parent reporting to clinician reporting, with the inclusion of more objective criteria for SDE (White and Arlt 2010).

Our data showed wide variation in the median number of SDEs occurring per patient year amongst centres. More than half of patients with SDEs were self-managed at home but the majority of those who had an AC were hospitalised. A number of those who were hospitalised did not have an AC reported, thus raising the issue about the overlapping definitions of SDE and ACs. In the absence of a clearer distinction between an AC and a SDE, it is possible that hospitalisation may be a better definition of a significant adverse event related to AI. It is of course possible that different centres may have a different threshold for 'hospitalising' a patient with an AI related adverse event. This may depend on healthcare delivery models, healthcare utilisation costs, patient education, as well as the perceived competence of the patient in self managing their condition (Rushworth, Falhammar et al. 2016, Burger-Stritt, Kardonski et al. 2018, Jenkins-Jones, Parviainen et al. 2018). Interestingly, patients from HIC countries had a higher median SDE per patient year compared to those from LMIC countries. One may expect that patients from LMIC and more deprived communities would have greater SDEs and ACs due to issues such as reduced access to hospital care and medication. The higher prevalence of SDEs in children from high-income countries could be attributed to greater vigilance and reporting of minor illnesses amongst parents and clinicians along with greater access to healthcare services and these results warrant further exploration.

The dose of 10–15 mg/m^2/day used in children with CAH is greater than that generally recommended for other forms of AI (Bornstein, Allolio et al. 2016). We reported that children were receiving maintenance GC within the recommended range in almost half of clinic visits, with FC doses within recommended dose ranges in 90% of visits. We also observed that the likelihood of SDEs was lowest in those who were on high doses of GC; it would be important for future studies to compare the health economic cost of the morbidity associated with high GC doses against that of AI related adverse events. Furthermore, the majority of patients in this study were very young children with a median age of 2 years at the time of clinic visits. It is recognised that children with CAH may have

differing requirements for GC throughout childhood (Hindmarsh 2009), thus further studies in larger cohorts of children of all ages are required.

A greater likelihood of SDE and sick day dosing was observed in boys compared with girls. This is contrary to the findings of others where these events were more likely to occur in girls (Rushworth, Chrisp et al. 2017, El-Maouche, Hargreaves et al. 2018). Whilst it is clear that newborn boys with CAH are more likely to present with a salt wasting crisis when the diagnosis is delayed, it is unclear why boys, or for that matter, girls on maintenance therapy would have a higher incidence of AI related adverse events. The majority of studies in adult populations have not revealed a gender difference although one study reported a higher incidence of adverse events in women with secondary AI (Hahner, Loeffler et al. 2010) and another reported a greater incidence in men with concomitant hypogonadism (Omori, Nomura et al. 2003).

Interestingly, children with a salt-wasting phenotype comprised 89% of cases of 21-hydroxylase deficiency in our cohort. This is higher than that previously reported in the literature (White and Speiser 2000) and may be attributed to the complex mix of cases being entered by international clinicians. In countries without newborn screening, such as the UK, affected boys may be missed or diagnosed with simple-virilising CAH much later when signs of androgen excess develop, which may perhaps lead to delayed entry into disease specific registries.

The current study also showed that younger (1 to 4 years) and older (15 to 18 years) age groups had the greatest risk of SDE. A higher rate of illness episodes in childhood and lower rates of administration of HC injection amongst very young children have been previously reported as reasons for this observation (Chrisp, Maguire et al. 2018, El-Maouche, Hargreaves et al. 2018), with young age also consistently recognised as a risk factor for AC (Eyal, Levin et al. 2019). These findings may reflect parental uncertainty or inexperience with regards to management of illness episodes in children (Fleming, Knafl et al. 2017, Simpson, Ross et al. 2018). A higher rate of SDE in adolescents may be attributed to the period of transition from paediatric to adult services, greater patient autonomy and reduced adherence to therapy (Gleeson, Davis et al. 2013, Merke and Poppas 2013).

Infectious illnesses were the commonest event associated with SDE and AC, reported in over two-thirds of all SDE and almost half of all cases of AC, consistent with previous literature (Reisch, Willige et al. 2012, Rushworth, Falhammar et al. 2016, Chrisp, Maguire et al. 2018, El-Maouche, Hargreaves et al. 2018, Ishii, Adachi et al. 2018).

6.7.2 Strengths

The structured manner of real-world data collection within the I-CAH registry, the large cohort and its potential to represent global practice with the availability of adverse events data for more than half of registered patients under the age of 18 years were clear strengths of this study. Although, the investigators did not have recourse to source data from the I-CAH registry, the data that have been collected have previously been reported to have a high degree of validity, consistency and accuracy (Kourime, Bryce et al. 2017).

6.7.3 Limitations

It is possible that this study may experience clinician and patient retrospective recall bias with subjective reporting and a potential for under- or over-reporting of SDE and AC. There may have also been a degree of selection bias, as not every patient at a centre had been included in the I-CAH registry and amongst those who had been included in this registry, a variable number of cases had a sufficient amount of data to be included in the study.

The lack of a universal definition for SDE and AC can be considered a limitation. The definitions used herein were based on self-reported physician diagnosis and clinical judgement of the reporting clinician of these events. A combination of the variable criteria for defining these events as well as a variable threshold for reporting these adverse events may be an explanation for the observed differences.

Interestingly, there was no difference in the number of AC events between patients from high-income and low-middle income countries, suggesting an equally effective level of illness management and AC prevention. Due to the small number of AC events overall, further studies in a larger cohort are

required to investigate factors that may influence differences in the prevalence of AC as well as SDE. A better definition of SDE may be any episode that requires an increase in GC replacement above the routine replacement dose, as per local sick day rules and to avoid an AC. However, there is a need for further research to achieve a more effective definition of SDE that provides real clinical significance. Furthermore, an online system for collecting patient reported accounts of SDE and their management may also prove useful in understanding the variation between centres. The study did not attempt to assess clinical variables such as the biochemical adequacy of steroid replacement in this cohort of children (Smans, Van der Valk et al. 2016, Iwasaku, Tanaka et al. 2019).

In this study, the precipitating event in AC was unknown in half of all cases. In addition, there was no information regarding the specific aetiology of infectious illness in children having SDE and AC. Recently, studies have shown that patients with primary AI including CAH may have a greater predisposition to infections, particularly lower respiratory tract and gastrointestinal infections (Tresoldi, Sumilo et al. 2020) and these associations require further investigation.

6.7.4 Summary

The real-world data that are collected within the I-CAH registry show wide variability in the reported occurrence of SDE and AC between centres. These data can be used to identify clinical benchmarks for CAH care, providing a framework that can be used for studying the effect of targeted interventions that are aimed at improving the care of children with CAH. The real-world data within the I-CAH registry are also a valuable resource for identifying factors that place a child with CAH at a higher risk of acute adverse events and may be used in prediction models for calculating individual risk. This study also highlights the need for further research to improve and standardise the definition and management of sick day episodes and adrenal crises.

CHAPTER 7

Management of acute adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia- An international survey of specialist centres

The findings of this chapter have been published by **Ali SR**, Bryce J, Krone NP, Claahsen-van der Grinten HL, Ahmed SF. Current management of acute adrenal insufficiency related adverse events in children- results of an international survey of specialist centres. *Horm Res Paediatr*. 2022;95:363-373.

7 Management of acute adrenal insufficiency events in children with congenital adrenal hyperplasia- An international survey of specialist centres

7.1 Abstract

Background: There is wide variation in the reported rate of acute adrenal insufficiency (AI) related adverse events (sick day episodes and adrenal crises) between centres in children with congenital adrenal hyperplasia (CAH).

Objective: To evaluate the level of consensus on the criteria that should be considered 'essential' for defining and managing adverse events associated with acute AI in children.

Methods: Active users of the I-CAH/I-DSD registries (n=66), non-active users of the I-CAH/I-DSD registries (n=35) and users of the EuRRECa e-reporting registry (n=10) were approached to complete an online survey.

Results: Fifty-six centres from 27 countries responded to the survey; the response rates for the three groups of registry users were 42 (65%), 11 (31%) and 3 (30%), respectively. Steroid management plans, one to one patient education and contact details of health care staff were provided by over 90% of centres in high income countries. All 56 centres advised glucocorticoid sick day dosing in the event of fever. Less common indications for sick day dosing included vaccination and mild afebrile intercurrent illness, recommended by 17 (30%) and 9 (16%) centres, respectively. The most frequently reported sick day dosing regimens were tripling the total daily dose of hydrocortisone and administering 3 times daily and doubling or tripling the largest daily hydrocortisone dose depending on the nature of the trigger and administering 3 times daily, recommended by 24 (43%) and 21 (38%) centres, respectively. Vomiting was the most common indication for intramuscular hydrocortisone injection, reported by 34 (61%) centres. Over 50% of respondents indicated that essential clinical criteria for adrenal crisis should include fatigue, nausea or vomiting, hypotension, hyponatraemia, hyperkalaemia and clinical improvement following parenteral glucocorticoids. In the event of an adrenal crisis, 47 (84%) reported

that the majority of patients were admitted to hospital. For the management of an adrenal crisis, a bolus parenteral injection of hydrocortisone was the most frequently administered medication, reported by 50 (89%) centres.

Conclusion: Although there is variation in the definition and management of AI related adverse events in children amongst centres, there is also a good level of consensus on specific aspects including the definition of adrenal crisis that can lead to greater benchmarking of care.

7.2 Introduction

Adrenal insufficiency (AI) is a potentially life-threatening condition. It can be caused by the destruction of adrenocortical cells by inborn alterations of steroidogenesis (primary AI) or by impairment of pituitary or hypothalamic stimulation of the adrenal cortex (secondary AI) (Bancos, Hahner et al. 2015). Impairment of adrenal function leads to insufficient production of glucocorticoids, and in the case of primary AI also insufficient production of mineralocorticoids. In children, congenital adrenal hyperplasia (CAH), an autosomal recessive condition with an incidence of around 1 in 15,000, is the commonest cause of primary AI (Capalbo, Moracas et al. 2021, Claahsen-van der Grinten, Speiser et al. 2022). The most common form of CAH occurs due to 21-hydroxylase deficiency (21-OHD), resulting in a variable level of glucocorticoid and mineralocorticoid deficiency (Krone, Dhir et al. 2007) and a life-long risk of acute AI related adverse events (Shulman, Palmert et al. 2007, Falhammar, Frisén et al. 2014). Adrenal crisis (AC) is a life-threatening complication in patients with AI and a leading cause of death (Falhammar, Frisén et al. 2014). AC occurs when the physiological requirement for cortisol is greater than the amount present in the circulation, for example, during periods of stress or infection when higher concentrations of cortisol are necessary (Rushworth, Torpy et al. 2019, Husebye, Pearce et al. 2021). Cortisol dose escalation, also known as ‘sick day dosing’ or ‘stress dosing’ is the cornerstone of AC prevention (Arlt and Society for Endocrinology Clinical 2016). The reported incidence of AC is very variable with rates of 3.9 to 10.9 per 100 patient years described in children with CAH (Odenwald, Nennstiel-Ratzel et al. 2016, Rushworth, Falhammar et al. 2016, El-Maouche, Hargreaves et al. 2018, Ishii, Adachi et al. 2018, Ali, Bryce et al. 2021). Recent studies have offered insight into the epidemiology of adrenal crises and their prodrome, sick day episodes (SDE), showing wide variation in reports of acute AI related adverse events between centres (Ali, Bryce et al. 2021).

Despite over 50 years of experience with glucocorticoid therapy in CAH, the prevention and management of AC in children remains challenging due to the rarity of the condition, varying presentations and a lack of consensus and evidence-based recommendations. This has resulted in the adoption of pragmatic definitions of AC (Allolio 2015, Arlt and Society for Endocrinology

Clinical 2016, Rushworth, Torpy et al. 2019, Husebye, Pearce et al. 2021, Nowotny, Ahmed et al. 2021), however, there remains a need to improve our understanding of the current definitions and management of acute AI related adverse events. A greater standardisation of the definition of these events as well as their prevention and management would facilitate benchmarking and improvement in patient care.

7.3 Aims

The aim of this study was to survey international endocrinologists delivering specialist care to children with CAH to:

- Investigate current definitions and clinical approaches in the management of SDE and AC

- Evaluate the level of consensus on the criteria that should be considered essential for defining and managing adverse events (SDE and AC) associated with acute AI in children

7.4 Methods

7.4.1 Ethics approval and consent

The survey was approved by the Data Access Committees of the I-CAH/I-DSD and EuRRECa Registries. Ethics approval was not required, as per the UK's Policy Framework for Health and Social Care Research (2021), as this study was performed as a health service evaluation and did not require any information on patients or human participants. Participant consent was inferred from survey completion.

7.4.2 Participants

A total of 111 centres encountering patients aged less than 18 years old were identified through the International congenital adrenal hyperplasia (I-CAH)/ International disorders of sex development (I-DSD) registries and the e-Reporting platform for rare endocrine conditions (e-REC) within the European Registries for Rare Endocrine Conditions (EuRRECa) project and invited to participate in an international survey.

7.4.3 International survey

The survey was prepared by the project group consisting of three paediatric endocrinologists from UK centres and the Netherlands, a paediatric clinical research fellow and the I-CAH/I-DSD registries project manager. The survey was

performed in English using Webropol (https://webropol.com/), a secure online platform that is endorsed and supported by NHS Greater Glasgow & Clyde and NHS Scotland. All information within Webropol is kept in compliance with the UK Data Protection Act (2018) and General Data Protection Regulation (GDPR 2016/679). All centres were invited to complete the survey in the last quarter of 2020.

7.4.4 Data collection

The survey contained 11 questions divided into two main sections (Table 7-1). The first section of the survey sought to ascertain events requiring an increase in glucocorticoid dosing (sick day/stress dosing), sick day dose options for moderate/severe/all stress, the use of different methods of parenteral hydrocortisone for sick day events and the duration of sick day dosing. The second section focused on AC including the essential or desirable criteria for defining an AC, clinical, physical and laboratory parameters routinely recorded in patients, the management setting of patients (community or hospital) and medication administered in a hospital setting. Respondents were asked to complete their responses for each question using pre-set answer categories with multiple-choice or single option responses, with some questions allowing for a 'Not applicable' option, or 'Other' option to be selected to enable a short individual response. Additional questions enquired regarding the availability and provision of resources to patients (e.g. a written steroid management plan), other issues that respondents felt to be important in relation to AI related adverse events and whether centres would be interested in joining a working group that informs the development of a consensus on the definition and management of AI related adverse events in children.

Table 7-1. Acute adrenal insufficiency related adverse events survey items (abbreviated version).
[a]Mandatory field. AI, adrenal insufficiency; GC, glucocorticoid; HC, hydrocortisone; IM, intramuscular; IV, intravenous; SC, subcutaneous.

Question	Responses available	Response type
Respondent details[a]		
Contact details	Clinician name Email Institution	Free text
Are patients within your centres provided with any of the following	Written steroid replacement and management plan Medic-Alert bracelet Steroid-aware emergency cards App with details on how to manage adrenal crisis One to one patient/parent education (specify how often) Patient/family information and support events (specify how often) Website for your service Contact details of a nurse or doctor	Select all responses that apply
Sick day episodes		
Are patients advised to increase GC ('sick day dosing') if any of the following events occur	Mild intercurrent illness, afebrile Fever (please specify temperature threshold) Severe infection, e.g. pneumonia Major emotional or mental stress, e.g. death of relative School examination Exhaustive strenuous exercise Vaccinations Minor surgery, including hospital dental procedures Major surgery Dental procedures in community Other, please specify	Select all responses that apply
The sick day dose will be	Largest daily HC dose doubled and given 3 times daily Largest daily HC dose tripled and given 3 times daily Largest daily HC dose may be doubled or tripled and given 3 times daily Total daily dose tripled and given 3 times daily Total daily dose tripled and given 4 times daily Total daily dose as 30 mg/m^2/day given 4 times daily Other, please specify	For each response available, select one option from: Moderate stress, Severe stress, All stress, Not applicable
Do you advise parenteral HC if any of the following events occur	Vomiting Diarrhoea Minor surgery including dental procedures in hospital Major surgery Dental procedures in community Other, please specify	For each response available, select all that apply from: SC injection, IM injection, IV injection, IV infusion
How long are patients advised to continue on an increased GC dose ('sick day dose') prior to returning to a normal dose after the end of the following events	Mild intercurrent illness, afebrile Fever Severe infection, e.g. pneumonia Major emotional or mental stress, e.g. death of relative School examination Exhaustive strenuous exercise Vaccinations Minor surgery, including hospital dental procedures Major surgery Dental procedures in community Other, please specify	For each response available, select one option from: At the time of event only, for 24 hours, for 48 hours, for >48 hours, not applicable
Adrenal Crises		
In your opinion, the essential or desirable criteria for an	A. Clinical symptoms Abdominal pain Back and leg cramps Confusion	For each response available, select one option from

'adrenal crisis' should include the following	Reduced conscious level Fatigue Nausea, vomiting B. Physical examination Fever Low blood pressure Skin pigmentation Weight loss C. Lab findings Hyponatraemia Hyperkalaemia Hypoglycaemia Normochromic anaemia Elevated serum creatinine D. Other Clinical improvement following parenteral GC Other, please specify:	a choice of: Essential, desirable, not applicable
What measures are routinely checked and recorded on history, examination and investigations in a child with an 'adrenal crisis' who presents to your centre	A. Clinical symptoms Abdominal pain Back and leg cramps Confusion Reduced conscious level Fatigue Nausea, vomiting B. Physical examination Temperature Blood pressure Skin pigmentation Weight Capillary refill time Hydration status C. Lab findings Hyponatraemia Hyperkalaemia Hypoglycaemia Normochromic anaemia Elevated serum creatinine D. Other Clinical improvement following parenteral GC administration Other, please specify:	For each response available, select one option from: Always, sometimes, never
In the event of an adrenal crisis, are the majority of your patients	Managed at home and do not attend hospital Attend emergency room only Attend hospital and stay for: less than 1 day, less than less than 2 days, less than 3 days or more than 3 days	Select one response
For management of adrenal crisis in the hospital, what medication are patients likely to receive at your centre	Bolus injection (IV or IM) of HC Continuous infusion of HC IV isotonic saline solution Antihypoglycaemic drugs e.g. glucagon Glucose infusion Prednisolone Sodium supplementation Other, please specify:	For each response available, select one option from: Always, sometimes, never
Are there any other issues related to acute AI related adverse events (sick day episodes and adrenal crisis) that you would like to comment on?		Free text
We would like to form a working group that informs the development of a consensus on the definition and management of AI related adverse events in children. Are you interested in joining this group and receiving further information?		Select one response: Yes, No

7.4.5 Statistical analysis

Categorical data were analysed using descriptive statistics. For the assessment of geographical differences in the availability and provision of resources (e.g. written steroid management plans, emergency cards and bracelets, one to one education, contact details for a doctor/nurse, support events and mobile phone applications (Apps) for managing adrenal crisis), participating countries were categorised as those from a low or middle income country (LMIC) or from a high income country (HIC) as defined by the 2019 World Bank classification (http://datahelpdesk.worldbank.org). The Fisher Exact Test was performed to compare proportions in different groups. Results are reported as frequencies and percentages and median (with ranges) values. Numerical data were collated and analysed using Minitab version 18 statistical software (Minitab LLC, State College, PA, USA).

7.5 Results

7.5.1 Survey response

Of the 111 clinicians invited to participate in the survey, 101 were identified as centre leads from the I-CAH/I-DSD Registries; 66 of these 101 centre leads were actively using the registries for entering cases and 35 had not entered any cases but were registered as clinical users of the registries. Of the 66 active centres that were sent the survey, 42 (65%) responded and of the 35 inactive centres, 11 (31%) responded to the survey. Of the 10 e-REC users who were sent the survey, 3 (30%) responded (Figure 7-1). In total, 56 (50%) centres from 27 countries within Europe (n=16, 59%), Asia (n=7, 26%), South America (n=2, 7%) and Africa (n=2, 7%) responded to the survey, with 38 and 18 centres from HIC and LMIC countries, respectively (Table 7-1).

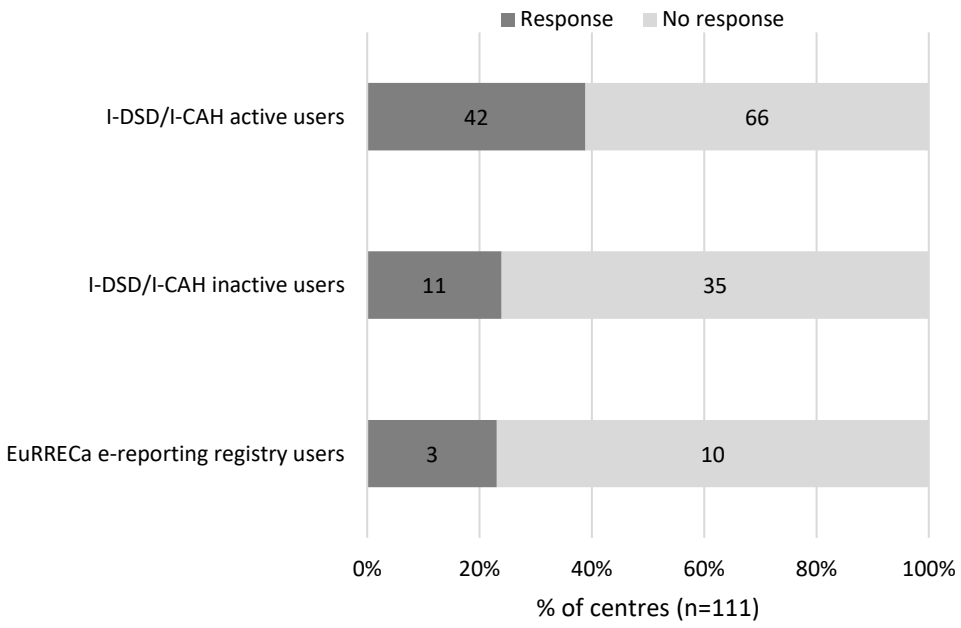


Figure 7-1. Survey response rate.
I-DSD, International disorders of sex development registry; I-CAH; International disorders of congenital adrenal hyperplasia registry; EuRRECa, European registries for rare endocrine conditions.

Table 7-2. Regional distribution of survey respondents.
[a]The survey was distributed to the clinician registered as the centre lead from each specialist centre.

Region (n, %)	Country	Specialist Centres[a], n
Europe	UK	8
(n= 16, 59%)	Italy	6
	Switzerland	5
	Netherlands	4
	Germany	3
	Romania	2
	Poland	2
	Belgium	1
	Ukraine	1
	Serbia	1
	Greece	1
	Spain	1
	Sweden	1
	Denmark	1
	Lithuania	1
	Bulgaria	1
South America	Brazil	2
(n=2, 7%)	Argentina	1
Africa	Egypt	2
(n=2, 7%)	Morocco	1
Asia	Turkey	4
(n=7, 26%)	Sri Lanka	2
	Hong Kong	1
	Thailand	1
	India	1
	Armenia	1
	Israel	1
Total	27	56

7.5.2 Resources

Of the 56 centres that responded to the survey, 54 (96%) reported that patients within their centre were provided with a written steroid management plan. Steroid emergency cards and medic-alert bracelets were provided by 33 (59%) and 12 (21%) centres, respectively, with 49 (88%) reporting that contact details of a nurse or doctor were provided to patients. One to one patient/parent education was provided by 51 (91%) centres, at a median interval of 6 months (range 3, 12). Of the 56, 18 (32%) documented that there was provision of patient/family information and support events at their centre, at a median of 1 yearly intervals (range 0.5, 2). A website for patients and an App with details on how to manage adrenal crisis were reported to be available by 10 (18%) and 5 (9%) centres, respectively. There was a difference in resource provision between

centres from HIC and LMIC, with a greater number of centres from HIC reporting routine provision of steroid emergency cards (71% vs 33%, p=0.01), contact details of a health professional (95% vs 72%, p=0.03) and access to family information events (45% vs 6%, p=0.01) (Figure 7-2). Less than 75% of centres in HIC reported the routine use of steroid emergency cards, the provision of information and support events for families, medic-alert bracelets, a website or a mobile app (Figure 7-2).

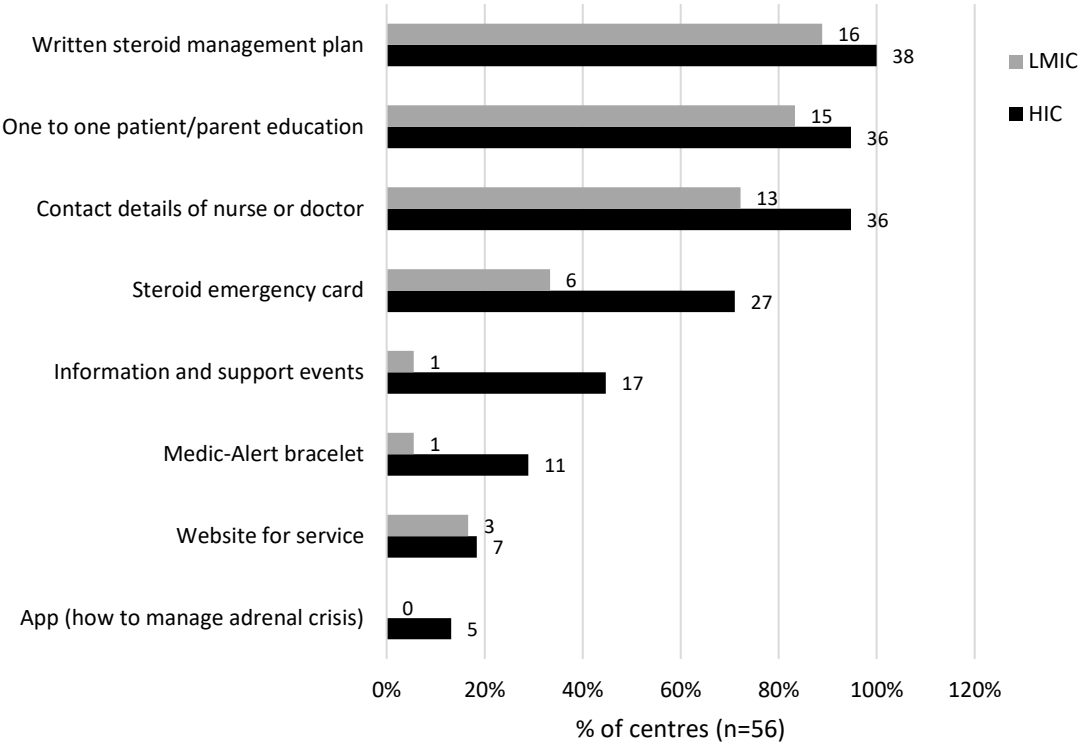


Figure 7-2. Resource provision in HIC and LMIC.
The numbers next to each bar represent the number of centres that reported routine use of the resource at their centre (n). HIC, high income countries; LMIC, low-middle income countries.

7.5.3 Events requiring glucocorticoid sick day dosing

All 56 (100%) centres advised an increase in glucocorticoid dosing in the event of fever. Of 22 (39%) centres that specified a temperature threshold, this was defined as 38.5, 38 and 37.8 degrees Celsius by 17 (77%), 4 (18%) and 1 (5%) centres, respectively. Of the 56, 55 (98%), 53 (95%) and 45 (80%) centres advised glucocorticoid sick day dosing in the event of severe infection (e.g. pneumonia), major surgery and minor surgery (e.g. dental procedures in hospital), respectively. Less common indications necessitating sick day doses of glucocorticoids were dental procedures taking place in the community, major

emotional or mental stress (e.g. death of a relative), exhaustive strenuous exercise, vaccinations, mild afebrile intercurrent illness and school examinations, recommended by 23 (41%), 22 (39%), 20 (35%), 17 (30%), 9 (16%) and 3 (5%) centres, respectively. Other specific indications for sick day dosing reported by centres included gastrointestinal illness (vomiting and diarrhoea) and major trauma (Figure 7-3).

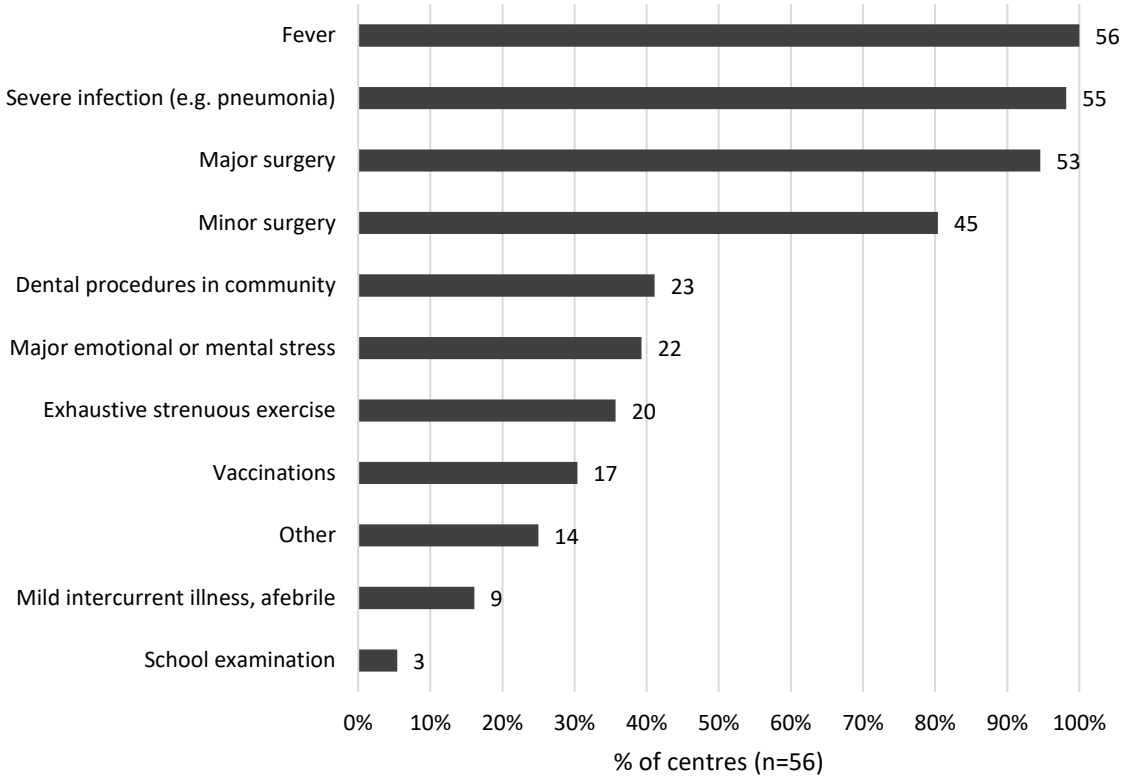


Figure 7-3. Indications for glucocorticoid sick day dosing.
The numbers next to each bar represent the number of centres (n).

7.5.4 Sick dosing regimens

The most frequently reported glucocorticoid sick day dosing regimen for any type of stress (moderate/severe/all stress) was tripling the total daily dose and administering 3 times daily and doubling or tripling the largest daily hydrocortisone dose depending on the nature of the trigger and administering 3 times daily, recommended by 24 (43%) and 21 (38%) centres, respectively (Figure 7-4). A total daily dose of 30mg/m^2/day 4 times daily and tripling the total daily dose and administering 4 times daily were indicated by 13 (23%) and 11 (20%) centres, respectively. Other dosing regimens reported by 16 (29%) centres included doubling the total daily dose and administering 3 times daily, doubling

the largest daily dose and giving 3 times daily and 50 to 75 mg/m^2/day administered 3 or 4 times daily (Figure 7-4).

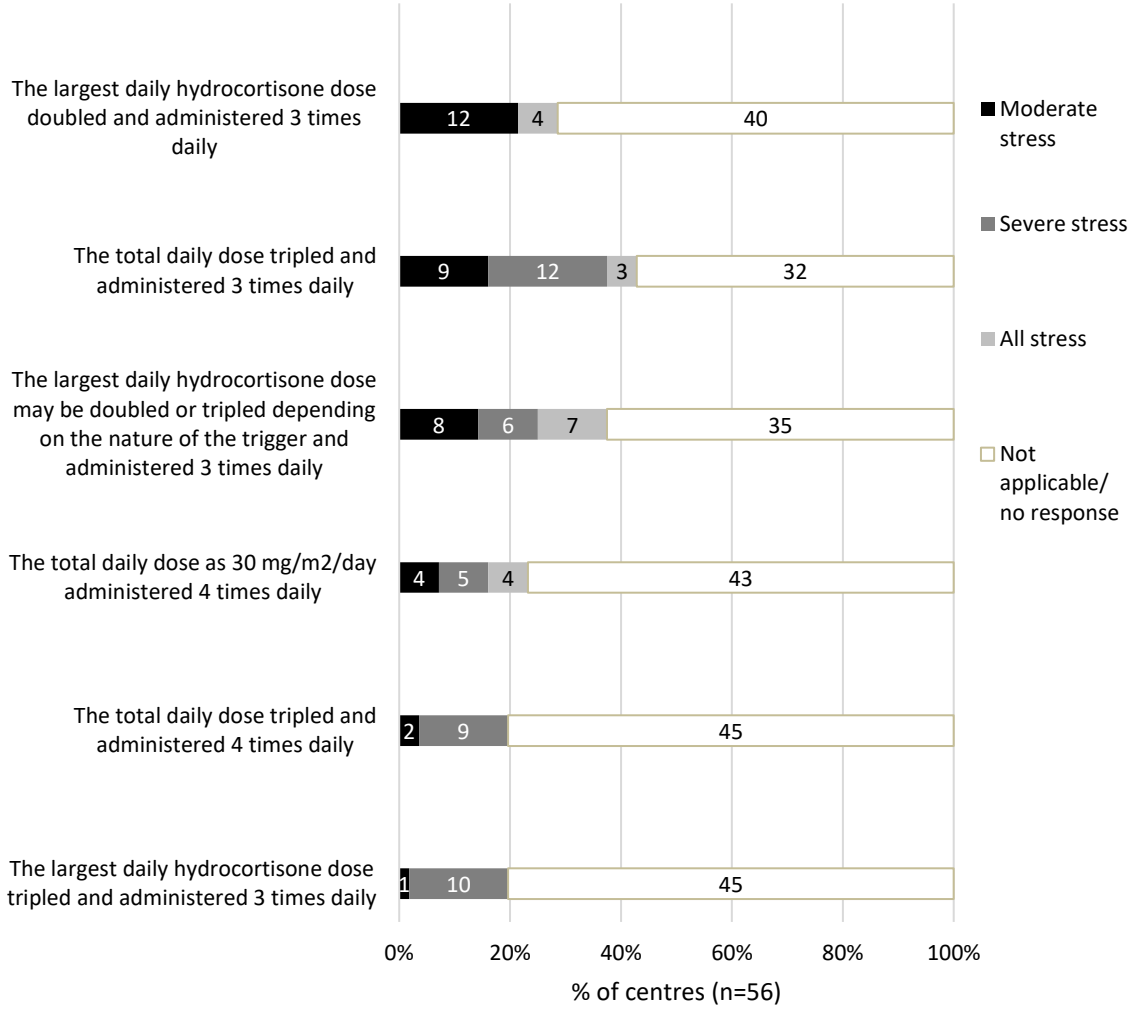


Figure 7-4. Centre preference for dose of sick day dosing according to the severity of the stress.
The numbers within each bar represent the number of centres (n).

7.5.5 Duration of sick day dosing

For events such as exhaustive strenuous exercise, dental procedures in the community, mild intercurrent illness and major emotional stress, 28 (50%), 16 (29%), 14 (25%) and 13 (23%) centres recommended sick day dosing at the time of the event only (Figure 7-5). For fever and minor surgery, 23 (41%) and 19 (34%) centres, recommended sick day dosing at time of the event only. For severe infections (e.g. pneumonia) and major surgery, sick day dosing was advised by 20 (36%) and 29 (52%) centres for ≥48 hours, respectively.

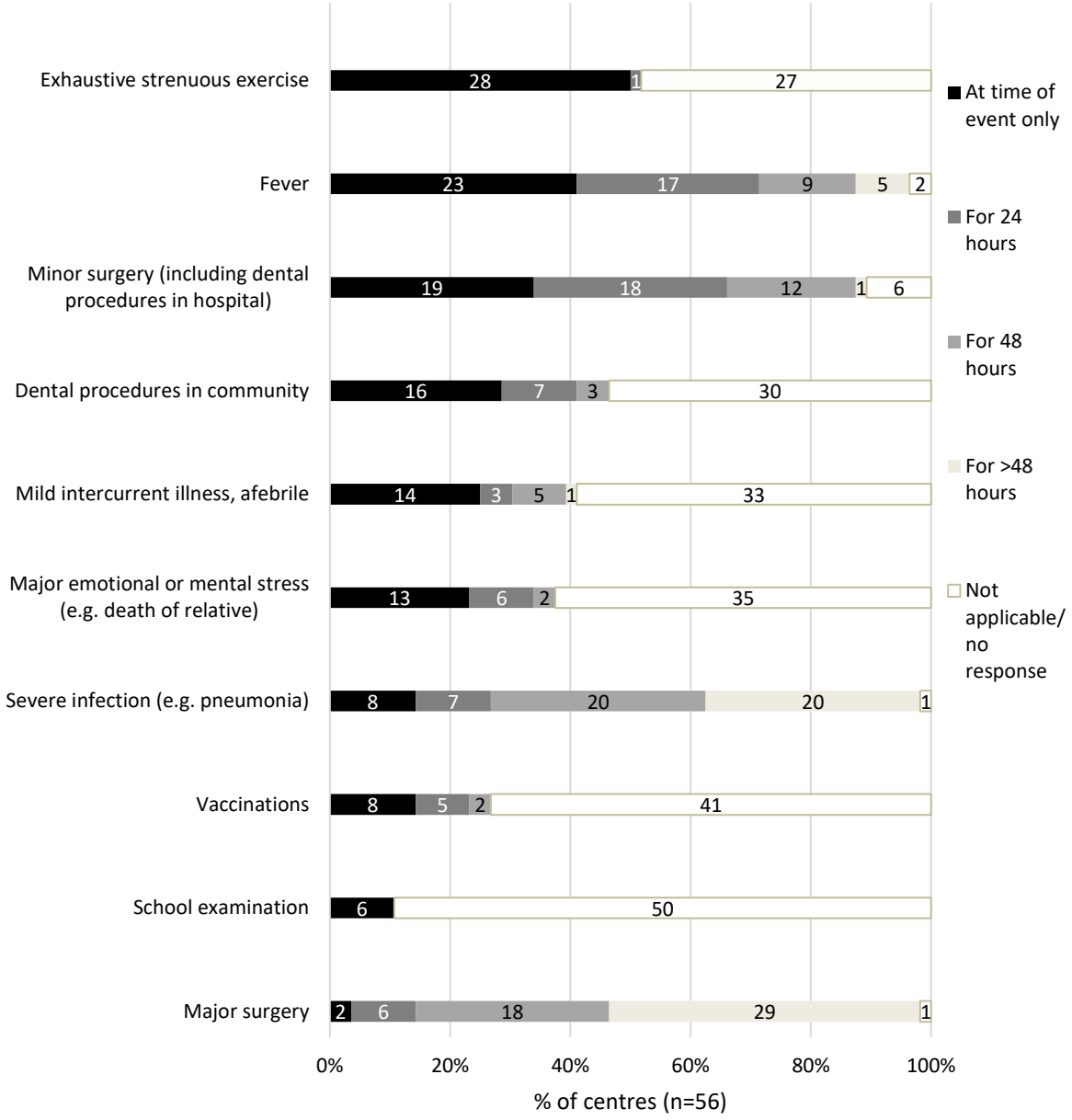


Figure 7-5 Centre preference for duration of sick day dosing in the event of stress events. The numbers within each bar represent the number of centres (n).

7.5.6 Parenteral hydrocortisone during stress events

In the event of vomiting or diarrhoea, 34 (61%) and 25 (45%) centres recommended intramuscular (IM) hydrocortisone injection, respectively; intravenous (IV) hydrocortisone injection was recommended by 22 (39%) and 14 (25%) centres and subcutaneous (SC) hydrocortisone injection by 8 (14%) and 5 (9%) centres for these conditions, respectively. For minor surgery, 13 (23%) and 15 (27%) advised IM and IV hydrocortisone injection, respectively. IV hydrocortisone injection and IV hydrocortisone infusion for major surgery were recommended by 28 (50%), with 9 (16%) recommending SC or IM hydrocortisone injections. Of the 56 centres, 28 (50%), 10 (18%) and 4 (7%) specified that

parenteral hydrocortisone was not applicable for dental procedures in the community, diarrhoea and vomiting, respectively (Figure 7-6).

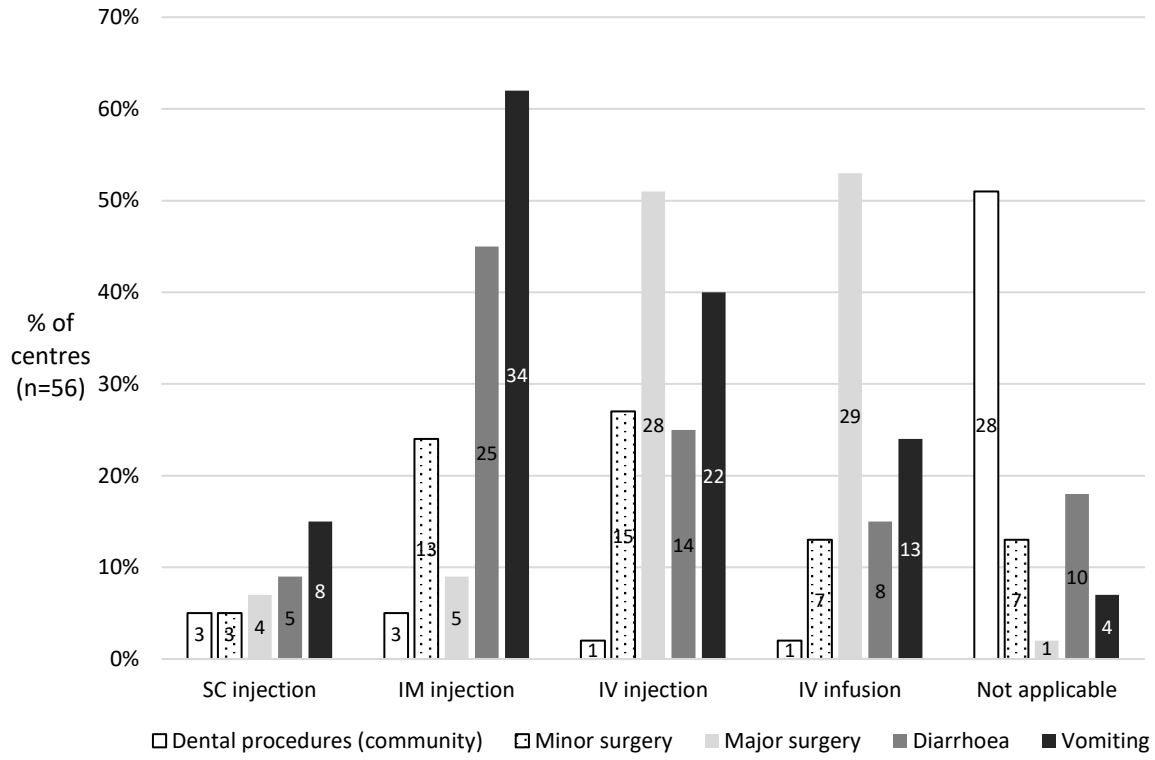


Figure 7-6. Indications for parenteral hydrocortisone and routes of administration.
The numbers within each bar represent the number of centres (n).

7.5.7 Criteria for defining adrenal crisis

Of the 56 centres, over half selected the following features as essential for defining an adrenal crisis: clinical improvement after glucocorticoid (n,37; 66%), hyponatraemia (n,37; 66%), low blood pressure (n,36; 64%), hyperkalaemia (n,34; 61%), fatigue (n,32; 57%) and nausea or vomiting (n,30; 54%) (Table 7-2). Desirable criteria included hypoglycaemia (n,28; 50%) and abdominal pain (n,27; 48%). Of the 56 centres, one third or more centres reported that skin pigmentation (n,21; 38%), normochromic anaemia (n,31; 55%) and elevated serum creatinine (n,22; 39%) did not constitute essential or desirable features of an adrenal crisis. Other criteria specified by less than 5% of centres included metabolic acidosis, a history of autoimmune disease and glucocorticoid use.

Table 7-3. Levels of consensus for criteria used to define an adrenal crisis and parameters routinely checked in children presenting to hospital.
Criteria that were considered essential by more than 50% of respondents or reported to be assessed always by more than 50% of respondents are highlighted in bold.

	Criteria for adrenal crisis				**Parameters routinely checked in adrenal crisis**				**Criteria for adrenal crisis proposed in recent publications**				
	Essential, n (%)	Desirable, n (%)	Not Applicable, n (%)	No response, n (%)	Always, n (%)	Sometimes, n (%)	Never, n (%)	No response, n (%)	Allolio 2015	Arlt 2016	Rushworth 2019	Nowotony 2021	Husebye 2021
A. Clinical symptoms													
Fatigue	**32 (57%)**	21 (38%)	1 (2%)	2 (4%)	**48 (86%)**	6 (11%)	0 (0%)	2 (4%)	+	+	+	+	+
Nausea, vomiting	**30 (54%)**	24 (43%)	1 (2%)	1 (2%)	**51 (91%)**	3 (5%)	0 (0%)	2 (4%)	+	+	+	+	+
Reduced conscious level	22 (39%)	23 (41%)	4 (7%)	7 (13%)	**47 (84%)**	4 (7%)	2 (4%)	3 (5%)	-	+	+	-	+
Confusion	20 (36%)	22 (39%)	6 (11%)	8 (14%)	**43 (77%)**	8 (14%)	2 (4%)	3 (5%)	-	+	+	+	+
Abdominal pain	18 (32%)	27 (48%)	9 (16%)	2 (4%)	**39 (70%)**	12 (21%)	3 (5%)	2 (4%)	-	+	+	+	+
Back and leg cramps	6 (11%)	21 (38%)	19 (34%)	10 (18%)	20 (36%)	19 (34%)	11 (20%)	6 (11%)	-	+	+	-	+
B. Physical examination													
Blood pressure (low)	**36 (64%)**	17 (30%)	2 (4%)	1 (2%)	**51 (91%)**	3 (5%)	0 (0%)	2 (4%)	+	+	+	+	+
Weight loss	17 (30%)	19 (34%)	16 (19%)	4 (7%)	**51 (91%)**	3 (5%)	0 (0%)	2 (4%)	-	+	+	-	-
Skin pigmentation	14 (25%)	15 (27%)	21 (38%)	6 (11%)	**42 (75%)**	9 (16%)	3 (5%)	2 (4%)	-	+	+	+	-
Fever/ temperature	8 (14%)	23 (41%)	16 (29%)	9 (16%)	**48 (86%)**	5 (9%)	0 (0%)	3 (5%)	+	+	+	+	-
Hydration status	-	-	-	-	**49 (88%)**	4 (7%)	1 (2%)	2 (4%)	-	-	-	-	-
Capillary refill time	-	-	-	-	**44 (79%)**	6 (11%)	2 (4%)	4 (7%)	-	-	+	-	-
C. Lab findings													
Hyponatraemia	**37 (66%)**	18 (32%)	1 (2%)	0 (0%)	**52 (93%)**	2 (4%)	0 (0%)	2 (4%)	+	+	+	+	+
Hyperkalaemia	**34 (61%)**	20 (36%)	2 (4%)	0 (0%)	**52 (93%)**	2 (4%)	0 (0%)	2 (4%)	+	+	+	+	+
Hypoglycaemia	24 (43%)	28 (50%)	2 (4%)	2 (4%)	**50 (89%)**	3 (5%)	0 (0%)	3 (5%)	+	+	+	+	+
Elevated serum creatinine	5 (9%)	18 (32%)	22 (39%)	11 (20%)	**33 (59%)**	16 (29%)	2 (4%)	5 (9%)	-	+	-	+	+
Normochromic anaemia	2 (4%)	14 (25%)	31 (55%)	9 (16%)	23 (41%)	20 (36%)	7 (13%)	6 (11%)	-	+	-	+	-
D. Other													
Clinical improvement after parenteral glucocorticoid	**37 (66%)**	16 (29%)	0 (0%)	3 (5%)	**50 (89%)**	3 (5%)	0 (0%)	3 (5%)	+	-	+	-	-

7.5.8 Parameters checked in adrenal crisis

Around 90% of centres reported that they always routinely checked and recorded the following features on 1) history: nausea or vomiting (n,51; 91%), fatigue (n,48; 86%), reduced conscious level (n,47; 84%); 2) examination: blood pressure (n,51; 91%), weight (n,51; 91%), hydration status (n,49; 88%), temperature (n,48; 86%), assessment of clinical improvement following parenteral glucocorticoid administration (n,50; 89%); and 3) investigations: hyponatraemia (n,52; 93%), hyperkalaemia (n,52; 93%), hypoglycaemia (n,50; 89%), in a child with an adrenal crisis (Table 7-3). Other routine measures specified by centres included a history of prolonged jaundice and poor feeding in neonates, capillary blood gas analysis (pH, serum bicarbonate values) and medication history.

7.5.9 Medical management of adrenal crisis

In the event of an adrenal crisis, 51 (91%) centres stated that the majority of their patients attended hospital; of these, 4 (7%) stated that patients would attend the emergency room only. Of 56 centres, 5 (9%) managed patients with an adrenal crisis at home. A hospital stay of 1 to 3 days and more than 3 days was reported by 38 (68%) and 9 (16%) centres, respectively. For the management of adrenal crisis in a hospital setting, medications that were reported to be always administered by centres included a bolus IV or IM injection of hydrocortisone (n,50; 89%), continuous infusion of hydrocortisone (n,21; 38%), IV isotonic saline (n,47; 84%), glucose infusion (n,32; 57%) and sodium supplementation (n,12; 21%) (Figure 7-7). More than 60% of centres reported that patients in their centre would never receive prednisolone (n,35; 63%) and antihypoglycaemic drugs, e.g. glucagon (n,35; 63%) for an adrenal crisis. Other medications used by centres included fludrocortisone (n,2) and IV methylprednisolone (n,2) in LMIC countries where IV hydrocortisone was not widely available.

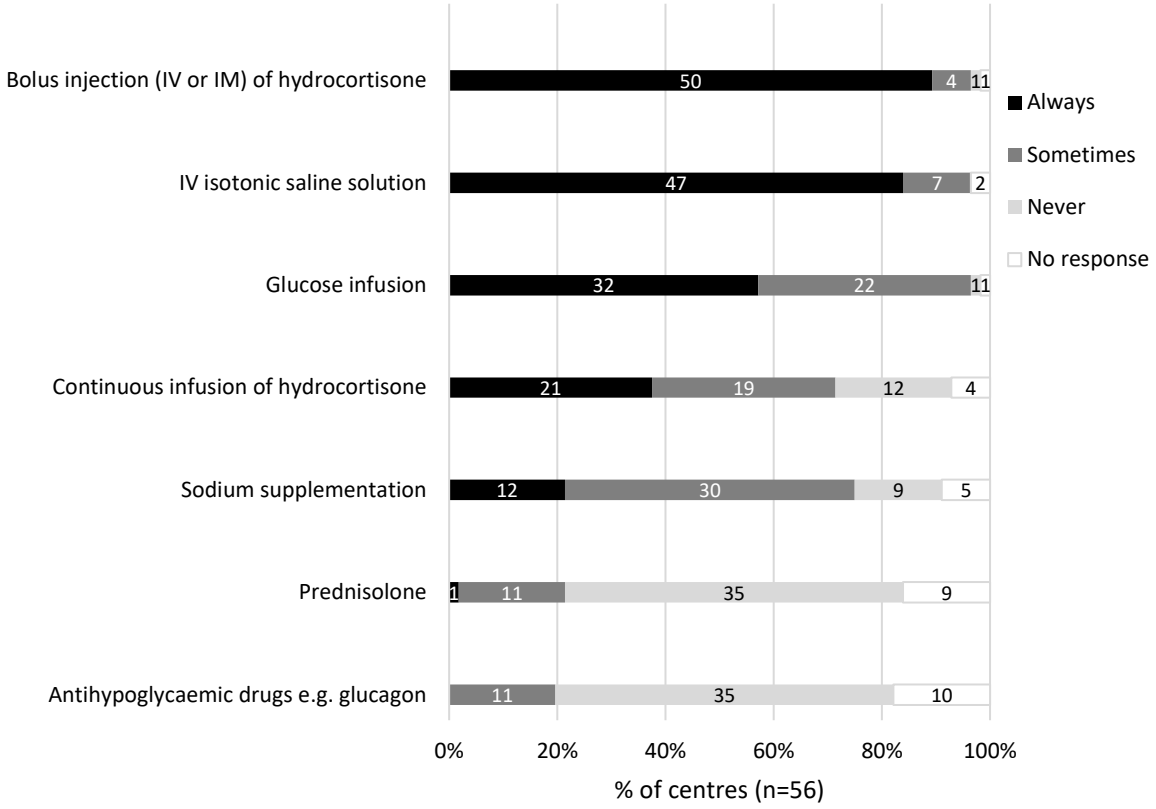


Figure 7-7. Centre preference for therapeutic regimens in the event of an adrenal crisis. The numbers within each bar represent the number of centres (n).

7.6 Discussion

7.6.1 Key findings

This large international survey of endocrinologists delivering specialist care for children with CAH involved clinicians from 56 centres in 27 countries from 4 continents. The survey evaluated the definitions and management of acute adrenal insufficiency related adverse events (sick day episodes and adrenal crises) in children, providing objective insight into the current practice and preferences of centres within an international network. Although the project targeted centres managing children with CAH, it is likely that the results of the survey also apply to the paediatric management of adrenal insufficiency, in general.

In almost all centres, it was routine practice to provide patients with a written steroid management plan and one to one parent/patient education. Despite increased availability of steroid emergency cards for children and adults across Europe (Nowotny, Ahmed et al. 2021), the current study reported that the provision of steroid emergency cards or alert bracelets to patients occurred less often. In addition, many centres did not provide access to electronically accessible information in the form of Apps or websites. Infrequent use and inadequate provision of such resources may be due to a lack of awareness of such tools amongst clinicians (Shepherd, Tahrani et al. 2017) or, due to a lack of financial support (Mofokeng, Beshyah et al. 2020), as also suggested by the findings of the current study. These information resources are considered to be important for families to increase their awareness of the appropriate management of sick day episodes and to reduce the risk of adrenal crisis (Burger-Stritt, Eff et al. 2020). Given that several of these resources were also not used in centres within HIC raises the possibility that there may be a need to gather further evidence to demonstrate the effectiveness of these resources in averting acute adrenal insufficiency.

Regarding the indications for glucocorticoid sick day dosing, all centres recommended sick day dosing in the event of fever. For surgery, the survey enquired separately for major and minor surgery. Generally, major surgery is defined as surgery requiring a general anaesthetic, usually lasting for over an

hour and where the child's oral intake is expected to be delayed. Minor surgery is defined as short procedures usually lasting less than an hour, after which the child is expected to eat and drink normally (Claahsen-van der Grinten, Speiser et al. 2022). For glucocorticoid sick day dosing in surgery, 95% and 80% of centres recommended sick day dosing for major and minor surgery, respectively. Considerable uncertainty still persists regarding the recommendation of sick day dosing for less commonly specified stress events including major emotional or mental stress, exhaustive strenuous exercise, vaccinations, school examinations and mild afebrile intercurrent illness, with less than 40% of centres recommending sick day dosing for these events. Previous studies have described no advantage of sick day dosing in patients with CAH undergoing short-term, high intensity exercise and this is in accordance with published guidelines (Weise, Drinkard et al. 2004, Speiser, Arlt et al. 2018). The decision to sick day dose in these scenarios may be based on individual patient's circumstances, for example, some patients may report higher levels of anxiety or distress during competitive sporting events or examinations.

Oral glucocorticoid sick day dosing aims to mimic the physiological stress response to illness. Although hydrocortisone doses used in emergency situations may be high and result in higher peak cortisol concentrations, the half-life of cortisol of around 90 minutes leads to rapid elimination of bioavailable cortisol (Charmandari, Lichtarowicz-Krynska et al. 2001). Moreover, oral hydrocortisone pharmacokinetics are variable and patients with rapid metabolism may have a less marked response to modest dose manipulations (Werumeus Buning, Touw et al. 2017). As a result, considerable variation exists with regards to sick day dosing regimens and the duration of sick day dosing, with a multitude of regimens often specified for mild, moderate or severe stress (Allolio 2015). Our survey showed that during acute illness, the most commonly recommended schedules were increasing glucocorticoid dose two or three-fold and administering three times daily and this observation was consistent with previous studies (Riepe, Krone et al. 2002). However, guidelines issued by the North American Endocrine Society for patients with CAH due to 21-hydroxylase deficiency suggest that sick day dosing should be given every 6 hours to avoid significant episodes of low cortisol concentration during stress (Speiser, Arlt et al. 2018); this regimen was only followed by around 20% of centres in the current

survey. Notably, none of the centres that were involved in the current survey were from North America.

Expert guidance also recommends that children with symptoms of vomiting or diarrhoea receive parenteral hydrocortisone (Rushworth, Torpy et al. 2017). In this study, more than 60% of centres recommended IM hydrocortisone as the recommended route of glucocorticoid administration in a child that was vomiting. Around 20% of centres also recommended SC hydrocortisone for vomiting or diarrhoea, a method that has been reported to have greater acceptability to parents and patients and deserves further study (Hahner, Burger-Stritt et al. 2013). Some centres specified that they would not use parenteral hydrocortisone for diarrhoea or vomiting. The reasons for this were not explored in the current study but may relate to unavailability of parenteral hydrocortisone in resource limited settings. Previous studies have reported that rectal hydrocortisone is a safe alternative to parenteral administration (De Vroede, Beukering et al. 1998, M, Fallon et al. 2003), however, it is not currently accepted as a standard treatment modality for children with an adrenal crisis and further studies are required. None of the centres in the survey reported the use of rectal hydrocortisone use in the event of an adrenal crisis.

Previous studies evaluating adrenal crises have used varying clinical and biochemical parameters to define an adrenal crisis (Allolio 2015, Arlt and Society for Endocrinology Clinical 2016, Rushworth, Torpy et al. 2017, Husebye, Pearce et al. 2021, Nowotny, Ahmed et al. 2021). Despite proposals for standardised criteria for defining an adrenal crisis, there is no universally accepted definition (Rushworth, Torpy et al. 2019). The current study indicates that there is a level of consensus amongst the international community of expert centres regarding the criteria that should be used to define an adrenal crisis. Essential criteria, as reported by over half of respondents, were fatigue, nausea or vomiting, low blood pressure, hyponatraemia, hyperkalaemia and clinical improvement after glucocorticoid. In addition, desirable criteria were abdominal pain and hypoglycaemia. These clinical and biochemical characteristics correspond with those highlighted in previous definitions of an adrenal crisis (Allolio 2015, Arlt and Society for Endocrinology Clinical 2016, Rushworth, Torpy et al. 2017, Husebye, Pearce et al. 2021, Nowotny, Ahmed et al. 2021). Hypoglycaemia was

considered to be an essential criteria by less than 50% of respondents in this survey, however, this clinical feature was the only criterion highlighted by all the publications above and has also been highlighted as an important feature of CAH-related adrenal crises (Odenwald, Nennstiel-Ratzel et al. 2016). Thus, based on the results of this study and previous studies, we propose the use of these seven criteria (fatigue, nausea or vomiting, low blood pressure, hyponatraemia, hyperkalaemia, hypoglycaemia and clinical improvement after glucocorticoid) as a core dataset that should be collected when assessing an adrenal crisis in children. In a child with known AI, at least four of these seven criteria may be sufficient to reach a diagnosis of adrenal crisis, however, further work is required to evaluate the clinical utility and reliability of using this approach.

In this survey, over 90% of centres stated that the majority of their patients attended hospital in the event of an adrenal crisis, with over 80% of patients requiring hospital admission. Previous studies have reported that hospitalisation in the case of an imminent adrenal crisis was recommended (Riepe, Krone et al. 2002). Moreover, there appears to be a level of consensus amongst the international community regarding the medical management of patients presenting with an adrenal crisis. Around 90% of centres stated that patients at their centre would always receive an IV bolus or IM injection of hydrocortisone and an IV infusion of isotonic saline. More than 70% of centres reported that patients at their centre would never receive prednisolone or antihypoglycaemic drugs, such as glucagon, and these observations are consistent with previous physician questionnaire based studies (Riepe, Krone et al. 2002). Furthermore, our results indicate that almost 60% of centres would always administer a glucose infusion which is consistent with previous recommendations (Rushworth, Torpy et al. 2019).

7.6.2 Strengths

An international perspective was obtained from a large number of centres delivering specialist care for children with adrenal insufficiency and CAH, representing a range of practices and resource settings with diverse patient populations. The overall survey response rate of 50% is also markedly higher than reported in other physician-based surveys (Cook, Wittich et al. 2016).

7.6.3 Limitations

Due to the nature of the questionnaire-based study, there are limitations inherent due to the type of data collected and potential response bias. It is possible that the centres that demonstrated greater adherence to proposed standards of care responded to the survey. Given that there is wide variation in adrenal crisis rates (Ali, Bryce et al. 2021), obtaining more detailed centre and patient specific information and relating it to the available resources would also be advantageous. Other factors that were not covered in this survey include an assessment of the availability and preference of medication and devices for adrenal insufficiency, the pre-hospital management of adrenal crisis including the use of IM hydrocortisone, the timing of attendance to hospital in relation to the onset of acute illness and increasing carbohydrate and fluid intake during sick day episodes (El-Maouche, Hargreaves et al. 2018). However, in this questionnaire-based study, a balance needed to be struck between maximising the information available for collection and reducing respondent burden. Another limitation of this survey includes the preponderance of responses from specialist centres within Europe, with almost 60% of centres within Europe.

7.6.4 Summary

In summary, this international survey has provided insight into the definitions and management of acute AI related adverse events recommended by endocrinologists delivering specialist care for children with CAH. Although there is considerable variation in the definition and management of AI related adverse events in children amongst centres, there is also good evidence of consensus that can be used to develop standardised criteria for defining an adrenal crisis, facilitating the development of clinical benchmarks for care. This survey paves the way for the development of more uniform guidance and also highlights the necessity for further work.

CHAPTER 8

Parent reported outcomes in young children with disorders or differences of sex development

The findings of this chapter have been published by **Ali SR**, Macqueen Z, Gardner M, et al. Parent reported outcomes in young children with disorders/differences of sex development. *Int J Pediatr Endocrinol*. 2020;2020:3.

8 Parent reported outcomes in young children with disorders or differences of sex development

8.1 Abstract

Background: There is a paucity of tools that can be used in routine clinical practice to assess the psychosocial impact of disorders/differences of sex development (DSD) on parents and children.

Objective: To evaluate the use of parent reported outcome questionnaires in the routine outpatient setting and to evaluate the psychosocial impact of DSD on parents and affected children.

Methods: Previously validated DSD-specific and generic items were combined to develop a parent self-report questionnaire and a parent proxy-report questionnaire for children under 7 years. Of 111 children approached at one tertiary paediatric hospital, the parents of 95 children (86%) with DSD or other endocrine conditions completed questionnaires.

Results: Questionnaires took under 10 minutes to complete and parents reported ease of comprehension. Compared to reference, fathers of children with DSD reported less stress associated with Clinic Visits ($p = 0.02$) and managing their child's Medication ($p= 0.04$). However, parents of children with either DSD or other endocrine conditions reported more symptoms of Depression ($p= 0.03$). Mothers of children with DSD reported greater Future Concerns in relation to their child's condition (median SDS − 0.28; range − 2.14, 1.73) than mothers of children with other endocrine conditions (SDS 1.17; − 2.00, 1.73) ($p= 0.02$). Similarly, fathers of children with DSD expressed greater Future Concerns (median SDS -1.60; − 4.21, 1.00) than fathers of children with other endocrine conditions (SDS 0.48; − 2.13, 1.52) ($p= 0.04$).

Conclusion: Brief parent-report tools in DSD can be routinely used in the outpatient setting to assess and monitor parent and patient needs. DSD was associated with greater parental concerns over the child's future than other endocrine conditions.

8.2 Introduction

Disorders or differences of sex development (DSD) can impose a high degree of stress on patients and their families, exerting a wide range of effects on social and psychosexual adjustment, mental health, quality of life and social participation (Suorsa, Mullins et al. 2015). Uncertainties regarding diagnosis, limited coping strategies and distress related to shame and 'stigma' associated with DSD may lead to an increased risk of adverse psychosocial outcomes disproportionate to the severity of the DSD (Brinkmann, Schuetzmann et al. 2007, Rolston, Gardner et al. 2015, Alpern, Gardner et al. 2017, Meyer-Bahlburg, Khuri et al. 2017). A significant minority of parents of children with DSD experience symptoms suggestive of post-traumatic stress disorder with accompanying difficulties in communicating news of their child's condition with relatives and close friends, an independent risk factor for emotional distress (Duguid, Morrison et al. 2007, Pasterski, Mastroyannopoulou et al. 2014). Yet, there is a paucity of studies evaluating the feasibility of routine, longitudinal psychosocial screening for parents in the context of usual care (Stout, Litvak et al. 2010, Ahmed, Gardner et al. 2014, Sharkey, Bakula et al. 2018, Lee, Schober et al. 2012).

There has been growing interest in adopting standardised tools for assessing subjective experiences of patients and incorporating reports of parent/caregiver proxies in young children in the context of ongoing patient care (Services 2006). The assessment of a child's adaptation to their medical condition is also becoming increasingly common (Janssens, Thompson Coon et al. 2015) with the use of parent-proxy reporting playing an important role in overcoming challenges associated with assessing the subjective experience of young children (Varni, Limbers et al. 2011). Parent/patient reported outcome measures (PROM) can be generic (i.e., applicable to all populations), for example, the 'Patient-Reported Outcomes Measurement Information System' (PROMIS) (Irwin, Gross et al. 2012) and the 'Patient Health Questionnaire for Depression and Anxiety' (PHQ-4) (Kroenke, Spitzer et al. 2009) or can be condition-specific, for example, the 'Pediatric Asthma Scale' (Yeatts, Stucky et al. 2010). Recently DSD-specific health-related quality of life measures were developed for parents of children under 7 years of age including parent-proxy report (PPR) and parent self-report (PSR) questionnaires (Alpern, Gardner et al. 2017). Whereas these tools were

developed for use within multidisciplinary DSD clinics with dedicated behavioural health specialists, it is unclear whether their use would be feasible in settings with more limited staffing and time constraints. Thus, there is a need to explore tools that can overcome the perceived challenges of managing patients in a busy clinic setting and have maximum acceptability by parents and professionals (Sandberg, Gardner et al. 2017, Ernst, Gardner et al. 2018).

8.3 Aims

The aims of this study were to:

- To develop a PSR questionnaire for parents of children aged from birth to under 7 years and a parallel PPR questionnaire for parents of children aged 2 to < 7 years, using existing validated DSD-specific (Rolston, Gardner et al. 2015, Alpern, Gardner et al. 2017) and generic items (Irwin, Gross et al. 2012) for parents of young children

- To assess the impact of DSD on parents and their children

8.4 Methods

8.4.1 Ethics approval and consent

The study was approved by the National Research Ethics Service in Scotland as routine health service evaluation study. Parents and caregivers provided verbal informed consent prior to undertaking questionnaire completion.

8.4.2 Participant selection

Parents of children under the age of 7 years attending DSD and endocrine outpatient clinics at one tertiary paediatric centre in Scotland, were approached between February 2017 and February 2019. Exclusion criteria included the need for an interpreter for questionnaire completion, thus, parental eligibility was restricted to those whose primary language was English.

Parents were approached at the end of clinic consultations, advised verbally and provided with a cover note that participation of at least one parent was required and participation was optional. The completed paper questionnaires were scanned into each child's electronic health record as part of routine clinical care. All parents returned completed questionnaires prior to leaving the clinic. A section at the end of the questionnaire sought parental feedback on simplicity of the questionnaire, acceptability of the length of time for completion and comprehension of questions. The completed questionnaires were available to the

DSD multidisciplinary team assessing care and for discussion at subsequent pre-clinic meetings for evaluation of ongoing care.

8.4.3 Parent self-report (PSR) questionnaire

The 40-item PSR (Table 8-1) was developed for parents of children aged from birth to <7 years to assess parental feelings and experiences in relation to their child's condition (DSD or other endocrine conditions). The PSR was comprised of 8 scales (Healthcare Communication and Information, Talking to Others, Future Concerns, Medication, Clinic Visit, Surgery, Stigma, and Anxiety/Depression). These scales were selected from the previously validated Quality of Life DSD Parent report (QOL-DSD-Parent) (Alpern, Gardner et al. 2017), parent-focused items of the Experiences and Reactions questionnaire assessing DSD-related experienced or anticipated stigma (Rolston, Gardner et al. 2015), and the PHQ-4 (Kroenke, Spitzer et al. 2009), a screening scale for depression and anxiety (Table 8-3).

Table 8-1. Parent self-report questionnaire scales and items.
[a]Option to omit question by selecting option 'too young'. [b]Option to select 'no surgery'.

Questionnaire scale	Items	Scoring options
Healthcare Communication & Information	I feel overwhelmed by the amount of information about my child's condition I hear confusing medical information about my child's condition	Always true / Usually true / Sometimes / Seldom true / Never true
Talking to Others	I feel comfortable talking with my child about his/her condition[a] I feel comfortable talking to close family members about my child's condition I am comfortable explaining my child's needs (e.g. diaper changing, using the bathroom) to people other than family I am not sure how much to tell others about my child's condition I worry about talking to others about my child's condition because of how they might react	
Experiences and Reactions	I worry my child will look different from other teenagers or adults because of his/her condition I worry my child won't be/isn't able to do things he/she wants to do because of their condition I feel that I am odd or abnormal because of my child's condition There have been times when I have felt ashamed about having a child with this condition I feel self-conscious about my child's condition People treat me the way they always have when they find out I have a child with this condition I feel embarrassed about my child's condition People look down on me because I have a child with this condition People say negative or unkind things about me behind my back because I have a child with this condition I have been excluded from social gatherings because I have a child with this condition	
Future Concerns	I am concerned about how my child's genitals will look I am concerned about how my child's genitals will function I worry about my child dying due to the condition and/or its treatment I worry that my child will have fertility issues (e.g. will not be able to have a biological child) I worry that my child will have social problems, like being teased about his/her condition I worry about my child's future relationships (e.g. dating, marriage) I worry that my child will not be comfortable with his/her gender as an adult	
Medications	How much stress do you experience … Remembering to give your child his/her medications related to the condition (e.g. hormones such as growth hormone, steroids, thyroxine, testosterone)? Making sure your child receives his/her medications for the condition when he/she is away from you (e.g. at school or daycare)?[a] Giving your child his/her medication? Managing the side effects of your child's condition?	A great deal / Moderate / Some / None / N/A / No medication
Visit to the Endocrine Clinic	How long ago was your child's most recent endocrine clinic visit?	Today-2 weeks ago / 2 weeks- 3 months ago / 3- 6 months ago / 6- 12 months ago / 1-2 years ago / Over 2 years ago

	How much stress did you experience … Talking with your child before the visit?[a] Not knowing what to expect at the visit? Managing your child's behaviour during the visit?	A great deal / Moderate / Some / A little / None / N/A
Surgery[b]	How long ago was your child's most recent surgery related to the condition?	Today-2 weeks ago / 2 weeks- 3 months ago / 3- 6 months ago / 6- 12 months ago / 1-2 years ago / Over 2 years ago
	How much stress did you experience … Talking with your child before the surgery?[a] During the surgery? After the surgery (e.g. dealing with your child's needs for extra care, wondering about the outcome)?	A great deal / Moderate / Some / A little / None / N/A
PHQ-4	Over the past 2 weeks, how often have you been bothered by the following problems: Little interest or pleasure in doing things Feeling down, depressed or hopeless Feeling nervous, anxious or on edge Not being able to stop or control worrying	Not at all / Several days / More than half the days/ Nearly every day

8.4.4 Parent proxy-report (PPR) questionnaire

The 30-item PPR (Table 8-2) was developed for parents of children aged 2 to <7 years to capture their perceptions of the child's feelings and experiences related to their condition (DSD or other endocrine condition). The PPR comprised 8 scales (Anxiety, Depression, Anger, Peer Relationships, Stigma, Clinic Visits, Medications, and Missed School Days). These scales were selected from the Quality of Life DSD Proxy report (QOL-DSD-Proxy) (Alpern, Gardner et al. 2017), child-focused items of the Experiences and Reactions questionnaire (Rolston, Gardner et al. 2015) and select PROMIS Parent-Proxy scales (Irwin, Gross et al. 2012) (Table 8-3).

Table 8-2. Parent proxy-report questionnaire scales and items.

Questionnaire scale	Items	Scoring options
Anxiety	My child felt nervous My child felt worried My child felt like something awful might happen My child worried when he/she was at home	Never / Almost Never / Sometimes / Often / Almost Always
Depressive Symptoms	My child felt everything in his/her life went wrong My child felt lonely My child felt sad It was hard for my child to have fun	
Anger	My child felt mad My child was so angry he/she felt like yelling at somebody My child was so angry he/she felt like throwing something My child felt upset When my child got mad, he/she stayed mad	
Peer Relationships	My child felt accepted by other kids his/her age My child was able to count on his/her friends My child and his/her friends helped each other out Other kids wanted to be my child's friend	
Experiences and Reactions	People who know that my child has the condition treat him/her differently It really doesn't matter what I say to people about my child's condition, they usually have their minds made up In many people's minds, having this condition attaches a stigma or label to my child Because of the condition, my child will have problems in finding a boyfriend or girlfriend (husband or wife)	Always true / Usually true / Sometimes / Seldom true / Never true
Visit to the Endocrine Clinic	How long ago was the endocrine clinic visit or procedure? What did the endocrine clinic visit or procedure involve? (write in) How much stress did your child experience … Before the endocrine clinic visit or procedure (e.g. on way to the appointment, in the waiting room)? Having endocrine clinic visits e.g. physical exams? Having doctors examine the private parts of my child's body? Having medical procedures (e.g. blood tests)? After the visit/procedure?	Today-2 weeks ago / 2 weeks- 3 months ago / 3- 6 months ago / 6- 12 months ago / 1-2 years ago / Over 2 years ago A great deal / Moderate / Some / None / N/A / No exam
Medications	How much stress did your child experience Taking medication for the condition?	A great deal / Moderate / Some / None / N/A / No medication
Missed School Days	Over the past six months, excluding school holidays, how many days of school has your child missed because of the condition he/she attends the clinic for?	Number of days

Table 8-3. Parent self-report and proxy-report scales, score representation and reference mean (SD).
[a]Sample mean (SD) from reference data was used to calculate median SDS for each scale (Kroenke, Spitzer et al. 2009, Irwin, Gross et al. 2012, Rolston, Gardner et al. 2015, Alpern, Gardner et al. 2017). [b]Mean (SD) represents the mean (SD) T score for PROMIS scales.

Questionnaire scales	Items	Scales derived from:	High subscale scores indicate:	Sample mean (SD) from reference sample[a,b]			Reference sample
				Mothers	Fathers	Sample- All	
Parent self-report							
Communication & Information	2	QOL-DSD	Better outcome	74.86 (16.93)	69.97 (23.15)	-	Alpern et al. 2017
Talking to Others	5	QOL-DSD	Better outcome	64.03 (24.52)	85.55 (16.80)	-	
Future Concerns	7	QOL-DSD	Better outcome	55.37 (25.86)	79.14 (13.71)	-	
Medication	4	QOL-DSD	Better outcome	70.39 (28.20)	49.10 (28.31)	-	
Clinic Visit	4	QOL-DSD	Better outcome	72.08 (27.81)	33.38 (25.80)	-	
Surgery	4	QOL-DSD	Better outcome	38.03 (25.12)	81.10 (24.51)	-	
Stigma	10	Experiences & Reactions: Parent focused	Poorer outcome	1.76 (0.63)	1.56 (0.44)	-	Rolston et al. 2015
PHQ-4	4	Patient Health Questionnaire-4	Poorer outcome	-	-	2.5 (2.8)	Kroenke et al. 2009
Parent proxy-report							
Anxiety	4	PROMIS	Poorer outcome	-	-	50 (10)	Irwin et al. 2012
Depression	4	PROMIS	Poorer outcome	-	-	50 (10)	
Anger	5	PROMIS	Poorer outcome	-	-	50 (10)	
Peer Relations	4	PROMIS	Better outcome	-	-	50 (10)	
Stigma	4	Experiences & Reactions: Child focused	Poorer outcome	2.28 (0.91)	2.05 (0.81)	-	Rolston et al. 2015
Clinic Visit & Medication	7 1	QOL-DSD	Better outcome	64.98 (24.49)	78.10 (22.56)	-	Alpern et al. 2017

8.4.5 Questionnaire scoring

DSD reference data were obtained from a previous study validating DSD-specific, parent-reported, health-related quality of life measures for children under the age of 7 years (Alpern, Gardner et al. 2017). For both PSR and PPR questionnaires, parents rated their experiences/perceptions on 5-point Likert scales (Table 8-1 and 8-2). For each scale, a scale average was obtained if at least half of the items were completed, and these were incorporated into the calculation of the median standard deviation score (SDS). Responses were standardised from 0-100, with higher scores in the majority of scales indicating better quality of life and more positive adaptation (Table 8-3). The Experiences and Reactions (Stigma) scale (Rolston, Gardner et al. 2015) were also scored on a 5-point scale, with higher scores indicating a greater level of stigma. Median standard deviation scores (SDS), i.e., the number of SDs away from the mean, for questionnaire scales stemming from the QOL-DSD-Parent, QOL-DSD-proxy reports (Alpern, Gardner et al. 2017) and the Experiences and Reaction (Parent-Focused and Child-Focused) questionnaire (Rolston, Gardner et al. 2015), were calculated using separate mother and father means and SDs obtained from reference data (Table 8-3). Total scores for the PHQ-4 screening scale (Kroenke, Spitzer et al. 2009) for depression and anxiety were categorised as normal (0 - 2), mild (3 - 5), moderate (6 - 8), and severe (9 - 12); on each subscale, a score of 3 or greater was considered positive for screening purposes. As per recommended scoring procedures (healthmeasures.net), PROMIS raw scale scores for Anxiety, Depression, Anger and Peer Relationships were converted to standardised “T scores” (mean 50; SD 10) employing the Health Measures Scoring Service (healthmeasures.net) which utilises norms for healthy 5 to 17 year old children in the U.S. general population as the referent sample. For Anxiety, Depression and Anger, a higher score, for example T=60, was representative of a +1SD elevation in symptoms relative to the normative sample (PROMIS scoring manuals; healthmeasures.net). In the case of Peer Relationships, T=60 reflected better social interactions by the same +1SD.

8.4.6 Statistical analysis

Data analysis was performed using Minitab version 18 statistical software (Minitab LLC, State College, PA, USA). All data were described as medians and ranges (minimum, maximum). Comparison between groups was performed by the Kruskal-Wallis test for continuous variables and subsequently adjusted for multiple comparisons using false discovery rates (FDR) (Benjamini and Hochberg 1995).For DSD-specific and generic scales, the mean (SD) derived from previously validated reference data was used in the calculation of median SDS for each scale (Table 8-3). For DSD-specific scales, the median SDS of mothers and fathers within DSD and endocrine groups were analysed to enable cross-parent comparisons. For all scales within both questionnaires, the median SDS of the DSD group was compared to the median SDS of the endocrine group and the median SDS of each group (DSD and endocrine) was also compared to SDS of zero. Mothers and fathers scores were combined for the PROMIS measures as per scoring guidelines. A p value of less than 0.05 was considered statistically significant.

8.5 Results

8.5.1 Response rates

Of the 111 children whose parents were approached to complete questionnaires, 95 (86%) completed questionnaires (Figure 8-1). Questionnaires were provided to one parent/carer attending clinic with their child with the exception of four cases for whom both mothers and fathers completed questionnaires. Two respondents who completed questionnaires were not biological parents, however, all were referred to as 'mothers' and 'fathers'.

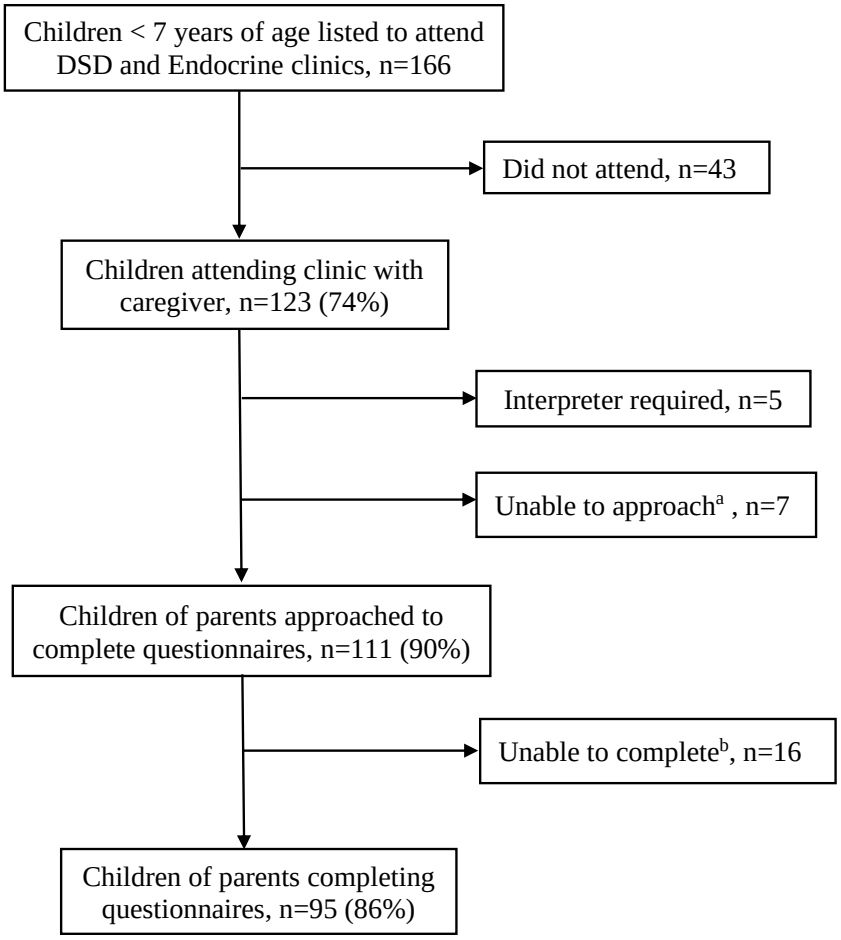


Figure 8-1. Selection of cases and recruitment details.
DSD, Disorder of sex development. [a]Caregivers not approached due to consultation running simultaneously (n=7) [b]Caregivers not able to complete questionnaires as insufficient time after clinic (n=8), other commitments (n=7) or already completed a separate hospital questionnaire (n=1).

8.5.2 Participant characteristics

Characteristics of DSD cases

For the PSR questionnaire, data were available for 55 parents (42 mothers and 13 fathers) of 54 children. For the PPR, data were available for 25 parents (18 mothers and 7 fathers) of 25 children (Table 8-4). The median age of the 54 children for whom PSR questionnaires were completed was 1.8 years (range 0.03, 6.8 years) and of these, 44 (82%) were reared as boys. The median age of the 25 children for whom PPR questionnaires were completed was 4.5 years (2.0, 6.65) and of these, 16 (64%) were boys. Amongst the 54 DSD cases, 40 (74%) had 46, XY DSD with 28 (51%) having a diagnosis of a non-specific DSD (e.g. bilateral cryptorchidism or proximal hypospadias). Sex chromosome DSD and 46, XX DSD accounted for 7 (13%) cases each. Of the 54 cases, 16 (30%) had other conditions including cardiorespiratory disease, non-sex chromosome abnormalities or developmental delay.

Characteristics of endocrine cases

For the PSR questionnaire, data were available for 43 parents (34 mothers and 9 fathers) of 41 children. For the PPR, data were available for 23 parents (17 mothers and 6 fathers) of 22 children (Table 8-4). The median age of the 41 children for whom parents completed PSR questionnaires was 2 years (0.1, 6.8) and of these 41 children, 23 (56%) were raised as boys. The median age of the 22 children for whom PPR questionnaires were available was 5 years (2.3, 6.9) and of these, 13 (59%) were boys. The most frequent endocrine diagnoses amongst the 41 children who had PSR questionnaires were short stature or growth hormone deficiency conditions in 14 (34%) children and bone disorders in 11 (27%) children. In the 22 children who had PPR questionnaires completed, these two diagnoses were present in 11 (50%) and 4 (18%) children, respectively. Other endocrine diagnoses in cases for whom PSR and PPR questionnaires were completed accounted for less than 7% of conditions amongst the endocrine cases and included thyroid disease and adrenal insufficiency (Table 8-4). Of the 41 endocrine cases, 17 (41%), had other co-morbidity including cardiac, respiratory or neurological problems.

Table 8-4. Characteristics of children with DSD and endocrine diagnoses.
[a]Parent self-report (PSR) questionnaire completed by parents of children from birth to 2 years. [b]Parent proxy-report (PPR) questionnaire completed by parents of children aged 2 to 6 years. [c]For one child, both parents completed PSR. [d]For two children, both parents completed PSR and for one child, both parents completed PPR.

	Parental questionnaire	
DSD sample	**Self-report[a]**	**Proxy-report[b]**
Index cases (*n)*	54	25
Parents (*n)*[c]	55	25
Mother	42	18
Father	13	7
Child gender (*n*, %)		
Male	44 (81.5%)	16 (64.0%)
Female	10 (18.5%)	9 (36.0%)
Child age, years (median, range)	1.8 (0.03, 6.8)	4.5 (2.0, 6.5)
DSD category and diagnosis:		
Sex chromosome (*n*, %)	7 (13.0%)	6 (24.0%)
Turner syndrome	4 (7.4%)	4 (16.0%)
Other sex chromosome DSD (e.g. Klinefelter syndrome, 45X/46Y primary gonadal dysgenesis, XO/X isodicentric Y chromosome complement)	3 (5.5%)	2 (8.0%)
46, XX (*n*, %)	7 (13.0%)	6 (24.0%)
Disorder of androgen excess (congenital adrenal hyperplasia)	6 (11.1%)	5 (20.0%)
Other 46, XX DSD (e.g. vaginal atresia)	1 (1.9%)	1 (4.0%)
46, XY (*n*, %)	40 (74.0%)	13 (52.0%)
Disorder of gonadal (testicular) development (e.g. bilateral anorchia)	1 (1.9%)	1 (4.0%)
Non-specific disorder of undermasculinisation (e.g. bilateral cryptorchidism, isolated hypospadias)	28 (51.2%)	9 (36.0%)
Other 46, XY DSD (e.g. combination of hypospadias and bilateral cryptorchidism or micropenis)	11 (20.4%)	3 (12.0%)
Endocrine sample		
Index cases (*n)*	41	22
Parents (*n)*[d]	43	23
Mother	34	17
Father	9	6
Child gender (*n*, %)		
Male	23 (56.1%)	13 (59%)
Female	18 (43.9%)	9 (40.9%)
Child age, years (median, range)	2.0 (0.1, 6.8)	5.0 (2.3, 6.9)
Endocrine category (*n*, %):		
Disorders of short stature or growth hormone deficiency	14 (34%)	11 (50.0%)
Disorder of calcium and phosphate homeostasis	11 (26.9%)	4 (18.1%)
Disorder of thyroid gland	7 (17.1%)	4 (18.1%)
Disorder of adrenal gland	3 (7.3%)	2 (9.1%)
Disorder of pituitary gland	2 (4.9%)	0
Genetic disorders of glucose and insulin homeostasis	2 (4.9%)	0
Other (e.g. primary polydipsia, premature tooth exfoliation)	2 (4.9%)	1 (4.5%)

8.5.3 Parent self-report scores− comparison to reference

Fathers of children with DSD had lower median SDS for Future Concerns [SDS -1.60 (-4.21, 1.00); p=0.02], indicating greater apprehension, compared to reference data (Table 8-5, Figure 8-2). However, these fathers had a higher median SDS for Medication [SDS 1.80 (1.01, 1.80); p=0.04] and Clinic Visits [SDS 2.10 (0.16, 2.58); p=0.02], indicating lesser degrees of stress relating to their child's medication regimen and clinic visits. Mothers of children with other endocrine conditions had a higher median SDS for Talking to Others [SDS 0.78 (-0.83, 1.47); p=0.02], Future Concerns [SDS 1.17 (-2.00, 1.73); p=0.02) and Clinic Visits [SDS 0.70 (-1.37, 0.99); p=0.02], indicative of less concerns in each of these scales. Fathers of children with other endocrine conditions also had a higher SDS for Clinic Visits [SDS 1.37 (0.64, 2.60); p=0.04], indicating less stress associated with clinic attendances, compared to reference data.

8.5.4 Parent self-report scores− DSD versus endocrine cases

Mothers of children with DSD had lower median SDS for Future Concerns, indicating a greater level of concerns, than mothers of children with other endocrine conditions [SDS -0.28 (-2.14, 1.73) vs SDS 1.17 (-2.00, 7.73); p=0.02] (Table 8-5, Figure 8-2). Similarly, fathers of children with DSD had a lower median SDS for Future Concerns compared with fathers of children with other endocrine conditions [SDS -1.60 (-4.21, 1.00) vs SDS 0.48 (-2.13, 1.52); p=0.04] indicating greater concerns in fathers of children with DSD. For both DSD and endocrine groups, median PHQ-4 scores were not in the range associated with clinically significant symptomology and there was no significant difference in PHQ-4 scores between mothers and fathers of children with DSD compared with mothers and fathers of children with other endocrine conditions ($p>0.05$).

Table 8-5. Parent self-report questionnaire scores for children with DSD and children with other endocrine conditions.
[a]n's vary by scale due to item responses and not all children have had surgery or take medication. [b]SDS, standard deviation score; subscale values are presented as SDS based on reference data. [c]p values have been adjusted for multiple comparisons using false discovery rates; significance has been assigned at adjusted p<0.05. *p<0.05, compared to SDS of zero. All p values have been adjusted for multiple comparisons.

	DSD sample			Endocrine sample			DSD *vs* Endocrine
Self-report scales	***n*[a]**	**Subscale score, median (range)**	**SDS[b], median (range)**	***n*[a]**	**Subscale score, median (range)**	**SDS[b], median (range)**	***p* value[c]**
Communication and Information							
Mothers	42	75.00 (37.50, 100.00)	0.01 (-2.21, 1.49)	34	75.00 (25.00, 100.00)	0.01 (-2.95, 1.49)	NS
Fathers	13	75.00 (37.50, 87.50)	0.22 (-1.40, 0.76)	9	62.5 (0.00, 87.50)	-0.32 (-3.02, 0.76)	NS
Talking to Others							
Mothers	41	62.50 (35.00, 100.00)	-0.06 (-1.18, 1.47)	34	83.13 (43.75, 100.00)	0.78* (-0.83, 1.47)	NS
Fathers	12	81.25 (37.50, 100.00)	-0.25 (-2.86, 0.86)	9	90.00 (45.00, 100.00)	0.27 (-2.41, 0.86)	NS
Future Concerns							
Mothers	42	50.00 (0.00, 100.00)	-0.28 (-2.14, 1.73)	35	85.71 (3.57, 100.00)	1.17* (-2.00, 1.73)	0.02
Fathers	13	57.14 (21.43, 92.86)	-1.60* (-4.21, 1.00)	9	85.71 (50.00, 100.00)	0.48 (-2.13, 1.52)	0.04
Medication							
Mothers	14	66.67 (0.00, 100.00)	-0.13 (-2.50, 1.05)	25	83.33 (0.00, 100.00)	0.31 (-2.50, 1.05)	NS
Fathers	6	100.00 (77.78, 100.00)	1.80* (1.01, 1.80)	3	100.00 (75.00, 100.00)	1.80 (0.92, 1.80)	NS
Clinic Visit							
Mothers	38	70.83 (56.25, 100.00)	-0.05 (-1.69, 1.00)	32	91.67 (33.33, 100.00)	0.70* (-1.37, 0.99)	NS
Fathers	11	87.50 (37.50, 100.00)	2.10* (0.16, 2.58)	8	68.75 (50.00, 91.67)	1.37* (0.64, 2.60)	NS
Surgery							
Mothers	11	12.50 (0.00, 91.67)	-1.02 (-1.51, 2.14)	4	31.30 (0.00, 83.30)	0.47 (-1.02, 1.80)	NS
Fathers	4	41.70 (25.0, 100.00)	-1.61 (-2.29, 0.77)	1	12.50 (12.50, 12.50)	-2.80 (-2.80,-2.80)	NS
Stigma							
Mothers	42	1.60 (1.00. 2.67)	-0.25 (-1.21, 1.44)	35	1.40 (1.00, 3.20)	-0.57 (-1.21, 2.29)	NS
Fathers	13	1.40 (1.00, 2.10)	-0.36 (-1.27, 1.23)	9	1.60 (1.00, 2.11)	0.09 (-1.27, 1.25)	NS
PHQ-4							
Mothers	40	1.00 (0.00, 8.00)	0.54 (0.89, 1.96)	34	0.00 (0.00, 6.00)	0.89 (-1.25, 0.89)	NS
Fathers	12	0.00 (0.00, 6.00)	0.89 (0.89, 1.25)	9	0.00 (0.00, 4.00)	0.89 (-0.54, 0.89)	NS

8.5.5 Parent proxy-report scores− comparison to reference

Parents of children with DSD had higher median SDS for Depression [SDS 1.28 (-1.52, 1.28); p=0.03] indicative of greater depressive symptoms, compared to reference data (Table 8-6). Similarly, parents of children with other endocrine conditions reported more symptoms of Depression [SDS 0.64 (-1.01, 1.28); p=0.03]. There was no significant difference in other proxy-report scales (including Anxiety, Anger and Peer Relations, Stigma, Clinic Visits and Medication) between parents of children with DSD or other endocrine conditions, compared to reference data.

8.5.6 Parent proxy-report scores− DSD versus endocrine cases

There was no significant difference in the PROMIS scores for Anxiety, Depression, Anger and Peer Relationships between parents of children with DSD and parents of children with other endocrine conditions (Table 8-6). In addition, there were no differences between parents of children with DSD compared with other endocrine conditions with regards to DSD-specific scales including Stigma, Clinic Visits or Medications. Parents of children with DSD reported a median of 0 Missed School Days (0.0, 3.0) over the previous 6-month period compared to 0.5 days (0.0, 5.0) for children with other endocrine conditions.

Table 8-6. Parent proxy-report questionnaire scores for children with DSD and other endocrine conditions.
[a]n's vary by scale due to item responses and not all children take medication. [b]For anxiety, depression, anger and peer relations, the subscale score represents the PROMIS T-score. [c]SDS, standard deviation score, calculated using mean and SD from reference data. [d]p values have been adjusted for multiple comparisons using false discovery rates; significance has been assigned at adjusted p<0.05. *p<0.05, compared to SDS of zero. All p values have been adjusted for multiple comparisons.

	DSD sample			Endocrine sample			DSD *vs* Endocrine
Proxy-report scales	***n*[a]**	**Subscale score[b], median (range)**	**SDS[c], median (range)**	***n*[a]**	**Subscale score[b], median (range)**	**SDS, median (range)**	***p* value[d]**
Anxiety	23	43.60 (36.30, 68.60)	0.64 (-1.86, 1.37)	21	46.00 (36.30, 75.30)	0.40 (-2.53, 1.37)	NS
Depression	23	37.20 (37.20, 65.20)	1.28* (-1.52, 1.28)	22	43.60 (37.20, 60.10)	0.64* (-1.01, 1.28)	NS
Anger	23	43.40 (29.00, 62.70)	0.66 (-1.27, 2.10)	22	42.50 (29.00, 67.70)	0.75 (-1.77, 2.10)	NS
Peer Relations	23	50.60 (27.30, 60.80)	0.06 (-2.27, 1.08)	22	48.25 (19.10, 60.80)	-0.18 (-3.09, 1.08)	NS
Stigma							
Mothers	17	1.33 (1.00, 4.00)	-1.04 (-1.41, 1.89)	16	1.70 (1.00, 4.25)	-0.63 (-1.41, 2.17)	NS
Fathers	6	1.13 (1.00, 3.00)	-1.14 (-1.30, 1.17)	6	1.75 (1.00, 2.50)	-0.37 (-1.30, 0.56)	NS
Clinic Visit/ Medication							NS
Mothers	16	81.67 (3.33, 100.00)	0.68 (-2.52, 1.43)	17	93.30 (54.17, 100.00)	1.16 (-2.65, 1.43)	NS
Fathers	6	75.00 (40.00, 83.33)	-0.14 (-1.69, 0.23)	6	87.50 (66.67, 100.00)	0.42 (-0.51, 0.97)	NS

8.5.7 Questionnaire acceptability

Of the 111 children whose parents were approached, the parents of 95 children with DSD or other endocrine conditions completed the questionnaires (86%). In all cases, parents completed the questionnaires in less than 10 minutes and all parents reported that the time taken to complete the questionnaire was acceptable, questions were ‘easy to understand’ and ‘easy to follow’.

8.6 Discussion

8.6.1 Key findings

This is the first study to report on the use of parent self-report and parent proxy-report questionnaires in a routine clinic setting for parents of young children with DSD, incorporating DSD-specific and generic items. Preliminary results demonstrate that the screening approach was feasible in the clinical context, acceptable to patients and can be routinely used in the outpatient setting to assess and monitor parent and patient needs.

Compared with parents of children with other endocrine conditions, mothers and fathers of children with DSD reported greater Future Concerns with regards to their child's condition. These results highlight the need for ongoing parental support and effective communication between the multidisciplinary team and families (Cools, Nordenström et al. 2018) and the provision of early psychological input for parents of young children with DSD (Sharkey, Bakula et al. 2018). Interestingly, despite greater future concerns, fathers of children with DSD reported less stress when attending Clinic Visits and administering and managing Medication required for their child's condition. Previous studies have shown that mothers and fathers have different perceptions with regards to their child's medical condition and often perceive their child's behaviour and emotions differently (Wolfe-Christensen, Fedele et al. 2014, Rolston, Gardner et al. 2015). These preliminary findings need to be confirmed in a larger sample size with a broad spectrum of DSD diagnoses. Approximately a quarter of cases of DSD are associated with co-morbidity (Cox, Bryce et al. 2014) and in our cohort, a third of children with DSD had other co-existing chronic conditions; the contribution of these co-morbidities to psychosocial well-being is not well established.

Parents of children with DSD and other endocrine conditions reported more Depression compared to reference data; however, our results did not show any significant difference for any of the four PROMIS scales (Anger, Anxiety, Depressive symptoms and Peer relationships) between parents of children with DSD and parents of children with other endocrine conditions. For many scales including Healthcare Communication & Information and Stigma, scores were similar for parents of children with DSD and other endocrine conditions, perhaps

implying that parents of children with DSD have more positive experiences than anecdotal experience may suggest. There was no significant difference in the number of Missed School Days between DSD and endocrine samples, however, this was an important scale for inclusion as previous studies have shown that children with chronic health conditions have greater school absenteeism and lower academic achievement than children who do not have chronic conditions (Wolfe 1985, Morgan, Mara et al. 2017).

8.6.2 Strengths

The rationale guiding the selection of the psychosocial scales to be included within our questionnaires was the same as that used for psychosocial assessments within the DSD-Translational Research Network (Sandberg, Gardner et al. 2017) (i.e., that the measures deliver actionable information for the individual patient/family). The purpose of the questionnaires was to proactively monitor both patient and family psychosocial adaptation at a specific point in time enabling rapid quantification and insight into the experiences of children with DSD and other endocrine conditions. Although the assessment approach adopted in selecting questionnaire items to characterise the adaptation of parents and young children with these chronic medical conditions was largely "non-categorical", the finalised questionnaires included items that focussed on issues specific to, and shared by young patients born with DSD, and their families, that are not otherwise covered by generic health-related quality of life measures.

8.6.3 Limitations

Questionnaires were introduced to patients following the clinic consultation; however, pre-clinic questionnaire completion and scoring would enable clinicians to review and act on results at the time of clinic visits, perhaps increasing their clinical utility. A quicker and simpler way of instantaneously displaying the results in the clinic setting could also increase the acceptability as well as the implementation of the tool (Schepers, Sint Nicolaas et al. 2017). The current report relates to evaluation of cross-sectional data from questionnaires collected from a large group of cases with a wide range of DSD conditions. In the future, it will also be valuable to obtain longitudinal data and observe the

temporal variation in outcomes in children with an assessment of factors (e.g. psychology services, timing of surgical interventions) that may influence a change in reported adaptation over time. As a larger sample of cases is collected with time, further psychometric validation including construct validity could be tested to determine the extent to which the questionnaires discriminate between groups that are known to differ on the items of interest.

The questionnaires were designed for parents of children under the age of 7 years, thus, there is a need to develop similar tools for older children and adults. Furthermore, the questionnaires were developed in the English language, thus, lack of availability of the questionnaires in other languages may have provided a barrier for completion for some parents. The translation of questionnaires into other languages and their validation in different countries will need to be addressed in the future (Gjersing, Caplehorn et al. 2010).

8.6.4 Summary

Parent reported outcome questionnaires are useful tools for collecting psychosocial data for parents and young children with DSD and this study showed that DSD was associated with greater parental concerns over the child's future than other endocrine conditions. Future work exploring the development and validation of short form parent-reported tools which further reduce respondent burden would facilitate a greater understanding of the effect of the child's condition on individual carers whilst providing longitudinal data on psychosocial morbidity in these patients and families and improve targeting of resources. A combination of generic and condition-specific scales may be more helpful than generic scales alone for identifying particular issues that need to be addressed in children with DSD and their families. Aggregating such data longitudinally and across multiple centres will create the opportunity for developing robust reference data which can be employed as clinical benchmarks useful in guiding a process of continuous quality improvement in the care of these patients and their families.

CHAPTER 9

Development and validation of short versions of the quality of life DSD questionnaires for parents of young children with DSD

9 Development and validation of short versions of the quality of life DSD questionnaires for parents of young children with DSD

9.1 Abstract

Background: Disorders/differences of sex development (DSD) may be associated with adverse psychosocial and psychosexual outcomes in adults. However, there is a paucity of information on health-related quality of life (HRQoL) outcomes in parents and children with DSD and a lack of instruments available for evaluating these outcomes. Recently, this has led to the development of parent self-report and proxy-report QoL questionnaires (QoL-DSD), validated measures for parents of young children with DSD, comprising 63 items within 13 scales and 25 items within 5 scales, respectively.

Objective: To develop short forms of the QoL-DSD questionnaires, optimising their use in routine clinic settings.

Methods: While retaining the original scale structure of the QoL-DSD questionnaires, short forms of the DSD-QoL parent self-report (QoL-DSD short PSR) and parent proxy-report (QoL-DSD short PPR) questionnaires were developed following exploratory factor analysis, using previous QoL-DSD data from 132 parents. Long and resulting short form online questionnaires were completed by 24 parents of children with DSD, under 7 years of age, attending endocrine and urology clinics at one tertiary hospital in Scotland.

Results: Item selection for the short forms — QoL-DSD Short PSR and QoL-DSD Short PPR — based on item factor loadings of >0.8, produced questionnaires containing 16 and 7 items, respectively. Twenty-four parents completed both long and short forms of the parent self-report for children aged <7 years, and a subset of these (n=19) also completed long and short forms of the parent proxy-report for children aged 2 to 7 years. Of the 24 target children, 21 (88%) were boys, 11 (46%) had proximal hypospadias and children had a median age of 3.6 years (range 0.1, 6.6). Overall, agreement was achieved between the short and long questionnaires in 11 out of 12 (92%) scales on the parent self-report and 4 out of 5 (80%) scales on the parent proxy-report. Parental feedback (n=24)

regarding the acceptability of the short versus long forms was evaluated using a 5-point Likert score: 75% of parents agreed the length of time (less than 3 minutes) taken to complete short forms was acceptable, compared with 67% of parents who agreed that the length of time taken to complete the long versions was acceptable. In addition, 41% of parents preferred the short forms compared with 21% whom preferred the longer version, 42% (versus 25%) stated a preference to complete the short forms should they be implemented routinely at clinic visits in the future.

Conclusion: Short forms of the QoL-DSD for parents of young children with DSD may be more acceptable for use in a routine outpatient setting to evaluate psychosocial distress experienced by young children with DSD and their caregivers. Further psychometric validation in a larger cohort is warranted.

9.2 Introduction

Disorders or differences of sex development (DSD) may be associated with adverse psychosocial and psychosexual outcomes in adults (Schützmann, Brinkmann et al. 2009, Stout, Litvak et al. 2010, Amaral, Inacio et al. 2015, Bennecke, Thyen et al. 2017). Studies have shown that a subset of parents of children with DSD experience high levels of depression, anxiety and stress related to concerns regarding their child's future (Pasterski, Mastroyannopoulou et al. 2014, Perez, Delozier et al. 2019, Ali, Macqueen et al. 2020). However, there is relatively little information regarding psychosocial functioning and health-related quality of life (QoL) outcomes in parents and young children with DSD (Duguid, Morrison et al. 2007, Rolston, Gardner et al. 2015, Meyer-Bahlburg, Khuri et al. 2017) and a lack of validated instruments available for evaluating these outcomes longitudinally in a routine clinic setting.

Distress relating to a child's diagnosis of a DSD may be secondary to uncertainty regarding a formal diagnosis or late diagnosis, clinical symptoms related to the DSD diagnosis including difficulties with urination, uncertainty regarding surgical outcomes, the need for life-long medical treatment, hospital visits and gender identity concerns (Suorsa, Mullins et al. 2015, Wisniewski 2017, Sharkey, Bakula et al. 2018, Roberts, Sharkey et al. 2020, Boucher, Alkazemi et al. 2022). Recent studies have shown that caregivers perceptions of uncertainty regarding their child's DSD are highest soon after a diagnosis is made, which is frequently prenatally or soon after birth in many cases of DSD, and illness uncertainty continues to predict both anxiety and depressive symptoms over time (Sharkey, Bakula et al. 2018). Thus, longitudinal assessment which can help to monitor health and quality of life status may help early identification of parental and child distress, providing opportunities for timely intervention and psychosocial support for parents and children. In addition, the development of DSD-specific health related QoL assessment tools are essential to aid clinical decision making, inform changes in practice and evaluate outcomes.

Until recently, there were no standardised measures to capture parental stressors in children with DSD. In 2016, health-related QoL questionnaires were developed for parents of young children with DSD (QoL-DSD) (Alpern, Gardner et al. 2017). Questionnaire items were derived from focus groups, including groups

of clinicians, parents and interviews. The steps of questionnaire development are outlined in Figure 9-1. In addition, psychometric properties were validated in 94 families and the questionnaires demonstrated adequate to good psychometrics, including internal consistency, test–retest reliability, convergent validity, and ability to detect known-group differences. The final questionnaires, the parent self-report (for parents of children aged from birth to under 7 years) and the parent proxy-report (for parents of children aged 2 to under 7 years) comprised 63 items (within 13 scales), and 25 items (within 5 scales), respectively. The study also found that parents reported greatest distress regarding early experiences, surgical management and future concerns regarding their child, highlighting the need for psychological support and follow-up in this cohort (Alpern, Gardner et al. 2017).

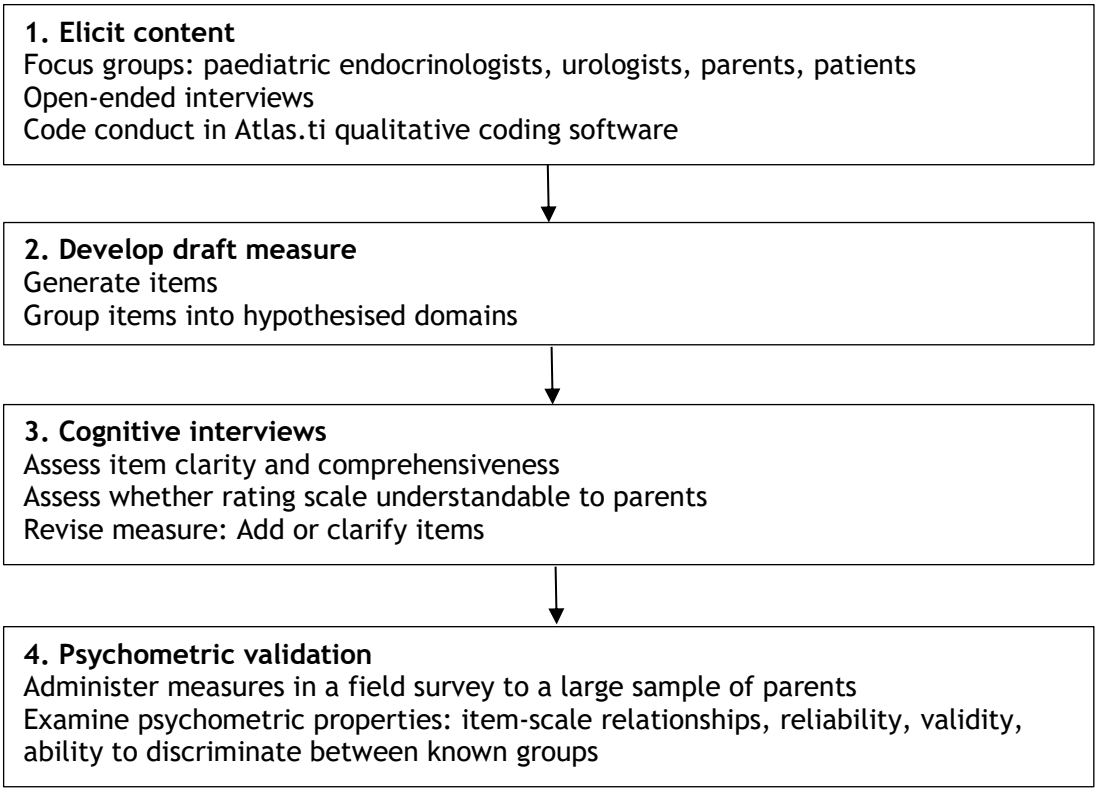


Figure 9-1. Steps of measure development (adapted from Alpern et al. 2016).
These steps are consistent with the Food and Drug Administration's (FDA) regulatory guidance on the development of patient-reported outcome measures.

9.3 Aims

The aims of this study were to:

- Develop short versions of the parent self-report and parent proxy-report QoL-DSD questionnaires

- Perform initial validation of the short questionnaires and determine the acceptability of the questionnaires amongst a cohort of parents of children with DSD

9.4 Methods

9.4.1 Ethics approval and consent

The study was approved by the West of Scotland Research Ethics Committee and written informed consent was obtained from study participants.

9.4.2 Participant selection

Parents or caregivers of children with DSD attending Endocrine/DSD or Urology clinics at the Royal Hospital for Children, Glasgow, between April 2021 and March 2022, were eligible for recruitment into the study. Patients were recruited from paediatric consultant-led clinics that included one endocrine/DSD clinic and four urology clinics.

To be enrolled into the study, parent/caregivers were required to provide valid written consent and have a child aged 0 to 6.9 years with any type of DSD. Parental/caregiver eligibility was restricted to those who fluency and literacy in English was such that they did not require a translator. One parent/caregiver completed the questionnaires per family.

9.4.3 Development of short questionnaires

For selection of items to be included in the short versions of the parent self-report (QoL-DSD Short PSR) and parent proxy-report (QoL-DSD Short PPR) questionnaires, raw data for 132 participants who had previously completed long

versions of the parent self-report and parent proxy-report QoL-DSD questionnaires (QoL-DSD Long PSR and QoL-DSD Long PPR) as part of a validation study were obtained (Alpern, Gardner et al. 2017). Exploratory factor analysis (EFA) with maximum likelihood and varimax rotation was performed using the previous data from those 132 participants. To maintain the original scale structure of the parent self-report and parent proxy-report long questionnaires, each scale was analysed separately and items with factor loadings (FL) of >0.8 were selected for consideration of inclusion into the short questionnaires. In the final step, clinical reasoning decisions via consultation with a team of paediatric endocrinologists and paediatric psychologists from the Department of Child Health, Glasgow and Child Health Evaluation and Research Center, Michigan, were incorporated to decide upon the items for inclusion into the short questionnaires.

9.4.4 Parental feedback

Participant feedback regarding the questionnaires was evaluated immediately following completion of the online questionnaires via an online form.

Participants were asked to score on a 5-point Likert scale (strongly agree/ agree/ neither agree nor disagree/ disagree/ strongly disagree) regarding the ease of completion of short and long questionnaires, comprehension, length of time for completion and preference (short/ long/ both/ neither) pertaining to questionnaires. A free text section was also available in the form for participants with additional comments relating to the questionnaires.

9.4.5 Administration of questionnaires

Participants were asked to complete short and long versions of the questionnaires on one occasion via a link sent by email. Parent self-report questionnaires were completed by parents of children aged from birth to 7 years old and parent proxy-report questionnaires were also completed by parents of children aged from 2 to 7 years old.

A computer-generated randomisation sequence using Microsoft Excel was applied to determine questionnaire allocations to participants, with half of the study

participants completing the short versions of the self-report and proxy-report questionnaires first, followed by the long versions of the self-report and proxy-report and vice versa. Following the process of informed consent and non-completion of questionnaires, a reminder email was sent to caregivers on one occasion within a two-week period with a link to complete the questionnaires.

All questionnaires and the feedback form were developed and hosted online via Webropol (https://webropol.com/), a secure online platform that is endorsed and supported by NHS Greater Glasgow & Clyde and NHS Scotland. All information within Webropol is kept in compliance with the UK Data Protection Act (2018) and General Data Protection Regulation (GDPR 2016/679).

9.4.6 Questionnaire scoring and statistical analysis

Scoring options were kept consistent within long and short versions of the parent self-report and parent proxy-report questionnaires; response options were categorised on a 5-point Likert scale assessing the level of agreement (always true/ usually true/ sometimes/ seldom true/ never true) or distress (a great deal/ moderate/ some/ a little/ none) in relation to questionnaire items. Not applicable (N/A) response options were available for items relating to surgery (e.g. child had not undergone surgery) medication (e.g. child does not take medication), if the item did not apply to child (e.g. administration of medication at school or day-care setting) or if the child was deemed too young to seek a response (e.g. talking with your child before a doctor's visit).

The items within each subscale were assigned values ranging from 0 to 4, a scale average was obtained, divided by 4 (the highest possible score) and multiplied by 100 to obtain an overall score for each scale. For each scale, a value ranging from 0 to 100 was obtained, with 100 representing the best (most optimal) score and better quality of life, and 0 representing the least optimal score. If a response of not applicable was provided, it was not included in the score.

The difference in overall scale scores between the short and long questionnaires amongst participants was determined and analysed using the Wilcoxon signed rank test. A p value of <0.05 was considered statistically significant. Concurrent validity was determined by the amount of agreement between the same items

within the short questionnaires and corresponding scales on the long questionnaires using Pearson's correlation coefficient.

9.5 Results

9.5.1 Development of short versions of parent self-report and proxy-report questionnaires

Following EFA, 18 items on the QoL-DSD Long PSR had FL >0.8 (Table 9-1). Of these 18 items, 13 items were selected for inclusion in the QoL-DSD Short PSR, along with an additional 3 items that had FL<0.8 but were selected based on clinical reasoning. The items based on clinical reasoning were: 1. I worry about talking to others about my child's condition because of how they might react (FL 0.7), 2. I am concerned about how my child's genitals look (FL 0.68), 3. Not knowing what to expect at doctor's visit (FL 0.6). The 3 items with factors loadings >0.8 that were dropped included two items in the healthcare communications and information scale which correspondeded with healthcare service evaluation and an item in the decision making scale enquiring regarding enough information about the child's condition to understand his/her needs.

Table 9-1. Parent self-report items on the QoL-DSD and factor loadings.
*Questionnaire items with factor loadings >0.8 are highlighted in bold.

Scales and corresponding items	Factor loading*
Decision Making	
Thinking about the past 2 weeks, how true are these statements for you:	
A1. I have enough information about my child's condition to understand what his/her needs are	**0.89**
A2. I have enough information about my child's condition to make decisions about his/her care	**0.94**
A3. I feel confident I made the best decisions about surgery for my child (including not having surgery)	0.36
A4. I agree with my child's doctors' current recommendations about care	0.53
Role Functioning & Family Activities	
In the past two weeks, how much stress did you experience:	0.62
B6. Fitting your child's care for his/her condition into your usual routines or daily activities	**0.87**
B7. Helping your child with toilet training or using the bathroom due to his/her condition	0.64
B8. Being protective of your child because of his/her condition	0.61
Gender Concerns	
Thinking about the past 2 weeks, how true are these statements for you:	
C9. I am confident my child's gender was identified correctly	**0.84**
C10. I feel comfortable with my child's gender behaviours (e.g., play interests, toy, and playmate choices)	0.59
C11. I am confident I am raising my child in the right gender	0.66
C12. I am confident my child feels comfortable with his/her gender	**0.87**
Social Functioning	
Thinking about the past 2 weeks, how true are these statements for you:	
D13. I feel disconnected from my family because of my child's condition	0.74
D14. My child's condition affects how often I go out socially	**0.87**
D15. I socialize with family and friends as much as I would like to	0.43
Emotional Functioning	
Thinking about the past 2 weeks, how true are these statements for you:	
E16. I feel happy	**0.99**
E17. I have difficulty sleeping at night	0.06
E18. I feel irritable	0.45
E19. I enjoy social activities	0.49
E20. I feel overwhelmed	0.41
E21. I feel upset	0.50
Future Concerns	
How true are these statements for you:	
F22. I am concerned about how my child's genitals will look	0.76
F23. I am concerned about how my child's genitals will function	**0.82**
F24. I worry about my child dying due to the condition and/or its treatment	0.42
F25. I worry that my child will have fertility issues (e.g., will not be able to have a biological child)	0.73
F26. I feel concerned my child will have social problems, like being teased about his/her condition	**0.80**
F27. I worry about my child's future relationships (e.g., dating, marriage)	**0.82**
F28. I worry that my child will not be comfortable with his/her gender as an adult	0.37
Healthcare Communication & Information	
Please answer the following questions while thinking about the present, even if your responses might have been very different in the past.	
G29. My child's doctors are knowledgeable about my child's condition	0.68
G30. I feel overwhelmed by the amount of information about my child's condition	0.33
G31. My child's doctors are sensitive (i.e., supportive, considerate) when communicating with me about my child's condition	**0.85**
G32. I hear conflicting medical information about my child's condition	

G33. My child's doctors explain everything clearly	**0.89**
G34. I feel stressed when dealing with health insurance and/or medical costs	0.21
Talking to Others	
How true are these statements for you currently:	
H35. I feel comfortable talking with my child about his/her condition	**0.92**
H36. I feel comfortable talking to close family members about my child's condition	0.57
H37. I am comfortable explaining my child's needs (e.g., diaper changing, using the bathroom) to people other than family	0.63
H38. I am not sure how much to tell others about my child's condition	0.70
H39. I worry about talking to others about my child's condition because of how they might react	0.76
Medications	
Thinking about the past 2 weeks, how much stress do you experience:	
If your child does not take any medications for his/her condition, please go to the next section (J).	
I40. Remembering to give your child his/her medications related to the condition (e.g., hormones such as cortisone, prednisone, or testosterone)	0.67
I41. Making sure your child receives his/her medications for the condition when he/she is away from you (e.g., at school or daycare)	**0.82**
I42. Giving your child his/her medication	0.76
I43. Managing the side effects of your child's medication	0.59
Surgery	
Thinking about your child's last surgery for his/her urogenital condition, how much stress did you experience:	
If your child has not had any surgeries, please go to the next section (K).	
J44. Talking with your child before the surgery	0.39
J45. During the surgery	**0.98**
J46. After the surgery (e.g., dealing with your child's need for extra care, wondering about the outcome)	0.61
Doctor's Visits	
Thinking about your child's last doctor's visit for his/her condition, how much stress did you experience:	
K47. Talking with your child before the visit	0.74
K48. Not knowing what to expect at the visit	0.60
K49. Managing your child's behaviour during the visit	**0.85**
Earliest Experiences	
Thinking back to the time when your child's condition was first noticed, how much stress did you experience:	
L50. Not knowing whether your child was a boy or a girl	0.66
L51. Waiting for your child's diagnosis	0.72
L52. Receiving your child's diagnosis	**0.88**
L53. Thinking about how this condition might affect your child	0.79
L54. Thinking about how this condition might affect you and your family	0.70
Clinical Items	
Thinking about the past two weeks, how true are these statements for you:	
M1. I am concerned about how my child's genitals look	0.68
M2. Because of the condition, I have disagreements with family members about whether I should raise my child as a typical boy or girl	0.03
M3. I worry I could have another child with the same condition	**1.00**
M4. I feel comfortable talking to my partner/spouse about my child's condition	0.26

Following EFA, 6 items on the QoL-DSD Long PPR had FL >0.8 (Table 9-2). Of these 6 items, 4 items were selected for inclusion in the QoL-DSD Short PPR and an additional 3 items were selected based on clinical reasoning. The items based on clinical reasoning were: 1. My child experiences physical pain when urinating (FL 0.69), 2. My child has concerns about going to a public restroom because of

his/her condition (FL 0.62) and 3. Stress experienced in relation to taking medication. Two items with factor loadings >0.8 in the gender concerns (My child has commented on being unhappy with how/his genitals look and function) and medical care (Stress experienced having doctors examine child's genitals) scales were omitted as these were subsumed by other selected items within these scales.

Table 9-2. Parent proxy-report items on the QoL-DSD and factor loadings.
*Questionnaire items with factor loadings >0.8 are highlighted in bold.

Scales and corresponding items	Factor loading*
Physical Functioning	
Thinking about the past 2 weeks, how true are these statements for your child:	
A1. Due to his/her condition, my child experiences physical pain when urinating	0.69
A2. My child experiences physical pain due to his/her condition other than during urination	0.25
A3. My child urinates differently than other children of his/her same gender (e.g., where urine comes from)	0.13
A4. Due to his/her condition, my child has difficulty with toilet training (if toilet trained: he/she has difficulty using the bathroom)	0.25
A5. My child's condition affects his/her activities (e.g., play dates, swimming, sports)	**0.96**
Gender Concerns	
B6. My child's play interests match his/her gender	0.45
B7. My child's playmate choices match his/her gender	0.49
B8. My child has commented on being unhappy with how his/her genitals look and function	**0.92**
B9. My child feels different from other children of the same gender due to his/her condition	**0.94**
Socio-Emotional Functioning	
Thinking about the past 2 weeks, how true are these statements for your child:	
C10. My child has concerns about going to a public restroom because of his/her condition	0.62
C11. My child is able to make friends	0.43
C12. My child adjusts well to new social situations	0.72
C13. My child seems happy	0.59
C14. My child gets into fights with other children (e.g., with siblings or peers)	0.37
C15. My child has as much fun as other children	0.80
C16. My child seems withdrawn	0.69
C17. My child has more difficulty being away from parents than other children his/her age	**0.84**
Medical Care	
Thinking about your child's last doctor's visit or medical procedure, how much stress did your child experience:	
D18. Before the doctor's visit or procedure (e.g., on the way to the appointment, in the waiting room)	0.65
D19. Having doctor's visits (e.g., physical exams)	**0.95**
D20. Having doctors examine his/her genitals	**0.85**
D21. Having medical procedures (e.g., blood draws)	0.56
D22. After the visit or procedure	0.56
Clinical Item	
Thinking about the past two weeks, how much stress does your child experience:	
E1. Taking medication for his/her condition	-

A total of 16 items within 13 scales were included in the QoL-DSD Short PSR and a total of 7 items within 5 scales were included in the QoL-DSD Short PPR (Table 9-3). Correlations between scale scores on the short and the long questionnaires ranged from 0.50 to 0.89 in 9 out of 12 scales on the parent self-report questionnaire and were 0.60 in 2 out of 5 scales in the parent proxy-report questionnaire.

Table 9-3. Items on the short questionnaires and corresponding scales on the QoL-DSD.

Parent self-report			
16 Items on short version (QoL-DSD Short PSR)	Corresponding scales on long version (QoL-DSD PSR)	*n*	*r**
• I have enough information about my child's condition to make decisions about his/her care	Decision Making	21	0.50
• Fitting your child's care for his/her condition into your usual routines or daily activities	Role Functioning & Family Activities	24	0.23
• I am confident my child's gender was identified correctly	Gender Concerns	24	0.05
• My child's condition affects how often I go out socially	Social Functioning	24	0.37
• I feel happy	Emotional Functioning	24	0.71
• I feel concerned my child will have social problems, like being teased about his/her condition	Future Concerns	24	0.70
• I worry about my child's future relationships (e.g., dating, marriage)			
• I feel comfortable talking with my child about his/her condition	Talking to Others	24	0.72
• I worry about talking to others about my child's condition because of how they might react			
• Making sure your child receives his/her medications for the condition when he/she is away from you (e.g., at school or daycare)	Medications	5	0.74
• During the surgery	Surgery	13	0.60
• Not knowing what to expect at the visit	Doctor's Visits	24	0.89
• Managing your child's behaviour during the visit			
• Receiving your child's diagnosis	Earliest Experiences	24	0.76
• I am concerned about how my child's genitals look	Clinical Items	24	0.80
• I worry I could have another child with the same condition			
Parent proxy-report			
7 Items on short version (QoL-DSD Short PPR)	Corresponding scales on long version (QoL-DSD PPR)	*n*	*r**
• Due to his/her condition, my child experiences physical pain when urinating	Physical Functioning	19	0.34
• My child's condition affects his/her activities (e.g., play dates, swimming, sports)			
• My child feels different from other children of the same gender due to his/her condition	Gender Concerns	5	-
• My child has concerns about going to a public restroom because of his/her condition	Socio-Emotional Functioning	9	0.56
• My child has more difficulty being away from parents than other children his/her age			
• Having doctor's visits (e.g., physical exams)	Medical Care	19	0.57
• Taking medication for his/her condition	Clinical Item	5	0.25

*r; Pearson's correlation coefficient

9.5.2 Response rates

The response rate was 69% (24/35) for caregivers that completed the study questionnaires and 66% (24/66) for caregivers that were approached to participate in the study and provided with the study information sheet (Figure 9-2). In total, 84 questionnaires, including 48 QoL-DSD Short and Long PSRs and 36 QoL-DSD Short and Long PPRs, were available for analysis.

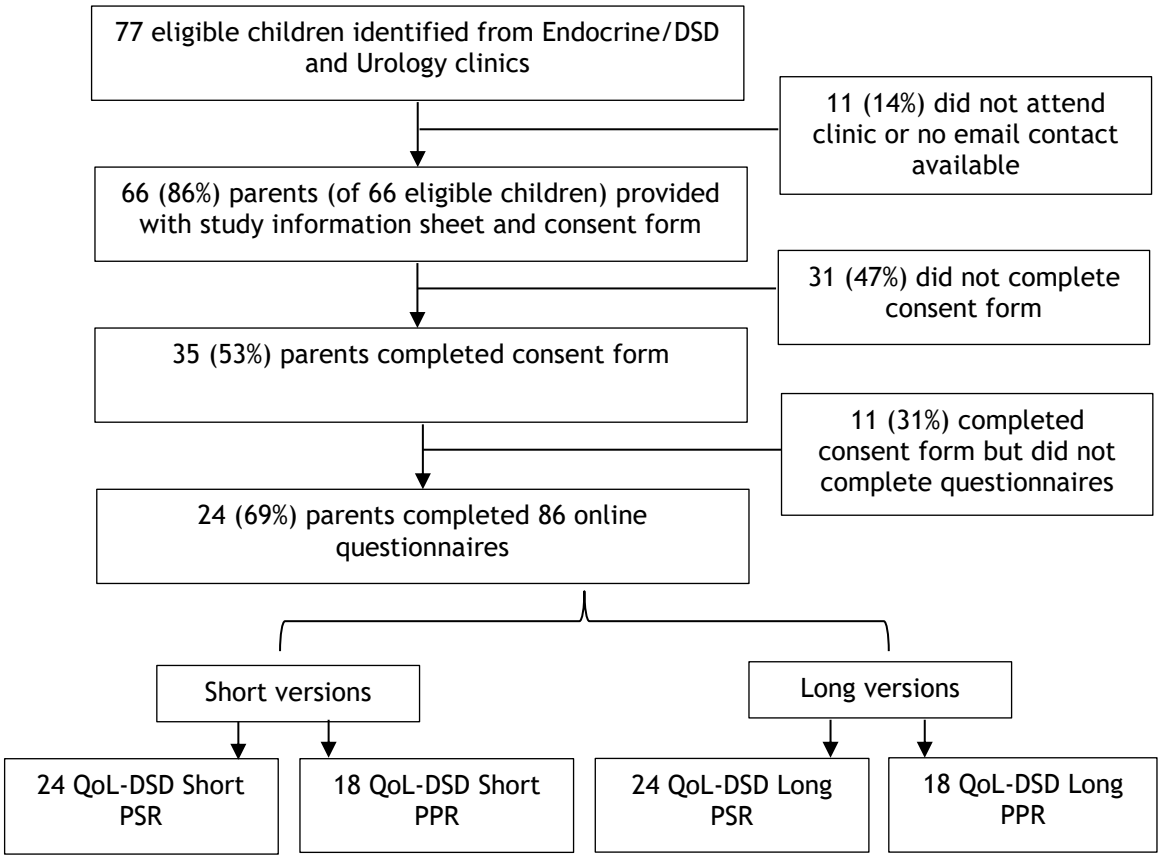


Figure 9-2. Flow diagram of response rates.

9.5.3 Participant characteristics

Caregivers

Twenty-four caregivers of 24 children completed 84 questionnaires (Figure 9-2). Of the 24 caregivers, 19 (79%) were mothers, 4 (17%) were fathers and 1 was a foster carer. Half of all caregivers were aged 35-44 years, 9 (38%) were aged 25-34 years, 1 (4%) was 16-24 years, 1 (4%) was 45-54 years and 1 caregiver preferred to not disclose their age. Of the 24 caregivers, 17 (71%) were married,

3 (13%) were not married, 2 (8%) were in a registered civil partnership and 2 (8%) preferred not to disclose their marital status. Of the 24, 9 (38%) had degree-level education (Bachelor's or Master's degree), 6 (25%) had tertiary education, 5 (21%) were educated to secondary level, 1 (4%) had early childhood education, 2 (8%) preferred not to answer and 1 (4%) specified that they had received a level of education not classified.

Children

Of the 24 children, 21 (88%) were boys and 3 (12%) were girls. Of the 21 boys, 11 (46%) had proximal hypospadias, 5 (21%) had distal hypospadias and 5 (24%) had other DSD diagnoses including partial gonadal dysgenesis (n,1), bilateral undescended testes (n,1), hypogonadotrophic hypogonadism (n,1), Klinefelter syndrome (n,1) and CAH (n,1). All 3 girls had a diagnosis of CAH. The median age of children was 3.6 years (range 0.1, 6.6). Fifteen children were recruited from the endocrine/DSD clinic and 9 were recruited from the paediatric urology clinic.

9.5.4 Short versus long questionnaires

The overall scale scores for the 12 scales on the QoL-DSD Short PSR were compared with concurrent scales on the QoL-DSD Long PSR (Figure 9-3). There was no significant difference in overall scale scores for 11 out of 12 (92%) scales (all p >0.05), with a significant difference noted only in the clinical items scale (p 0.00).

In addition, the overall scale scores for the 5 scales on the QoL-DSD Short PPR were compared with concurrent scales on the QoL-DSD Long PPR (Figure 9-4). Upon comparing the QoL-DSD Short PPR with the long version, there was no difference in overall scale scores for 4 out of 5 (80%) scales (all p>0.05), with a significant difference noted only in the physical functioning scale (p=0.03).

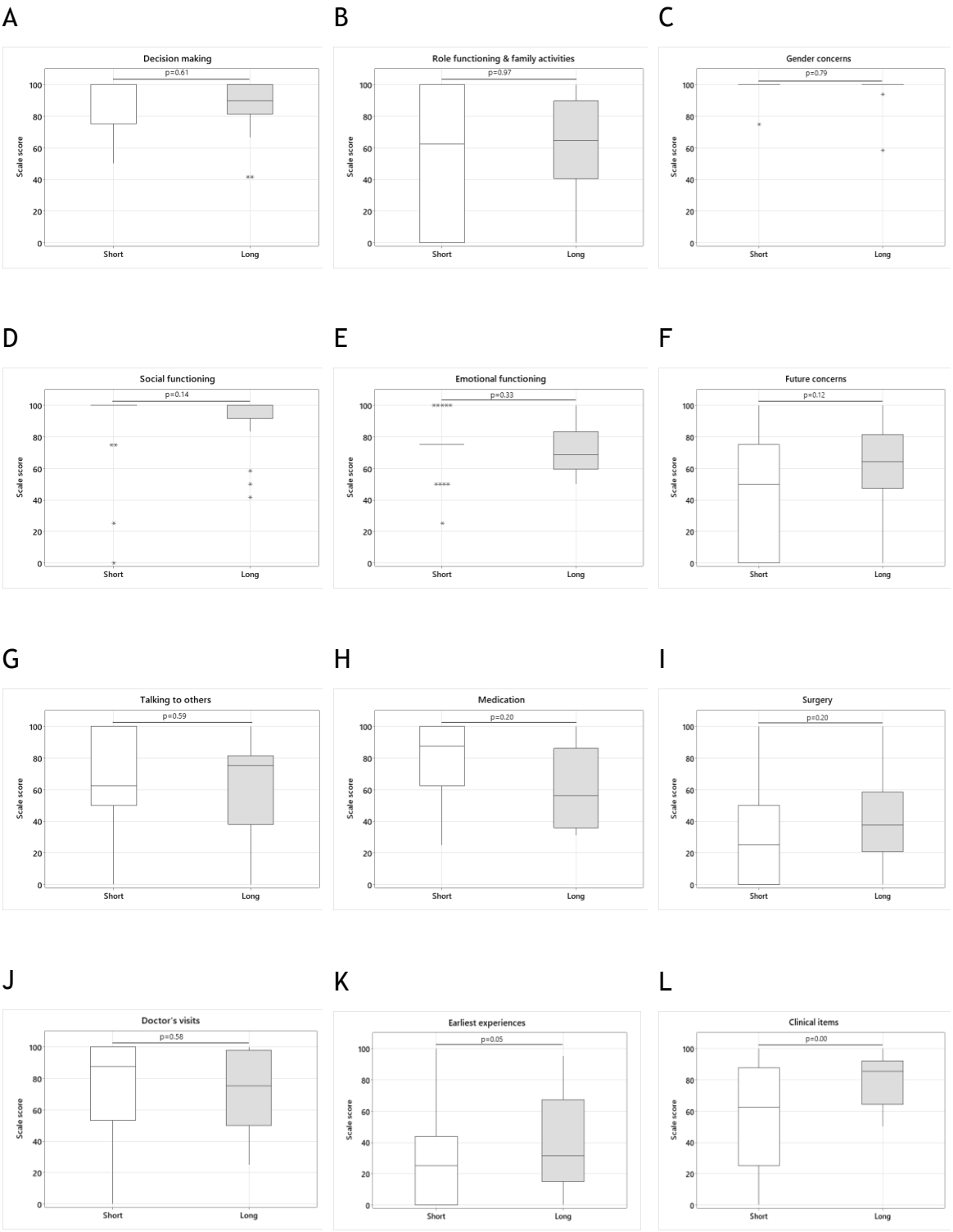


Figure 9-3. Comparison of overall scale scores for the QoL-DSD Short PSR and the QoL-DSD Long PSR.
There were no differences in the scores in the scales of decision making (A), role functioning and family activities (B), gender concerns (C), social functioning (D), emotional functioning (E), future concerns (F), talking to others (G) or medication (H), surgery (I), doctor's visits (J), earliest experiences (K).

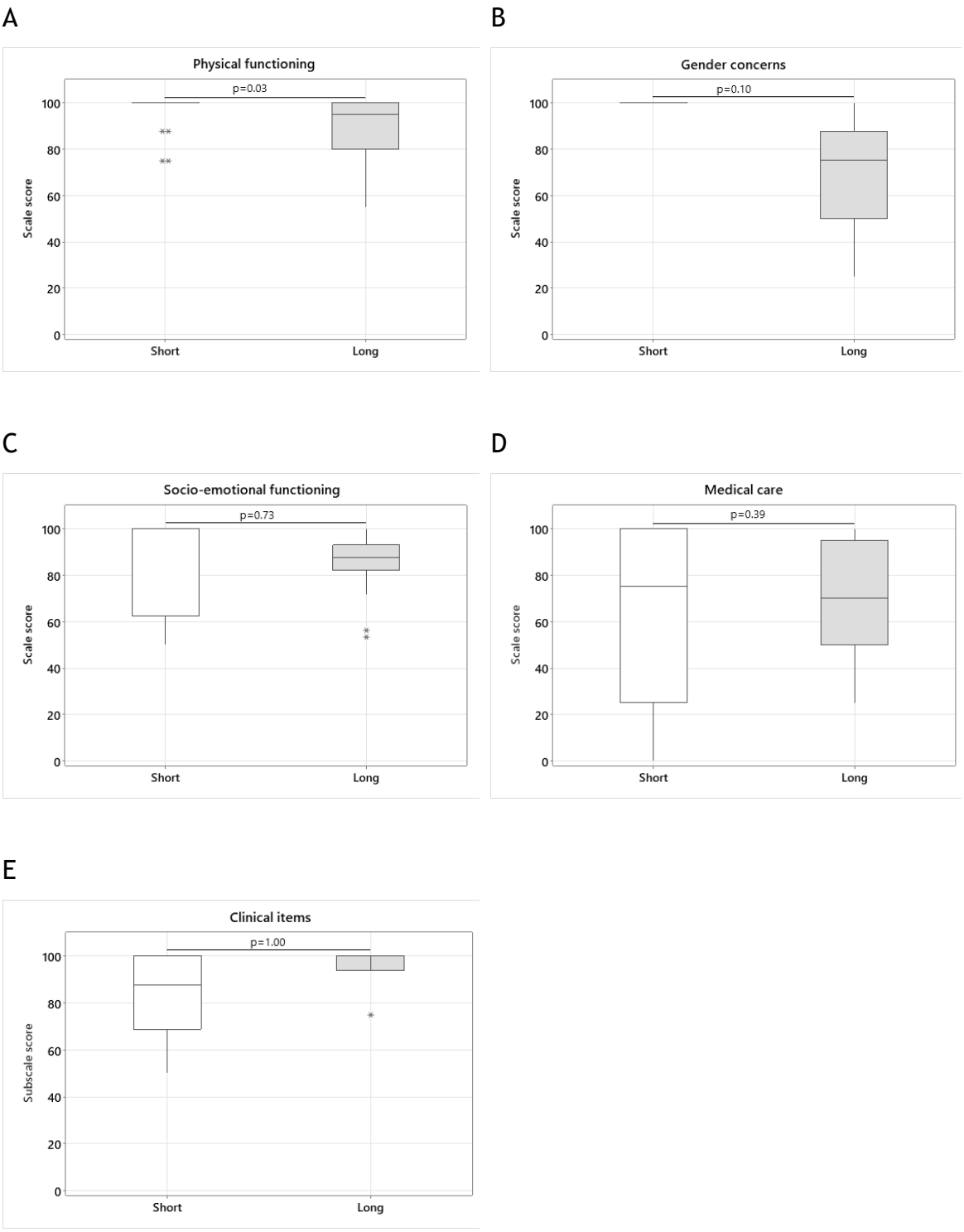


Figure 9-4. Comparison of overall scale scores for QoL-DSD Short PPR and QoL-DSD Long PPR.
There were no differences in the scores in the scales of gender concerns (B), socio-emotional functioning (C), medical care (D) and other clinical item (E).

9.5.5 Parental views

Regarding comprehension and understanding of the questionnaires, around 70% of participants agreed that both short versions and long versions of the questionnaires were easy to understand. Eighteen (75%) and 16 (67%) participants agreed that time for completion of short and long questionnaires was acceptable, respectively; of these, 12 (50%) versus 9 (38%) strongly agreed, respectively (Figure 9-5).

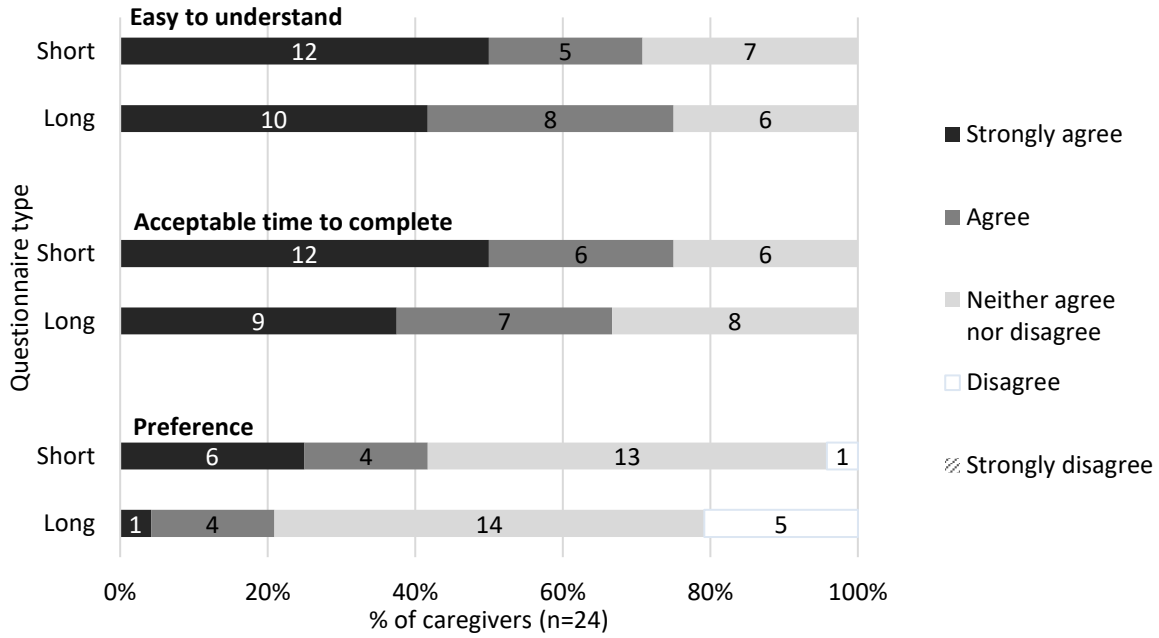


Figure 9-5. Participant feedback.
The numbers within each bar represent the number of caregivers (n).

Ten (42%) participants preferred the short version of the questionnaires, compared with 5 (21%) who preferred the long version. Ten (42%) stated a preference for completing the short questionnaires in the future should these be implemented as a routine screening tool, compared with 6 (25%) who stated a preference for the long questionnaires.

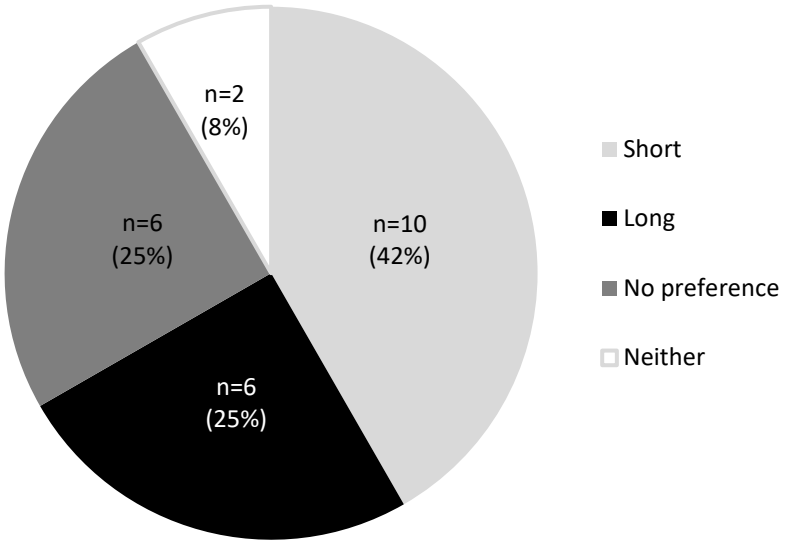


Figure 9-6 Participant preference regarding implementation of questionnaires as a routine screening tool.

9.6 Discussion

9.6.1 Key findings

This is the first study to report the development and first phase of validation of short PRO questionnaires that evaluate the health-related quality of life amongst parents and caregivers of young children with DSD.

Item reduction resulted in significantly shortened versions of the long questionnaires, with a 16-item short version of the QoL-DSD PSR and a 7-item short version of the QoL-DSD PPR. Short questionnaires were compared with long questionnaires which had been validated in a previous study (Alpern, Gardner et al. 2017). Our results showed that short questionnaires were largely representative of the long questionnaires. There was no significant difference in the overall scale scores when comparing short with long questionnaires in 11 out of 12 (92%) scales in the parent self-report. In addition, there was no significant difference in the overall scale scores when comparing short with long questionnaires in 4 out of 5 (80%) scales in the parent proxy-report. The differences in overall scale scores in the clinical items and physical functioning scales in the self-report and proxy-report questionnaires, respectively, may be attributed to the reduced number of items included within the final scales in these short questionnaires. Varied themes within select items resulting in different responses to items within each scale and the applicability of questions in relation to individual DSD conditions may also account for these differences. Furthermore, the age applicability of specific questions is another possible factor, almost half of the children for whom the proxy-reports were completed aged 2 to 4.9 years. Within the physical functioning scale of the short parent proxy-report, 2 out of 5 items were selected for inclusion, this included one item on physical pain experienced when urinating and a second item on the effect of the child's DSD condition on his/her activities (e.g. play dates, swimming, sports). The long version of the questionnaire had 5 items in the latter scale with 4 out of 5 items enquiring regarding urinary problems (pain, urinating differently from other children, difficulty with toilet training), thus, differences on this scale may be attributed to both the applicability of the items in relation to the DSD condition and age of the child. All items from the two scales where a statistical significant difference between the short and long questionnaires was

identified will be included in the final version of the short questionnaires that will undergo further validation.

The time to complete each short questionnaire was estimated at around 1 minute and around 5 minutes were required for completion of each long questionnaire. Thus, respondent time burden was significantly reduced with short questionnaires and three-quarters of caregivers agreed that the short questionnaires had an acceptable time for completion. Overall, almost half of caregivers stated a preference to complete the short questionnaires compared with less than a quarter who stated a preference for the long questionnaires. In addition, almost half of caregivers stated a preference to complete the short questionnaires should these be implemented as a routine screening tool in the future, suggesting that short versions may be more acceptable for use in routine outpatient setting.

9.6.2 Strengths

Regarding the short questionnaires, the response options were categorised on a 5-point Likert scale, the scale structure and wording of the questions remained consistent with the previously validated long questionnaires. This facilitated a direct comparison between short and long questionnaires. Retaining the same scale structure as the original long questionnaires also ensured preservation of the themes identified as important via previous research and focus groups (Alpern, Gardner et al. 2017). Another potential advantage of multi-item scales within questionnaires are more reliable findings and a greater distribution of responses to capture varying degrees of satisfaction.

Short questionnaires offer ease of administration and data entry by participants. It may also be the case that if concerns are identified via the short questionnaires in a routine clinic setting, that the provision of longer, more detailed questionnaires could be administered subsequently, allowing more targeted interventions including psychology input to improve outcomes.

The inclusion of participant demographic information in the questionnaires including caregiver age and educational status were also important. Previous studies have shown that the level of decisional regret (distress or remorse after

a healthcare decision) was related to factors including having a bachelor's level of education, increased levels of illness uncertainty preoperatively and persistent illness uncertainty at 12 months after genitoplasty for atypical genitalia (Ellens, Bakula et al. 2017, Roberts, Sharkey et al. 2020). Other factors including ethnicity that may influence responses would also be useful to evaluate in future studies as previous studies have shown that some groups including ethnic minority groups are less willing or able to participate in surveys (Ahlmark, Algren et al. 2015).

9.6.3 Limitations

Within the short and long questionnaires, some items within scales had ‘not applicable’ response options and these were not included in the overall scale scores. Some children were not taking medication, had not had previous surgery for their DSD condition or were too young for responses to be provided, thus the overall number of responses for individual scales was variable. There was also the potential for individuals completing these questionnaires to omit items or become confused by being asked similar questions phrased in a different manner, resulting in a reduction in reliability. Nevertheless, exploring potential multiple dimensions of a single concept is important.

Interestingly, when comparing response rates of this study to a pilot exercise performed previously at our centre (Ali, Macqueen et al. 2020), response rates were much lower. Only a third of parents of a child with DSD completed the PRO questionnaires when performed as part of a study compared to almost 90% of caregivers that completed PRO questionnaires when provided as part of routine healthcare service evaluation. Thus, the study sample may have introduced non-response bias. The reasons for the lower response rates require further exploration but may be attributed to an increased burden on study participants when reviewing study documents and completing consent forms even prior to the completion of the study questionnaires.

Almost 80% of caregivers completing questionnaires were mothers. Previous studies have shown that both mothers and fathers have greater future concerns about their child’s DSD condition (Ali, Macqueen et al. 2020), whilst other studies have shown that mothers experience greater levels of distress in relation

to their child's DSD condition compared with fathers (Wolfe-Christensen, Fedele et al. 2014, Rolston, Gardner et al. 2015, Wolfe-Christensen, Wisniewski et al. 2017). Similar to children with other chronic conditions, this may be due to mothers assuming the burden of care for their affected child (Hirose and Ueda 1990, Carmassi, Dell'Oste et al. 2020). Parental stress may lead to higher levels of anxiety, depression and reduced quality of life (Traino, Roberts et al. 2022), thus, negatively impacting a child's well-being. Therefore, it would be important to further investigate parental differences by the inclusion of a larger sample of male caregivers in future studies.

Over 80% of children in this study were male. Previous studies have suggested that the gender of the child is also important in predicting parental stress, with parents of boys at increased risk for psychosocial difficulties (Kirk, Fedele et al. 2011, Wolfe-Christensen, Wisniewski et al. 2017). This may be attributed to a lack of clinical diagnosis or the necessity for two-stage surgeries for many boys. Therefore, further evaluation of the association of a child's gender and the degree of parental distress is also warranted in the future.

9.6.4 Summary

Further quantitative measurements of the psychometric properties of the short questionnaires in a larger cohort, including test-retest reliability and group construct validity, will result in valid and reliable measures, facilitating their use in routine clinic settings. It may also be advantageous to perform future PRO studies in different languages in a range of international settings and amongst older age groups to determine differences in psychosocial outcomes. Using the data generated, it will be possible to investigate the extent of psychosocial distress experienced by young children with DSD and their families, to implement early psychosocial screening and to establish clinical benchmarks for these outcomes.

CHAPTER 10

Summary and future directions

10 Summary and future directions

10.1 Research questions and key findings

The focus of this thesis was on the evaluation of real-world data for rare endocrine conditions to facilitate the development of clinical benchmarks, with the overall aim of improving patient care. Firstly, I evaluated the current landscape of international registries for rare endocrine conditions, aiming to identify the levels of awareness and participation in rare disease registries amongst expert centres (Chapter 2). Subsequently, with the recent global expansion in the number of registries, it was imperative that a process for quality evaluation of registries was developed and I investigated the consensus amongst the rare disease community regarding the quality criteria that should be considered as essential for a disease registry (Chapter 3). In Chapter 4, I explored web-based methods of capturing the presentation of DSD and other rare endocrine conditions, using the EuRRECa e-REC platform to gather information on the epidemiology of these conditions. In addition, I studied the presentation of DSD at a national level in Scotland (Chapter 5) via a prospective electronic survey of clinicians within managed clinical networks to seek further information regarding the occurrence of atypical genitalia. Using DSD and CAH as models of care of rare endocrine conditions, I investigated the occurrence of acute AI related adverse events and factors which may influence these outcomes in a large international cohort of children with CAH using data from the I-CAH registry (Chapter 6). Next, I performed an international survey to determine the level of consensus in the definition and management of acute AI related adverse events amongst I-CAH centres (Chapter 7). Finally, I investigated the use of PRO tools to evaluate psychosocial outcomes amongst parents of young children with DSD and CAH (Chapter 8) followed by the development and initial validation of short PRO questionnaires that could be used in routine outpatient settings (Chapter 9).

The key findings are summarised as follows:

1) There are gaps in the awareness and use of existing international registries amongst expert centres.

Chapter 2 highlighted that international registries exist for 78% of conditions currently covered within Endo-ERN. However, Endo-ERN expert centres were aware of less than half of these registries or did not use these registries despite being aware of them. For some groups of conditions such as DSD, there was a high level of awareness and participation in international registries which may be attributed to the presence of already established secure platforms such as the I-DSD/I-CAH registries. Interestingly, conditions for which future registry development was considered high priority by expert centres were often those for which international registries already existed and this may reflect lack of awareness of existing registries.

2) There are high levels of consensus amongst the rare disease community for the quality criteria that should be considered as essential for a disease registry.

As demonstrated in Chapter 3, over 95% of respondents representing over 50 rare disease registries were in agreement that essential quality criteria should include establishment of a good governance system, procedures for checking data quality, an IT infrastructure complying with FAIR principles, procedures for authorised user access and erasing personal data, data breach procedures and a web interface. A contemporary survey of registry leaders representing international registries for rare endocrine conditions identified from a previous mapping exercise (Chapter 1) also showed that over 80% of registries that performed self-assessment of quality criteria met the proposed quality standards.

3) Epidemiological studies performed through e-surveillance methods can facilitate the creation of clinical benchmarks to understand the occurrence of rare endocrine conditions including DSD.

Chapter 4 showed that e-REC was a simple platform that could be used for capturing brief information on new encounters of rare endocrine conditions and had gained increasing acceptability over the over the study period of 3.5 years. Results showed an increase in the total number of centres reporting cases, with an increase in the total number of cases reported across most groups of rare endocrine conditions in both adults and children. Despite comparable numbers

of centres reporting paediatric and adult cases, a higher number of cases were reported in adults compared with children, 9,715 versus 4,243 cases, respectively. In addition, a greater number of suspected cases were reported in children compared with adults, 16% versus 11% of cases, respectively. Sex development conditions comprised 40% of all reported cases in children, with transgender cases accounting for almost 60% of cases in this group. By examining the centres that reported regularly and frequently, I was able to estimate the annual occurrence rates of these conditions presenting to centres within a network such as Endo-ERN, thus, these figures can be used as a clinical benchmark.

Chapter 5 demonstrated that atypical genitalia requiring specialist input are rare in term newborns, with a birth prevalence of 1 in 3,318 and sex assignment is delayed beyond birth in only a third of cases. This study provided new clinical benchmarks for comparing and improving the delivery of care in centres that manage these rare conditions.

4) Data from the I-CAH registry show that there is wide variability in the reported occurrence of AI related adverse events in children and these data can be used to formulate clinical benchmarks in CAH care.

As shown in Chapter 6, there is wide variability in the reported occurrence of SDE and AC between centres. These data also showed that there are specific factors which may place children at higher risk of AI related adverse events, including younger age, male sex and patients receiving normal or lower doses of glucocorticoids. In addition, these data highlighted the need to improve and standardise the definition of SDE and AC amongst expert centres. Chapter 7 demonstrated that there is consensus amongst the international community regarding the criteria used for the diagnosis of AC that can lead to greater benchmarking of care, paving the way forward for the development of more uniform guidance.

5) DSD are associated with greater parental concerns over a child's future than other endocrine conditions and PRO questionnaires can be routinely used to evaluate psychosocial distress experienced by young children with DSD and their caregivers.

Chapter 8 demonstrated that both mothers and fathers of children with DSD reported greater future concerns in relation to their child's condition than parents of children with other endocrine conditions. To evaluate the extent of psychosocial distress experienced by young children with DSD and their caregivers in a routine clinic setting, I developed short PRO questionnaires using a combination of statistical and theoretical methods (Chapter 9). Short questionnaires were largely representative of the previously validated long questionnaires, with agreement between the short and long versions achieved in 92% of scales on the parent self-report and 80% of scales on the parent proxy-report. Parental feedback demonstrated greater acceptability of short questionnaires compared with long questionnaires.

10.2 Challenges of this thesis

1) Methodological limitations of survey research

A potential for response bias amongst respondents and reporting centres may limit the precision of the conclusions drawn from the collected data. It is possible that those responding to surveys may have had a greater level of adherence to proposed quality standards for registries (Chapter 3) or proposed standards of care for children with CAH (Chapters 6 and 7). In addition, clinician or respondent retrospective recall bias with regards to newly encountered cases of rare endocrine conditions including DSD (Chapters 4 and 5), subjective reporting and a potential for under- or over-reporting of AI related adverse events (Chapter 6) are limitations that should be considered. In the latter study, there was also the potential for selection bias as not every patient at a centre with CAH had been included in the I-CAH registry and amongst those that had been included, a variable number had sufficient data to be included in the study. Due to the small number of AC events overall, the multilevel regression model parameters could not be reliably estimated. Thus, further real-world data collection in larger cohorts on the occurrence of AI related adverse events and reputed risk factors will facilitate temporal associations, providing the opportunity to confirm potential causality.

The provision of a small number of quality criteria considered essential for rare disease registries (Chapter 3) and the collection of a small core dataset within e-REC with information collected only on the details of the reporter, reporting centre and the number of cases of each rare endocrine condition encountered (Chapter 4) may also be considered limitations. The provision of more detailed information would have been advantageous, however, a balance needed to be struck between maximising the information available and reducing respondent burden, particularly in the e-REC study where clinicians were receiving an invitation on a monthly basis. With a preponderance of responses from specialist centres within Europe in the studies outlined in this thesis, longitudinal collection of more detailed information with the inclusion of a greater number of respondents from the international community would offer opportunities to strengthen the current findings.

2) Recruitment and data analysis for studies investigating PROs in DSD

With reference to the studies investigating PROs in DSD (Chapters 8 and 9), parent recruitment was limited to those whose primary language was English and those whom did not require an interpreter in the clinic setting. Recruitment was undertaken within DSD and urology clinics in one tertiary hospital. As this research was ongoing at the time of the COVID pandemic, a considerable amount of time was spent self-learning new statistical methodology including exploratory factor analysis and principal component analysis for the development of the short questionnaires. Moreover, study questionnaires were converted from a paper format to an online format, widening the scope for participation for those families unable to attend face to face clinic appointments. Results showed that when performed as a study, only a third of parents of a child with DSD completed a PRO, compared with 86% of parents who completed questionnaires when they were performed as part of routine health service evaluation. Reasons for not participating require further exploration and may include the increased length of time associated with reading study paperwork and completing consent forms.

10.3 Future directions

10.3.1 Quality evaluation of rare disease registries

The EuRRECa project aimed to address the gaps raised in the work described in Chapter 2 by promoting the awareness of registries amongst patients and professionals and facilitating interaction between existing and new disease registries. In addition, signposting health care providers and patients to high quality detailed disease registries was one of the central aims of EuRRECa. The quality criteria that should be considered as essential for a detailed disease registry were outlined in Chapter 3 and the simple self-assessment quality evaluation tool developed from this work will be incorporated into the EuRRECa website (http://eurreca.net) and completed by registries seeking affiliate status. The use of the standardised set of quality criteria will enable rare disease registries such EuRRECa to develop a pathway of vetting high quality registries with whom data can be shared. In the future, this quality evaluation tool may also be used by other networks to collaborate and engage with registries of an optimal quality, and by rare disease registries to enable assessment and improvement of organisational aspects ensuring their sustainability.

10.3.2 The e-reporting platform for rare endocrine conditions (e-REC)

As shown in Chapter 4, with almost 15,000 new encounters reported in e-REC since July 2018 across all Endo-ERN condition groups, the data within e-REC make it a valuable resource for future research seeking further understanding of the core features and presentation of these rare endocrine conditions. The development of secondary surveys would enable the collection of a small amount of data for quality assurance and for understanding the presentation, clinical outcome or extent of morbidity in specific groups of patients with rare endocrine conditions, including conditions affecting sex development (http://eurreca.net/secondary-surveys/).

Chapter 4 highlighted estimated annual occurrence rates for the groups of rare endocrine conditions within Endo-ERN. Further studies defining the epidemiology of these conditions with monitoring of the trends are vital due to implications

for planning of health service delivery models. Going forward, it would also be helpful to compare the reported data to the actual hospital activity data to ascertain the level of reporting accuracy.

10.3.3 AI related adverse events in children with CAH

Chapter 6 showed the potential of the I-CAH registry to act as a tool for creating clinical benchmarks in CAH care in children. The overall median rate of occurrence of SDE and AC were described for the 34 centres participating in the study, with benchmarks also defined for countries categorised as HIC or LMIC. At the conclusion of the project, participating centres were very interested to find out the median rate of these adverse events at their own centre. Based on this work, I-CAH centres were provided with an individualised report with information on the quality of care at their centre, as reflected by SDE and AC, in comparison to the overall global benchmark and the benchmark adjusted for whether their centre was from a HIC or LMIC. Within the report, I was also able to provide each centre with information on the quality of their data in the registry, as reflected by the number and median age of cases registered and percentage of cases with clinic visits data fields completed. Future work will incorporate a 3-yearly cycle of data collection for new and existing centres in the I-CAH registry to understand the change in this international benchmark for acute AI related adverse events benchmark over time.

Wide variation in adrenal crisis rates between centres were demonstrated in Chapter 6 and Chapter 7 showed that the availability of resources amongst HIC and LMIC centres may also vary significantly. Future work investigating the association between local health care resources and the occurrence of acute AI events in children with CAH by linking the real-world data from Chapter 6 to the results of the international survey from Chapter 7 would be beneficial.

In Chapter 6, risk factors for SDE were identified and in the future, it would be advantageous to use this data to develop prediction models for the risk of both SDE and AC in children with CAH.

10.3.4 PROs in parents of young children with DSD

Chapter 9 highlighted the development and initial phase of validation of short PRO questionnaires for parents of young children with DSD by comparing short versions with validated long versions of the questionnaires. The process of developing validated questionnaires is lengthy and to be able to incorporate the short PRO questionnaires as clinical instruments that can be used routinely in the clinic setting, further validation of the questionnaires will be required. Future studies will focus on the second phase of validation with further measurement of the psychometric properties of these questionnaires in the form of test re-test reliability and group construct validity in a larger cohort of parents. Investigating the value of PROs for clinical decision making, care quality improvement and research into therapies will become possible once these preliminary stages are completed.

The median age of children in this study was 3.6 years, thus, ethical approval could be sought to undertake studies in older age groups of children and adolescents. In the future, translating these validated PRO questionnaires into other languages and exploring their use across multiple centres would create the opportunity for developing robust reference data. This data could then be used to facilitate the development of clinical benchmarks for psychosocial outcomes, guiding a process of continuous quality improvement in the care of these patients and their families. In addition, incorporating PRO questionnaires into a patient accessible module within the I-DSD/I-CAH registry would also be beneficial in aggregating data and enabling longitudinal assessment of psychosocial outcomes.

10.3.5 Change to current clinical practice

The creation of the clinical benchmarks outlined in this thesis using real world data will enable a greater understanding of the occurrence and clinical outcomes of rare endocrine conditions including DSD and CAH in children, with implications for resource planning, future healthcare provision and healthcare costs.

The definitions of AI related adverse events proposed in this thesis have been used in the development of BSPED national guidance for the management of AI in children. The use of more uniform guidance will help to pave the way to greater benchmarking of care and ultimately improvements in patient care. Identification of risk factors for AI related adverse events also highlight the need for further targeted parent or patient educational strategies in those groups considered to be at higher risk of these events.

The routine use of PROs and patterns of parental reporting observed in DSD can not only improve targeting of resources such as psychology input or frequency of clinical follow-up, but also enable a greater understanding of the condition-specific or generic issues that need to be addressed in children with DSD and their carers.

10.3.6 Closing remarks

Continued collaboration with experts in the fields of rare endocrine conditions to further develop and optimise existing methods of reporting of these conditions and associated morbidity is vital and promoting the use of registry based methods for real world data collection amongst the international endocrine community is fundamental. The data presented in this thesis represent new clinical benchmarks that require further study and comparison to practice internationally.

References

Ahlmark, N., Algren, M. H., Holmberg, T., Norredam, M. L., Nielsen, S. S., Blom, A. B., Bo, A. and Juel, K. (2015). "Survey nonresponse among ethnic minorities in a national health survey--a mixed-method study of participation, barriers, and potentials." Ethn Health **20**(6): 611-632.

Ahmed, S. F., Achermann, J., Alderson, J., Crouch, N. S., Elford, S., Hughes, I. A., Krone, N., McGowan, R., Mushtaq, T., O'Toole, S., Perry, L., Rodie, M. E., Skae, M. and Turner, H. E. (2021). "Society for Endocrinology UK Guidance on the initial evaluation of a suspected difference or disorder of sex development (Revised 2021)." Clin Endocrinol (Oxf).

Ahmed, S. F., Bryce, J. and Hiort, O. (2014). "International networks for supporting research and clinical care in the field of disorders of sex development." Endocr Dev **27**: 284-292.

Ahmed, S. F., Dobbie, R., Finlayson, A. R., Gilbert, J., Youngson, G., Chalmers, J. and Stone, D. (2004). "Prevalence of hypospadias and other genital anomalies among singleton births, 1988-1997, in Scotland." Arch Dis Child Fetal Neonatal Ed **89**(2): F149-151.

Ahmed, S. F., Gardner, M. and Sandberg, D. E. (2014). "Management of children with disorders of sex development: new care standards explained." Psychology & Sexuality **5**(1): 5-14.

Ahmed, S. F., Khwaja, O. and Hughes, I. A. (2000). "The role of a clinical score in the assessment of ambiguous genitalia." BJU Int **85**(1): 120-124.

Ali, S. R., Bryce, J., Cools, M., Korbonits, M., Beun, J. G., Taruscio, D., Danne, T., Dattani, M., Dekkers, O. M., Linglart, A., Netchine, I., Nordenstrom, A., Patocs, A., Persani, L., Reisch, N., Smyth, A., Sumnik, Z., Visser, W. E., Hiort, O., Pereira, A. M. and Ahmed, S. F. (2019). "The current landscape of European registries for rare endocrine conditions." Eur J Endocrinol **180**(1): 89-98.

Ali, S. R., Bryce, J., Haghpanahan, H., Lewsey, J. D., Tan, L. E., Atapattu, N., Birkebaek, N. H., Blankenstein, O., Neumann, U., Balsamo, A., Ortolano, R., Bonfig, W., Claahsen-van der Grinten, H. L., Cools, M., Costa, E. C., Darendeliler, F., Poyrazoglu, S., Elsedfy, H., Finken, M. J. J., Fluck, C. E., Gevers, E., Korbonits, M., Guaragna-Filho, G., Guran, T., Guven, A., Hannema, S. E., Higham, C., Hughes, I. A., Tadokoro-Cuccaro, R., Thankamony, A., Iotova, V., Krone, N. P., Krone, R., Lichiardopol, C., Luczay, A., Mendonca, B. B., Bachega, T., Miranda, M. C., Milenkovic, T., Mohnike, K., Nordenstrom, A., Einaudi, S., van der Kamp, H., Vieites, A., de Vries, L., Ross, R. J. M. and Ahmed, S. F. (2021). "Real-World Estimates of Adrenal Insufficiency-Related Adverse Events in Children With Congenital Adrenal Hyperplasia." J Clin Endocrinol Metab **106**(1): e192-e203.

Ali, S. R., Bryce, J., Smythe, C., Hytiris, M., Priego, A. L., Appelman-Dijkstra, N. M. and Ahmed, S. F. (2021). "Supporting international networks through platforms for standardised data collection-the European Registries for Rare Endocrine Conditions (EuRRECa) model." Endocrine **71**(3): 555-560.

Ali, S. R., Bryce, J., Tan, L. E., Hiort, O., Pereira, A. M., van den Akker, E. L. T., Appelman-Dijkstra, N. M., Bertherat, J., Cools, M., Dekkers, O. M., Kodra, Y., Persani, L., Smyth, A., Smythe, C., Taruscio, D. and Ahmed, S. F. (2020). "The EuRRECa Project as a Model for Data Access and Governance Policies for Rare Disease Registries That Collect Clinical Outcomes." Int J Environ Res Public Health **17**(23).

Ali, S. R., Lucas-Herald, A., Bryce, J. and Ahmed, S. F. (2019). "The Role of International Databases in Understanding the Aetiology and Consequences of Differences/Disorders of Sex Development." Int J Mol Sci **20**(18).

Ali, S. R., Macqueen, Z., Gardner, M., Xin, Y., Kyriakou, A., Mason, A., Shaikh, M. G., Wong, S. C., Sandberg, D. E. and Ahmed, S. F. (2020). "Parent-reported outcomes in young children with disorders/differences of sex development." Int J Pediatr Endocrinol **2020**: 3.

Allolio, B. (2015). "Extensive expertise in endocrinology. Adrenal crisis." Eur J Endocrinol **172**(3): R115-124.

Alpern, A. N., Gardner, M., Kogan, B., Sandberg, D. E. and Quittner, A. L. (2017). "Development of Health-Related Quality of Life Instruments for Young Children With Disorders of Sex Development (DSD) and Their Parents." J Pediatr Psychol **42**(5): 544-558.

Amaral, R. C., Inacio, M., Brito, V. N., Bachega, T. A., Domenice, S., Arnhold, I. J., Madureira, G., Gomes, L., Costa, E. M. and Mendonca, B. B. (2015). "Quality of life of patients with 46,XX and 46,XY disorders of sex development." Clin Endocrinol (Oxf) **82**(2): 159-164.

Arlt, W. and Society for Endocrinology Clinical, C. (2016). "SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients." Endocr Connect **5**(5): G1-G3.

Auchus, R. J. (2004). "The backdoor pathway to dihydrotestosterone." Trends Endocrinol Metab **15**(9): 432-438.

Aydin, B. K., Saka, N., Bas, F., Bas, E. K., Coban, A., Yildirim, S., Guran, T. and Darendeliler, F. (2019). "Frequency of Ambiguous Genitalia in 14,177 Newborns in Turkey." J Endocr Soc **3**(6): 1185-1195.

Azzopardi-Muscat, N. and Brand, H. (2015). "Will European Reference Networks herald a new era of care for patients with rare and complex diseases?" Eur J Public Health **25**(3): 362-363.

Bacila, I., Adaway, J., Hawley, J., Mahdi, S., Krone, R., Patel, L., Alvi, S., Randell, T., Gevers, E., Dattani, M., Cheetham, T., Kyriakou, A., Schiffer, L., Ryan, F., Crowne, E., Davies, J. H., Ahmed, S. F., Keevil, B. and Krone, N. (2019). "Measurement of Salivary Adrenal-Specific Androgens as Biomarkers of Therapy Control in 21-Hydroxylase Deficiency." J Clin Endocrinol Metab **104**(12): 6417-6429.

Bacila, I., Freeman, N., Daniel, E., Sandrk, M., Bryce, J., Ali, S. R., Yavas Abali, Z., Atapattu, N., Bachega, T. A., Balsamo, A., Birkebaek, N., Blankenstein, O., Bonfig, W., Cools, M., Costa, E. C., Darendeliler, F., Einaudi, S., Elsedfy, H. H., Finken, M., Gevers, E., Claahsen-van der Grinten, H. L., Guran, T., Guven, A., Hannema, S. E., Higham, C. E., Iotova, V., van der Kamp, H. J., Korbonits, M., Krone, R. E., Lichiardopol, C., Luczay, A., Mendonca, B. B., Milenkovic, T., Miranda, M. C., Mohnike, K., Neumann, U., Ortolano, R., Poyrazoglu, S., Thankamony, A., Tomlinson, J. W., Vieites, A., de Vries, L., Ahmed, S. F., Ross, R. J. and Krone, N. P. (2021). "International practice of corticosteroid replacement therapy in congenital adrenal hyperplasia: data from the I-CAH registry." Eur J Endocrinol **184**(4): 553-563.

Bakula, D. M., Mullins, A. J., Sharkey, C. M., Wolfe-Christensen, C., Mullins, L. L. and Wisniewski, A. B. (2017). "Gender identity outcomes in children with disorders/differences of sex development: Predictive factors." Semin Perinatol **41**(4): 214-217.

Bakula, D. M., Sharkey, C. M., Wolfe-Christensen, C., Mullins, A. J., Meyer, J., Mullins, L. L. and Wisniewski, A. B. (2017). "Recommendations for the Establishment of Disorders/Differences of Sex Development Interdisciplinary Care Clinics for Youth." J Pediatr Nurs **37**: 79-85.

Baldovino, S., Moliner, A. M., Taruscio, D., Daina, E. and Roccatello, D. (2016). "Rare Diseases in Europe: from a Wide to a Local Perspective." Isr Med Assoc J **18**(6): 359-363.

Balsamo, A., Cacciari, E., Piazzi, S., Cassio, A., Bozza, D., Pirazzoli, P. and Zappulla, F. (1996). "Congenital adrenal hyperplasia: neonatal mass screening compared with clinical diagnosis only in the Emilia-Romagna region of Italy, 1980-1995." Pediatrics **98**(3 Pt 1): 362-367.

Balsamo, A., Cicognani, A., Baldazzi, L., Barbaro, M., Baronio, F., Gennari, M., Bal, M., Cassio, A., Kontaxaki, K. and Cacciari, E. (2003). "CYP21 genotype, adult height, and pubertal development in 55 patients treated for 21-hydroxylase deficiency." J Clin Endocrinol Metab **88**(12): 5680-5688.

Bancos, I., Hahner, S., Tomlinson, J. and Arlt, W. (2015). "Diagnosis and management of adrenal insufficiency." Lancet Diabetes Endocrinol **3**(3): 216-226.

Benjamini, Y. and Hochberg, Y. (1995). "Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing." Journal of the Royal Statistical Society. Series B (Methodological) **57**(1): 289-300.

Bennecke, E., Thyen, U., Grüters, A., Lux, A. and Köhler, B. (2017). "Health-related quality of life and psychological well-being in adults with differences/disorders of sex development." Clin Endocrinol (Oxf) **86**(4): 634-643.

Berglund, A., Johannsen, T. H., Stochholm, K., Viuff, M. H., Fedder, J., Main, K. M. and Gravholt, C. H. (2016). "Incidence, Prevalence, Diagnostic Delay, and Clinical Presentation of Female 46,XY Disorders of Sex Development." J Clin Endocrinol Metab **101**(12): 4532-4540.

Bever, Y. V., Brüggenwirth, H. T., Wolffenbuttel, K. P., Dessens, A. B., Groenenberg, I. A. L., Knapen, M., De Baere, E., Cools, M., van Ravenswaaij-Arts, C. M. A., Sikkema-Raddatz, B., Claahsen-van der Grinten, H., Kempers, M., Rinne, T., Hersmus, R., Looijenga, L. and Hannema, S. E. (2020). "Under-reported aspects of diagnosis and treatment addressed in the Dutch-Flemish guideline for comprehensive diagnostics in disorders/differences of sex development." J Med Genet **57**(9): 581-589.

Boehmer, A. L., Nijman, R. J., Lammers, B. A., de Coninck, S. J., Van Hemel, J. O., Themmen, A. P., Mureau, M. A., de Jong, F. H., Brinkmann, A. O., Niermeijer, M. F. and Drop, S. L. (2001). "Etiological studies of severe or familial hypospadias." J Urol **165**(4): 1246-1254.

Bornstein, S. R., Allolio, B., Arlt, W., Barthel, A., Don-Wauchope, A., Hammer, G. D., Husebye, E. S., Merke, D. P., Murad, M. H., Stratakis, C. A. and Torpy, D. J. (2016). "Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline." J Clin Endocrinol Metab **101**(2): 364-389.

Boucher, N. A., Alkazemi, M. H., Tejwani, R. and Routh, J. C. (2022). "Parents of Children With Newly Diagnosed Disorders of Sex Development Identify Major Concerns: A Qualitative Study." Urology **164**: 218-223.

Brinkmann, L., Schuetzmann, K. and Richter-Appelt, H. (2007). "Gender assignment and medical history of individuals with different forms of intersexuality: evaluation of medical records and the patients' perspective." J Sex Med **4**(4 Pt 1): 964-980.

Brosnan, P. G., Brosnan, C. A., Kemp, S. F., Domek, D. B., Jelley, D. H., Blackett, P. R. and Riley, W. J. (1999). "Effect of newborn screening for congenital adrenal hyperplasia." Arch Pediatr Adolesc Med **153**(12): 1272-1278.

Burger-Stritt, S., Eff, A., Quinkler, M., Kienitz, T., Stamm, B., Willenberg, H. S., Meyer, G., Klein, J., Reisch, N., Droste, M. and Hahner, S. (2020). "Standardised patient education in adrenal insufficiency: a prospective multi-centre evaluation." Eur J Endocrinol **183**(2): 119-127.

Burger-Stritt, S., Kardonski, P., Pulzer, A., Meyer, G., Quinkler, M. and Hahner, S. (2018). "Management of adrenal emergencies in educated patients with adrenal insufficiency-A prospective study." Clin Endocrinol (Oxf) **89**(1): 22-29.

Camp, R. C. (1998). Global Cases in Benchmarking: Best Practices from Organizations Around the World, American Society for Quality Control Quality Press.

Capalbo, D., Moracas, C., Cappa, M., Balsamo, A., Maghnie, M., Wasniewska, M. G., Greggio, N. A., Baronio, F., Bizzarri, C., Ferro, G., Di Lascio, A., Stancampiano, M. R., Azzolini, S., Patti, G., Longhi, S., Valenzise, M., Radetti, G., Betterle, C., Russo, G. and Salerno, M. (2021). "Primary Adrenal Insufficiency in Childhood: Data From a Large Nationwide Cohort." J Clin Endocrinol Metab **106**(3): 762-773.

Carmassi, C., Dell'Oste, V., Foghi, C., Bertelloni, C. A., Conti, E., Calderoni, S., Battini, R. and Dell'Osso, L. (2020). "Post-Traumatic Stress Reactions in Caregivers of Children and Adolescents/Young Adults with Severe Diseases: A Systematic Review of Risk and Protective Factors." Int J Environ Res Public Health **18**(1).

Charmandari, E., Brook, C. G. and Hindmarsh, P. C. (2004). "Classic congenital adrenal hyperplasia and puberty." Eur J Endocrinol **151 Suppl 3**: U77-82.

Charmandari, E., Lichtarowicz-Krynska, E. J., Hindmarsh, P. C., Johnston, A., Aynsley-Green, A. and Brook, C. G. (2001). "Congenital adrenal hyperplasia: management during critical illness." Arch Dis Child **85**(1): 26-28.

Chrisp, G. L., Maguire, A. M., Quartararo, M., Falhammar, H., King, B. R., Munns, C. F., Torpy, D. J., Hameed, S. and Rushworth, R. L. (2018). "Variations in the management of acute illness in children with congenital adrenal hyperplasia: An audit of three paediatric hospitals." Clin Endocrinol (Oxf) **89**(5): 577-585.

Claahsen-van der Grinten, H. L., Speiser, P. W., Ahmed, S. F., Arlt, W., Auchus, R. J., Falhammar, H., Flück, C. E., Guasti, L., Huebner, A., Kortmann, B. B. M., Krone, N., Merke, D. P., Miller, W. L., Nordenström, A., Reisch, N., Sandberg, D. E., Stikkelbroeck, N., Touraine, P., Utari, A., Wudy, S. A. and White, P. C. (2022). "Congenital Adrenal Hyperplasia-Current Insights in Pathophysiology, Diagnostics, and Management." Endocr Rev **43**(1): 91-159.

Cook, D. A., Wittich, C. M., Daniels, W. L., West, C. P., Harris, A. M. and Beebe, T. J. (2016). "Incentive and Reminder Strategies to Improve Response Rate for Internet-Based Physician Surveys: A Randomized Experiment." J Med Internet Res **18**(9): e244.

Cools, M., Nordenström, A., Robeva, R., Hall, J., Westerveld, P., Flück, C., Köhler, B., Berra, M., Springer, A., Schweizer, K. and Pasterski, V. (2018). "Caring for individuals with a difference of sex development (DSD): a Consensus Statement." Nat Rev Endocrinol **14**(7): 415-429.

Cox, K., Bryce, J., Jiang, J., Rodie, M., Sinnott, R., Alkhawari, M., Arlt, W., Audi, L., Balsamo, A., Bertelloni, S., Cools, M., Darendeliler, F., Drop, S., Ellaithi, M., Guran, T., Hiort, O., Holterhus, P. M., Hughes, I., Krone, N., Lisa, L., Morel, Y., Soder, O., Wieacker, P. and Ahmed, S. F. (2014). "Novel associations in disorders of sex development: findings from the I-DSD Registry." J Clin Endocrinol Metab **99**(2): E348-355.

Crafa, A., Calogero, A. E., Cannarella, R., Mongioi, L. M., Condorelli, R. A., Greco, E. A., Aversa, A. and La Vignera, S. (2021). "The Burden of Hormonal Disorders: A Worldwide Overview With a Particular Look in Italy." Front Endocrinol (Lausanne) **12**: 694325.

Crerand, C. E., Kapa, H. M., Litteral, J. L., Nahata, L., Combs, B., Indyk, J. A., Jayanthi, V. R., Chan, Y. M., Tishelman, A. C. and Hansen-Moore, J. (2019).

"Parent perceptions of psychosocial care for children with differences of sex development." J Pediatr Urol **15**(5): 522.e521-522.e528.

Cull, M. L. and Simmonds, M. (2010). "Importance of support groups for intersex (disorders of sex development) patients, families and the medical profession." Sex Dev **4**(4-5): 310-312.

Cutillo, C. M., Austin, C. P. and Groft, S. C. (2017). "A Global Approach to Rare Diseases Research and Orphan Products Development: The International Rare Diseases Research Consortium (IRDiRC)." Adv Exp Med Biol **1031**: 349-369.

Davies R, A. D. (2020). "Differences of sexual development and their clinical implications." The Obstetrician & Gynaecologist **22**(4): 257-266.

de Graaf, J. P., de Vries, F., Dirkson, A., Hiort, O., Pereira, A. M., Korbonits, M. and Cools, M. (2021). "Patients with rare endocrine conditions have corresponding views on unmet needs in clinical research." Endocrine **71**(3): 561-568.

de Graaf, N. M., Carmichael, P., Steensma, T. D. and Zucker, K. J. (2018). "Evidence for a Change in the Sex Ratio of Children Referred for Gender Dysphoria: Data From the Gender Identity Development Service in London (2000-2017)." J Sex Med **15**(10): 1381-1383.

de Vries, F., Bruin, M., Cersosimo, A., van Beuzekom, C. N., Ahmed, S. F., Peeters, R. P., Biermasz, N. R., Hiort, O. and Pereira, A. M. (2020). "An overview of clinical activities in Endo-ERN: the need for alignment of future network criteria." Eur J Endocrinol **183**(2): 141-148.

De Vroede, M., Beukering, R., Spit, M. and Jansen, M. (1998). "Rectal hydrocortisone during stress in patients with adrenal insufficiency." Arch Dis Child **78**(6): 544-547.

Debono, M., Mallappa, A., Gounden, V., Nella, A. A., Harrison, R. F., Crutchfield, C. A., Backlund, P. S., Soldin, S. J., Ross, R. J. and Merke, D. P. (2015). "Hormonal circadian rhythms in patients with congenital adrenal hyperplasia: identifying optimal monitoring times and novel disease biomarkers." Eur J Endocrinol **173**(6): 727-737.

Dessens, A., Guaragna-Filho, G., Kyriakou, A., Bryce, J., Sanders, C., Nordenskjöld, A., Rozas, M., Iotova, V., Ediati, A., Juul, A., Krawczynski, M., Hiort, O. and Faisal Ahmed, S. (2017). "Understanding the needs of professionals who provide psychosocial care for children and adults with disorders of sex development." BMJ Paediatr Open **1**(1): e000132.

Dewan, N. A., Daniels, A., Zieman, G. and Kramer, T. (2000). "The National Outcomes Management Project: a benchmarking collaborative." J Behav Health Serv Res **27**(4): 431-436.

Dineen, R., Thompson, C. J. and Sherlock, M. (2019). "Adrenal crisis: prevention and management in adult patients." Ther Adv Endocrinol Metab **10**: 2042018819848218.

Dörr, H. G., Wollmann, H. A., Hauffa, B. P. and Woelfle, J. (2018). "Mortality in children with classic congenital adrenal hyperplasia and 21-hydroxylase deficiency (CAH) in Germany." BMC Endocr Disord **18**(1): 37.

Duguid, A., Morrison, S., Robertson, A., Chalmers, J., Youngson, G. and Ahmed, S. F. (2007). "The psychological impact of genital anomalies on the parents of affected children." Acta Paediatr **96**(3): 348-352.

El-Fakhri, N., Williams, C., Cox, K., McDevitt, H., Galloway, P., McIntosh, N. and Ahmed, S. F. (2013). "An electronic surveillance system for monitoring the hospital presentation of nutritional vitamin D deficiency in children in Scotland." J Pediatr Endocrinol Metab **26**(11-12): 1053-1058.

El-Maouche, D., Hargreaves, C. J., Sinaii, N., Mallappa, A., Veeraraghavan, P. and Merke, D. P. (2018). "Longitudinal Assessment of Illnesses, Stress Dosing, and Illness Sequelae in Patients With Congenital Adrenal Hyperplasia." J Clin Endocrinol Metab **103**(6): 2336-2345.

Ellens, R. E. H., Bakula, D. M., Mullins, A. J., Scott Reyes, K. J., Austin, P., Baskin, L., Bernabé, K., Cheng, E. Y., Fried, A., Frimberger, D., Galan, D., Gonzalez, L., Greenfield, S., Kolon, T., Kropp, B., Lakshmanan, Y., Meyer, S., Meyer, T., Mullins, L. L., Nokoff, N. J., Palmer, B., Poppas, D., Paradis, A., Yerkes, E., Wisniewski, A. B. and Wolfe-Christensen, C. (2017). "Psychological Adjustment of Parents of Children Born with Atypical Genitalia 1 Year after Genitoplasty." J Urol **198**(4): 914-920.

Elliott, E. J., Nicoll, A., Lynn, R., Marchessault, V., Hirasing, R. and Ridley, G. (2001). "Rare disease surveillance: An international perspective." Paediatr Child Health **6**(5): 251-260.

Ellis, J. (2006). "All inclusive benchmarking." J Nurs Manag **14**(5): 377-383.

Ernst, M. M., Gardner, M., Mara, C. A., Délot, E. C., Fechner, P. Y., Fox, M., Rutter, M. M., Speiser, P. W., Vilain, E., Weidler, E. M. and Sandberg, D. E. (2018). "Psychosocial Screening in Disorders/Differences of Sex Development: Psychometric Evaluation of the Psychosocial Assessment Tool." Horm Res Paediatr **90**(6): 368-380.

Ettorchi-Tardy, A., Levif, M. and Michel, P. (2012). "Benchmarking: a method for continuous quality improvement in health." Healthc Policy **7**(4): e101-119.

Eyal, O., Levin, Y., Oren, A., Zung, A., Rachmiel, M., Landau, Z., Schachter-Davidov, A., Segev-Becker, A. and Weintrob, N. (2019). "Adrenal crises in children with adrenal insufficiency: epidemiology and risk factors." Eur J Pediatr **178**(5): 731-738.

Falhammar, H., Frisén, L., Hirschberg, A. L., Norrby, C., Almqvist, C., Nordenskjöld, A. and Nordenström, A. (2015). "Increased Cardiovascular and Metabolic Morbidity in Patients With 21-Hydroxylase Deficiency: A Swedish Population-Based National Cohort Study." J Clin Endocrinol Metab **100**(9): 3520-3528.

Falhammar, H., Frisén, L., Norrby, C., Hirschberg, A. L., Almqvist, C., Nordenskjöld, A. and Nordenström, A. (2014). "Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency." J Clin Endocrinol Metab **99**(12): E2715-2721.

Falhammar, H. and Nordenström, A. (2015). "Nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency: clinical presentation, diagnosis, treatment, and outcome." Endocrine **50**(1): 32-50.

Finkielstain, G. P., Kim, M. S., Sinaii, N., Nishitani, M., Van Ryzin, C., Hill, S. C., Reynolds, J. C., Hanna, R. M. and Merke, D. P. (2012). "Clinical characteristics of a cohort of 244 patients with congenital adrenal hyperplasia." J Clin Endocrinol Metab **97**(12): 4429-4438.

Fleming, L., Knafl, K., Knafl, G. and Van Riper, M. (2017). "Parental management of adrenal crisis in children with congenital adrenal hyperplasia." J Spec Pediatr Nurs **22**(4).

Ford, E. S., Li, C., Zhao, G., Pearson, W. S. and Mokdad, A. H. (2008). "Prevalence of the metabolic syndrome among U.S. adolescents using the definition from the International Diabetes Federation." Diabetes Care **31**(3): 587-589.

Gainotti, S., Torreri, P., Wang, C. M., Reihs, R., Mueller, H., Heslop, E., Roos, M., Badowska, D. M., de Paulis, F., Kodra, Y., Carta, C., Martìn, E. L., Miller, V. R., Filocamo, M., Mora, M., Thompson, M., Rubinstein, Y., Posada de la Paz, M., Monaco, L., Lochmüller, H. and Taruscio, D. (2018). "The RD-Connect Registry & Biobank Finder: a tool for sharing aggregated data and metadata among rare disease researchers." Eur J Hum Genet **26**(5): 631-643.

Gjersing, L., Caplehorn, J. R. and Clausen, T. (2010). "Cross-cultural adaptation of research instruments: language, setting, time and statistical considerations." BMC Med Res Methodol **10**: 13.

Gleeson, H., Davis, J., Jones, J., O'Shea, E. and Clayton, P. E. (2013). "The challenge of delivering endocrine care and successful transition to adult services in adolescents with congenital adrenal hyperplasia: experience in a single centre over 18 years." Clin Endocrinol (Oxf) **78**(1): 23-28.

Gliklich, R. E. and Dreyer, N. A. (2010). AHRQ Methods for Effective Health Care. Registries for Evaluating Patient Outcomes: A User's Guide. R. E. Gliklich and N. A. Dreyer. Rockville (MD), Agency for Healthcare Research and Quality (US).

Golden, S. H., Brown, A., Cauley, J. A., Chin, M. H., Gary-Webb, T. L., Kim, C., Sosa, J. A., Sumner, A. E. and Anton, B. (2012). "Health disparities in endocrine disorders: biological, clinical, and nonclinical factors--an Endocrine Society scientific statement." J Clin Endocrinol Metab **97**(9): E1579-1639.

Golden, S. H., Robinson, K. A., Saldanha, I., Anton, B. and Ladenson, P. W. (2009). "Clinical review: Prevalence and incidence of endocrine and metabolic

disorders in the United States: a comprehensive review." J Clin Endocrinol Metab **94**(6): 1853-1878.

Gomes, L. G., Mendonca, B. B. and Bachega, T. (2020). "Long-term cardio-metabolic outcomes in patients with classical congenital adrenal hyperplasia: is the risk real?" Curr Opin Endocrinol Diabetes Obes **27**(3): 155-161.

Groft, S. C., Posada, M. and Taruscio, D. (2021). "Progress, challenges and global approaches to rare diseases." Acta Paediatr.

Grossman, A., Johannsson, G., Quinkler, M. and Zelissen, P. (2013). "Therapy of endocrine disease: Perspectives on the management of adrenal insufficiency: clinical insights from across Europe." Eur J Endocrinol **169**(6): R165-175.

Hahner, S., Burger-Stritt, S. and Allolio, B. (2013). "Subcutaneous hydrocortisone administration for emergency use in adrenal insufficiency." Eur J Endocrinol **169**(2): 147-154.

Hahner, S., Loeffler, M., Bleicken, B., Drechsler, C., Milovanovic, D., Fassnacht, M., Ventz, M., Quinkler, M. and Allolio, B. (2010). "Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies." Eur J Endocrinol **162**(3): 597-602.

Hahner, S., Ross, R. J., Arlt, W., Bancos, I., Burger-Stritt, S., Torpy, D. J., Husebye, E. S. and Quinkler, M. (2021). "Adrenal insufficiency." Nat Rev Dis Primers **7**(1): 19.

Hannah-Shmouni, F., Morissette, R., Sinaii, N., Elman, M., Prezant, T. R., Chen, W., Pulver, A. and Merke, D. P. (2017). "Revisiting the prevalence of nonclassic congenital adrenal hyperplasia in US Ashkenazi Jews and Caucasians." Genet Med **19**(11): 1276-1279.

Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G., Delacqua, F., Kirby, J. and Duda, S. N. (2019). "The REDCap consortium: Building an international community of software platform partners." J Biomed Inform **95**: 103208.

Hindmarsh, P. C. (2009). "Management of the child with congenital adrenal hyperplasia." Best Pract Res Clin Endocrinol Metab **23**(2): 193-208.

Hiort, O., Cools, M., Springer, A., McElreavey, K., Greenfield, A., Wudy, S. A., Kulle, A., Ahmed, S. F., Dessens, A., Balsamo, A., Maghnie, M., Bonomi, M., Dattani, M., Persani, L. and Audi, L. (2019). "Addressing gaps in care of people with conditions affecting sex development and maturation." Nat Rev Endocrinol **15**(10): 615-622.

Hird, B. E., Tetlow, L., Tobi, S., Patel, L. and Clayton, P. E. (2014). "No evidence of an increase in early infant mortality from congenital adrenal hyperplasia in the absence of screening." Arch Dis Child **99**(2): 158-164.

Hirose, T. and Ueda, R. (1990). "Long-term follow-up study of cerebral palsy children and coping behaviour of parents." J Adv Nurs **15**(7): 762-770.

Hughes, I. A. (2008). "Disorders of sex development: a new definition and classification." Best Pract Res Clin Endocrinol Metab **22**(1): 119-134.

Husebye, E. S., Pearce, S. H., Krone, N. P. and Kampe, O. (2021). "Adrenal insufficiency." Lancet **397**(10274): 613-629.

Indremo, M., White, R., Frisell, T., Cnattingius, S., Skalkidou, A., Isaksson, J. and Papadopoulos, F. C. (2021). "Validity of the Gender Dysphoria diagnosis and incidence trends in Sweden: a nationwide register study." Sci Rep **11**(1): 16168.

Irwin, D. E., Gross, H. E., Stucky, B. D., Thissen, D., DeWitt, E. M., Lai, J. S., Amtmann, D., Khastou, L., Varni, J. W. and DeWalt, D. A. (2012). "Development of six PROMIS pediatrics proxy-report item banks." Health Qual Life Outcomes **10**: 22.

Ishii, T., Adachi, M., Takasawa, K., Okada, S., Kamasaki, H., Kubota, T., Kobayashi, H., Sawada, H., Nagasaki, K., Numakura, C., Harada, S., Minamitani, K., Sugihara, S. and Tajima, T. (2018). "Incidence and Characteristics of Adrenal Crisis in Children Younger than 7 Years with 21-Hydroxylase Deficiency: A Nationwide Survey in Japan." Horm Res Paediatr **89**(3): 166-171.

Isidori, A. M., Venneri, M. A., Graziadio, C., Simeoli, C., Fiore, D., Hasenmajer, V., Sbardella, E., Gianfrilli, D., Pozza, C., Pasqualetti, P., Morrone, S., Santoni, A., Naro, F., Colao, A., Pivonello, R. and Lenzi, A. (2018). "Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial." Lancet Diabetes Endocrinol **6**(3): 173-185.

Iwasaku, M., Tanaka, S., Shinzawa, M. and Kawakami, K. (2019). "Impact of underlying chronic adrenal insufficiency on clinical course of hospitalized patients with adrenal crisis: A nationwide cohort study." Eur J Intern Med **64**: 24-28.

Janssens, A., Thompson Coon, J., Rogers, M., Allen, K., Green, C., Jenkinson, C., Tennant, A., Logan, S. and Morris, C. (2015). "A systematic review of generic multidimensional patient-reported outcome measures for children, part I: descriptive characteristics." Value Health **18**(2): 315-333.

Jenkins-Jones, S., Parviainen, L., Porter, J., Withe, M., Whitaker, M. J., Holden, S. E., Morgan, C. L., Currie, C. J. and Ross, R. J. M. (2018). "Poor compliance and increased mortality, depression and healthcare costs in patients with congenital adrenal hyperplasia." Eur J Endocrinol **178**(4): 309-320.

Johannsson, G., Falorni, A., Skrtic, S., Lennernäs, H., Quinkler, M., Monson, J. P. and Stewart, P. M. (2015). "Adrenal insufficiency: review of clinical outcomes with current glucocorticoid replacement therapy." Clin Endocrinol (Oxf) **82**(1): 2-11.

Jonker, C. J., de Vries, S. T., van den Berg, H. M., McGettigan, P., Hoes, A. W. and Mol, P. G. M. (2021). "Capturing Data in Rare Disease Registries to Support

Regulatory Decision Making: A Survey Study Among Industry and Other Stakeholders." Drug Saf **44**(8): 853-861.

Kamrath, C., Hochberg, Z., Hartmann, M. F., Remer, T. and Wudy, S. A. (2012). "Increased activation of the alternative "backdoor" pathway in patients with 21-hydroxylase deficiency: evidence from urinary steroid hormone analysis." J Clin Endocrinol Metab **97**(3): E367-375.

Khalid, J. M., Oerton, J. M., Dezateux, C., Hindmarsh, P. C., Kelnar, C. J. and Knowles, R. L. (2012). "Incidence and clinical features of congenital adrenal hyperplasia in Great Britain." Arch Dis Child **97**(2): 101-106.

Kinsner-Ovaskainen, A., Lanzoni, M., Garne, E., Loane, M., Morris, J., Neville, A., Nicholl, C., Rankin, J., Rissmann, A., Tucker, D. and Martin, S. (2018). "A sustainable solution for the activities of the European network for surveillance of congenital anomalies: EUROCAT as part of the EU Platform on Rare Diseases Registration." Eur J Med Genet **61**(9): 513-517.

Kirk, K. D., Fedele, D. A., Wolfe-Christensen, C., Phillips, T. M., Mazur, T., Mullins, L. L., Chernausek, S. D. and Wisniewski, A. B. (2011). "Parenting characteristics of female caregivers of children affected by chronic endocrine conditions: a comparison between disorders of sex development and type 1 diabetes mellitus." J Pediatr Nurs **26**(6): e29-36.

Kodra, Y., Posada de la Paz, M., Coi, A., Santoro, M., Bianchi, F., Ahmed, F., Rubinstein, Y. R., Weinbach, J. and Taruscio, D. (2017). "Data Quality in Rare Diseases Registries." Adv Exp Med Biol **1031**: 149-164.

Kodra, Y., Weinbach, J., Posada-de-la-Paz, M., Coi, A., Lemonnier, S. L., van Enckevort, D., Roos, M., Jacobsen, A., Cornet, R., Ahmed, S. F., Bros-Facer, V., Popa, V., Van Meel, M., Renault, D., von Gizycki, R., Santoro, M., Landais, P., Torreri, P., Carta, C., Mascalzoni, D., Gainotti, S., Lopez, E., Ambrosini, A., Muller, H., Reis, R., Bianchi, F., Rubinstein, Y. R., Lochmuller, H. and Taruscio, D. (2018). "Recommendations for Improving the Quality of Rare Disease Registries." Int J Environ Res Public Health **15**(8).

Kolesinska, Z., Acierno, J., Jr., Ahmed, S. F., Xu, C., Kapczuk, K., Skorczyk-Werner, A., Mikos, H., Rojek, A., Massouras, A., Krawczynski, M. R., Pitteloud, N. and Niedziela, M. (2018). "Integrating clinical and genetic approaches in the diagnosis of 46,XY disorders of sex development." Endocr Connect **7**(12): 1480-1490.

Kourime, M. and Ahmed, S. F. (2018). "Virtual Networks for Exchanging Information and Biomaterials: Future Directions." Sex Dev **12**(1-3): 140-144.

Kourime, M., Bryce, J., Jiang, J., Nixon, R., Rodie, M. and Ahmed, S. F. (2017). "An assessment of the quality of the I-DSD and the I-CAH registries - international registries for rare conditions affecting sex development." Orphanet J Rare Dis **12**(1): 56.

Kroenke, K., Spitzer, R. L., Williams, J. B. and Löwe, B. (2009). "An ultra-brief screening scale for anxiety and depression: the PHQ-4." Psychosomatics **50**(6): 613-621.

Krone, N., Dhir, V., Ivison, H. E. and Arlt, W. (2007). "Congenital adrenal hyperplasia and P450 oxidoreductase deficiency." Clin Endocrinol (Oxf) **66**(2): 162-172.

Kyriakou, A., Dessens, A., Bryce, J., Iotova, V., Juul, A., Krawczynski, M., Nordenskjöld, A., Rozas, M., Sanders, C., Hiort, O. and Ahmed, S. F. (2016). "Current models of care for disorders of sex development - results from an International survey of specialist centres." Orphanet J Rare Dis **11**(1): 155.

Lazem, M., Sheikhtaheri, A. and Hooman, N. (2021). "Lessons learned from hemolytic uremic syndrome registries: recommendations for implementation." Orphanet J Rare Dis **16**(1): 240.

Lee, P., Schober, J., Nordenström, A., Hoebeke, P., Houk, C., Looijenga, L., Manzoni, G., Reiner, W. and Woodhouse, C. (2012). "Review of recent outcome data of disorders of sex development (DSD): emphasis on surgical and sexual outcomes." J Pediatr Urol **8**(6): 611-615.

Lee, P. A., Houk, C. P., Ahmed, S. F. and Hughes, I. A. (2006). "Consensus statement on management of intersex disorders. International Consensus Conference on Intersex." Pediatrics **118**(2): e488-500.

Long, D. N., Wisniewski, A. B. and Migeon, C. J. (2004). "Gender role across development in adult women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency." J Pediatr Endocrinol Metab **17**(10): 1367-1373.

Lucas-Herald, A. K., Rashid Ali, S., McMillan, C., Rodie, M. E., McMillan, M., Bryce, J. and Ahmed, S. F. (2022). "I-DSD - The first 10 years." Horm Res Paediatr.

Lynn, R. M., Pebody, R. and Knowles, R. (2006). "Twenty years of active paediatric surveillance in the the UK and Republic of Ireland." Euro Surveill **11**(7): E060720.060724.

M, N. C., Fallon, M., Kenny, D., Moriarty, S., Hoey, H. and Costigan, C. (2003). "Rectal hydrocortisone during vomiting in children with adrenal insufficiency." J Pediatr Endocrinol Metab **16**(8): 1101-1104.

Mah, P. M., Jenkins, R. C., Rostami-Hodjegan, A., Newell-Price, J., Doane, A., Ibbotson, V., Tucker, G. T. and Ross, R. J. (2004). "Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency." Clin Endocrinol (Oxf) **61**(3): 367-375.

Martinerie, L., Pussard, E., Foix-L'Hélias, L., Petit, F., Cosson, C., Boileau, P. and Lombès, M. (2009). "Physiological partial aldosterone resistance in human newborns." Pediatr Res **66**(3): 323-328.

Melmed, S. (2020). "Pituitary-Tumor Endocrinopathies." N Engl J Med **382**(10): 937-950.

Mendes-Dos-Santos, C. T., Martins, D. L., Guerra-Júnior, G., Baptista, M. T. M., de-Mello, M. P., de Oliveira, L. C., Morcillo, A. M. and Lemos-Marini, S. H. V. (2018). "Prevalence of Testicular Adrenal Rest Tumor and Factors Associated with Its Development in Congenital Adrenal Hyperplasia." Horm Res Paediatr **90**(3): 161-168.

Merke, D. P. and Auchus, R. J. (2020). "Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency." N Engl J Med **383**(13): 1248-1261.

Merke, D. P., Mallappa, A., Arlt, W., Brac de la Perriere, A., Lindén Hirschberg, A., Juul, A., Newell-Price, J., Perry, C. G., Prete, A., Rees, D. A., Reisch, N., Stikkelbroeck, N., Touraine, P., Maltby, K., Treasure, F. P., Porter, J. and Ross, R. J. (2021). "Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia." J Clin Endocrinol Metab **106**(5): e2063-e2077.

Merke, D. P. and Poppas, D. P. (2013). "Management of adolescents with congenital adrenal hyperplasia." Lancet Diabetes Endocrinol **1**(4): 341-352.

Meyer-Bahlburg, H. F. L., Khuri, J., Reyes-Portillo, J. and New, M. I. (2017). "Stigma in Medical Settings As Reported Retrospectively by Women With Congenital Adrenal Hyperplasia (CAH) for Their Childhood and Adolescence." J Pediatr Psychol **42**(5): 496-503.

Mofokeng, T. R. P., Beshyah, S. A., Mahomed, F., Ndlovu, K. C. Z. and Ross, I. L. (2020). "Significant barriers to diagnosis and management of adrenal insufficiency in Africa." Endocr Connect **9**(5): 445-456.

Moliner, A. M. (2010). "Creating a European Union framework for actions in the field of rare diseases." Adv Exp Med Biol **686**: 457-473.

Molitch, M. E. (2017). "Diagnosis and Treatment of Pituitary Adenomas: A Review." Jama **317**(5): 516-524.

Mönig, I., Steenvoorden, D., de Graaf, J. P., Ahmed, S. F., Taruscio, D., Beun, J. G., Johannsen, T. H., Juul, A., Hiort, O. and Pereira, A. M. (2021). "CPMS-improving patient care in Europe via virtual case discussions." Endocrine **71**(3): 549-554.

Morgan, E. M., Mara, C. A., Huang, B., Barnett, K., Carle, A. C., Farrell, J. E. and Cook, K. F. (2017). "Establishing clinical meaning and defining important differences for Patient-Reported Outcomes Measurement Information System (PROMIS(®)) measures in juvenile idiopathic arthritis using standard setting with patients, parents, and providers." Qual Life Res **26**(3): 565-586.

Mosteller, R. D. (1987). "Simplified calculation of body-surface area." N Engl J Med **317**(17): 1098.

Ngaosuwan, K., Johnston, D. G., Godsland, I. F., Cox, J., Majeed, A., Quint, J. K., Oliver, N. and Robinson, S. (2021). "Mortality Risk in Patients With Adrenal

Insufficiency Using Prednisolone or Hydrocortisone: A Retrospective Cohort Study." J Clin Endocrinol Metab **106**(8): 2242-2251.

Niranjan, U. and Natarajan, A. (2015). "Congenital adrenal hyperplasia in children--a survey on the current practice in the UK." J Pediatr Endocrinol Metab **28**(7-8): 847-851.

Notter, A., Jenni, S. and Christ, E. (2018). "Evaluation of the frequency of adrenal crises and preventive measures in patients with primary and secondary adrenal insufficiency in Switzerland." Swiss Med Wkly **148**: w14586.

Nowotny, H., Ahmed, S. F., Bensing, S., Beun, J. G., Brosamle, M., Chifu, I., Claahsen van der Grinten, H., Clemente, M., Falhammar, H., Hahner, S., Husebye, E., Kristensen, J., Loli, P., Lajic, S., Reisch, N. and Endo, E. R. N. (2021). "Therapy options for adrenal insufficiency and recommendations for the management of adrenal crisis." Endocrine **71**(3): 586-594.

Odenwald, B., Nennstiel-Ratzel, U., Dorr, H. G., Schmidt, H., Wildner, M. and Bonfig, W. (2016). "Children with classic congenital adrenal hyperplasia experience salt loss and hypoglycemia: evaluation of adrenal crises during the first 6 years of life." Eur J Endocrinol **174**(2): 177-186.

Omori, K., Nomura, K., Shimizu, S., Omori, N. and Takano, K. (2003). "Risk factors for adrenal crisis in patients with adrenal insufficiency." Endocr J **50**(6): 745-752.

Pacaud, D., Schwandt, A., de Beaufort, C., Casteels, K., Beltrand, J., Birkebaek, N. H., Campagnoli, M., Bratina, N., Limbert, C., Mp O'Riordan, S., Ribeiro, R., Gerasimidi-Vazeou, A., Petruzelkova, L., Verkauskiene, R. and Krisane, I. D. (2016). "A description of clinician reported diagnosis of type 2 diabetes and other non-type 1 diabetes included in a large international multicentered pediatric diabetes registry (SWEET)." Pediatr Diabetes **17 Suppl 23**: 24-31.

Pappas, K. B., Wisniewski, A. B. and Migeon, C. J. (2008). "Gender role across development in adults with 46,XY disorders of sex development including perineoscrotal hypospadias and small phallus raised male or female." J Pediatr Endocrinol Metab **21**(7): 625-630.

Pasterski, V., Mastroyannopoulou, K., Wright, D., Zucker, K. J. and Hughes, I. A. (2014). "Predictors of posttraumatic stress in parents of children diagnosed with a disorder of sex development." Arch Sex Behav **43**(2): 369-375.

Pasterski, V., Prentice, P. and Hughes, I. A. (2010). "Consequences of the Chicago consensus on disorders of sex development (DSD): current practices in Europe." Arch Dis Child **95**(8): 618-623.

Pereira, A. M. and Hiort, O. (2021). "Introduction to Endo-ERN-scope and mission." Endocrine **71**(3): 537-538.

Perez, M. N., Delozier, A. M., Aston, C. E., Austin, P., Baskin, L., Chan, Y. M., Cheng, E. Y., Diamond, D. A., Fried, A., Greenfield, S., Kolon, T., Kropp, B., Lakshmanan, Y., Meyer, S., Meyer, T., Nokoff, N., Palmer, B., Paradis, A.,

Poppas, D., Scott Reyes, K. J., Swartz, J. M., Tishelman, A., Wisniewski, A. B., Wolfe-Christensen, C., Yerkes, E. and Mullins, L. L. (2019). "Predictors of Psychosocial Distress in Parents of Young Children with Disorders of Sex Development." J Urol **202**(5): 1046-1051.

Pinto, D., Martin, D. and Chenhall, R. (2016). "The involvement of patient organisations in rare disease research: a mixed methods study in Australia." Orphanet J Rare Dis **11**: 2.

Pitarelli E., M. E. (2000). Benchmarking: The Missing Link Between Evaluation and Management?, Geneva: University of Geneva and Centre for European Expertise and Evaluation.

Porter, J., Blair, J. and Ross, R. J. (2017). "Is physiological glucocorticoid replacement important in children?" Arch Dis Child **102**(2): 199-205.

Regan, E. A., Vaidya, A., Margulies, P. L., Make, B. J., Lowe, K. E. and Crapo, J. D. (2019). "Primary adrenal insufficiency in the United States: diagnostic error and patient satisfaction with treatment." Diagnosis (Berl) **6**(4): 343-350.

Reincke, M. and Hokken-Koelega, A. (2021). "Perspectives of the European Society of Endocrinology (ESE) and the European Society of Paediatric Endocrinology (ESPE) on rare endocrine disease." Endocrine **71**(3): 539-541.

Reisch, N., Willige, M., Kohn, D., Schwarz, H. P., Allolio, B., Reincke, M., Quinkler, M., Hahner, S. and Beuschlein, F. (2012). "Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase deficiency." Eur J Endocrinol **167**(1): 35-42.

Repping-Wuts, H. J., Stikkelbroeck, N. M., Noordzij, A., Kerstens, M. and Hermus, A. R. (2013). "A glucocorticoid education group meeting: an effective strategy for improving self-management to prevent adrenal crisis." Eur J Endocrinol **169**(1): 17-22.

Riepe, F. G., Krone, N., Viemann, M., Partsch, C. J. and Sippell, W. G. (2002). "Management of congenital adrenal hyperplasia: results of the ESPE questionnaire." Horm Res **58**(4): 196-205.

Roberts, C. M., Sharkey, C. M., Bakula, D. M., Perez, M. N., Delozier, A. J., Austin, P. F., Baskin, L. S., Chan, Y. M., Cheng, E. Y., Diamond, D. A., Fried, A. J., Kropp, B., Lakshmanan, Y., Meyer, S. Z., Meyer, T., Nokoff, N. J., Palmer, B. W., Paradis, A., Reyes, K. J. S., Tishelman, A., Williot, P., Wolfe-Christensen, C., Yerkes, E. B., Aston, C., Wisniewski, A. B. and Mullins, L. L. (2020). "Illness Uncertainty Longitudinally Predicts Distress Among Caregivers of Children Born With DSD." J Pediatr Psychol **45**(9): 1053-1062.

Rodie, M., McGowan, R., Mayo, A., Midgley, P., Driver, C. P., Kinney, M., Young, D. and Ahmed, S. F. (2011). "Factors that influence the decision to perform a karyotype in suspected disorders of sex development: lessons from the Scottish genital anomaly network register." Sex Dev **5**(3): 103-108.

Rodie, M. E., Ali, S. R., Jayasena, A., Alenazi, N. R., McMillan, M., Cox, K., Cassim, S. M., Henderson, S., McGowan, R. and Ahmed, S. F. (2022). "A Nationwide Study of the Prevalence and Initial Management of Atypical Genitalia in the Newborn in Scotland." Sex Dev **16**(1): 11-18.

Rolston, A. M., Gardner, M., van Leeuwen, K., Mohnach, L., Keegan, C., Délot, E., Vilain, E. and Sandberg, D. E. (2017). "Disorders of sex development (DSD): Clinical service delivery in the United States." Am J Med Genet C Semin Med Genet **175**(2): 268-278.

Rolston, A. M., Gardner, M., Vilain, E. and Sandberg, D. E. (2015). "Parental Reports of Stigma Associated with Child's Disorder of Sex Development." Int J Endocrinol **2015**: 980121.

Rushworth, R. L., Chrisp, G. L., Dean, B., Falhammar, H. and Torpy, D. J. (2017). "Hospitalisation in Children with Adrenal Insufficiency and Hypopituitarism: Is There a Differential Burden between Boys and Girls and between Age Groups?" Horm Res Paediatr **88**(5): 339-346.

Rushworth, R. L., Falhammar, H., Munns, C. F., Maguire, A. M. and Torpy, D. J. (2016). "Hospital Admission Patterns in Children with CAH: Admission Rates and Adrenal Crises Decline with Age." Int J Endocrinol **2016**: 5748264.

Rushworth, R. L., Torpy, D. J. and Falhammar, H. (2017). "Adrenal crises: perspectives and research directions." Endocrine **55**(2): 336-345.

Rushworth, R. L., Torpy, D. J. and Falhammar, H. (2019). "Adrenal Crisis." N Engl J Med **381**(9): 852-861.

Sandberg, D. E., Gardner, M., Callens, N. and Mazur, T. (2017). "Interdisciplinary care in disorders/differences of sex development (DSD): The psychosocial component of the DSD-Translational research network." Am J Med Genet C Semin Med Genet **175**(2): 279-292.

Sandberg, D. E., Gardner, M. and Cohen-Kettenis, P. T. (2012). "Psychological aspects of the treatment of patients with disorders of sex development." Semin Reprod Med **30**(5): 443-452.

Schaeffer, T. L., Tryggestad, J. B., Mallappa, A., Hanna, A. E., Krishnan, S., Chernausek, S. D., Chalmers, L. J., Reiner, W. G., Kropp, B. P. and Wisniewski, A. B. (2010). "An Evidence-Based Model of Multidisciplinary Care for Patients and Families Affected by Classical Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency." Int J Pediatr Endocrinol **2010**: 692439.

Schepers, S. A., Sint Nicolaas, S. M., Haverman, L., Wensing, M., Schouten van Meeteren, A. Y. N., Veening, M. A., Caron, H. N., Hoogerbrugge, P. M., Kaspers, G. J. L., Verhaak, C. M. and Grootenhuis, M. A. (2017). "Real-world implementation of electronic patient-reported outcomes in outpatient pediatric cancer care." Psychooncology **26**(7): 951-959.

Schützmann, K., Brinkmann, L., Schacht, M. and Richter-Appelt, H. (2009). "Psychological distress, self-harming behavior, and suicidal tendencies in adults with disorders of sex development." Arch Sex Behav **38**(1): 16-33.

Services, U. S. D. o. H. a. H. (2006). "Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance." Health Qual Life Outcomes **4**: 79.

Sharkey, C. M., Bakula, D. M., Wolfe-Christensen, C., Austin, P., Baskin, L., Bernabé, K. J., Chan, Y. M., Cheng, E. Y., Delozier, A. M., Diamond, D. A., Ellens, R. E. H., Fried, A., Galan, D., Greenfield, S., Kolon, T., Kropp, B., Lakshmanan, Y., Meyer, S., Meyer, T., Nokoff, N. J., Scott Reyes, K. J., Palmer, B., Poppas, D. P., Paradis, A., Tishelman, A., Yerkes, E. B., Chaney, J. M., Wisniewski, A. B. and Mullins, L. L. (2018). "Parent-Rated Severity of Illness and Anxiety among Caregivers of Children Born with a Disorder of Sex Development Including Ambiguous Genitalia." Horm Res Paediatr **90**(5): 308-313.

Shepherd, L. M., Tahrani, A. A., Inman, C., Arlt, W. and Carrick-Sen, D. M. (2017). "Exploration of knowledge and understanding in patients with primary adrenal insufficiency: a mixed methods study." BMC Endocr Disord **17**(1): 47.

Shulman, D. I., Palmert, M. R., Kemp, S. F., Lawson Wilkins, D. and Therapeutics, C. (2007). "Adrenal insufficiency: still a cause of morbidity and death in childhood." Pediatrics **119**(2): e484-494.

Simpson, A., Ross, R., Porter, J., Dixon, S., Whitaker, M. J. and Hunter, A. (2018). "Adrenal Insufficiency in Young Children: a Mixed Methods Study of Parents' Experiences." J Genet Couns **27**(6): 1447-1458.

Smans, L. C., Van der Valk, E. S., Hermus, A. R. and Zelissen, P. M. (2016). "Incidence of adrenal crisis in patients with adrenal insufficiency." Clin Endocrinol (Oxf) **84**(1): 17-22.

Speiser, P. W., Arlt, W., Auchus, R. J., Baskin, L. S., Conway, G. S., Merke, D. P., Meyer-Bahlburg, H. F. L., Miller, W. L., Murad, M. H., Oberfield, S. E. and White, P. C. (2018). "Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline." J Clin Endocrinol Metab **103**(11): 4043-4088.

Stout, S. A., Litvak, M., Robbins, N. M. and Sandberg, D. E. (2010). "Congenital adrenal hyperplasia: classification of studies employing psychological endpoints." Int J Pediatr Endocrinol **2010**: 191520.

Suorsa, K. I., Mullins, A. J., Tackett, A. P., Reyes, K. J., Austin, P., Baskin, L., Bernabé, K., Cheng, E., Fried, A., Frimberger, D., Galan, D., Gonzalez, L., Greenfield, S., Kropp, B., Meyer, S., Meyer, T., Nokoff, N., Palmer, B., Poppas, D., Paradis, A., Yerkes, E., Wisniewski, A. B. and Mullins, L. L. (2015). "Characterizing Early Psychosocial Functioning of Parents of Children with Moderate to Severe Genital Ambiguity due to Disorders of Sex Development." J Urol **194**(6): 1737-1742.

Taruscio, D., Gainotti, S., Mollo, E., Vittozzi, L., Bianchi, F., Ensini, M. and Posada, M. (2013). "The current situation and needs of rare disease registries in Europe." Public Health Genomics **16**(6): 288-298.

Taruscio, D., Mollo, E., Gainotti, S., Posada de la Paz, M., Bianchi, F. and Vittozzi, L. (2014). "The EPIRARE proposal of a set of indicators and common data elements for the European platform for rare disease registration." Arch Public Health **72**(1): 35.

Taruscio, D., Vittozzi, L., Choquet, R., Heimdal, K., Iskrov, G., Kodra, Y., Landais, P., Posada, M., Stefanov, R., Steinmueller, C., Swinnen, E. and Van Oyen, H. (2015). "National registries of rare diseases in Europe: an overview of the current situation and experiences." Public Health Genomics **18**(1): 20-25.

Thompson, R., Johnston, L., Taruscio, D., Monaco, L., Béroud, C., Gut, I. G., Hansson, M. G., t Hoen, P. B., Patrinos, G. P., Dawkins, H., Ensini, M., Zatloukal, K., Koubi, D., Heslop, E., Paschall, J. E., Posada, M., Robinson, P. N., Bushby, K. and Lochmüller, H. (2014). "RD-Connect: an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research." J Gen Intern Med **29 Suppl 3**(Suppl 3): S780-787.

Thyen, U., Ittermann, T., Flessa, S., Muehlan, H., Birnbaum, W., Rapp, M., Marshall, L., Szarras-Capnik, M., Bouvattier, C., Kreukels, B. P. C., Nordenstroem, A., Roehle, R. and Koehler, B. (2018). "Quality of health care in adolescents and adults with disorders/differences of sex development (DSD) in six European countries (dsd-LIFE)." BMC Health Serv Res **18**(1): 527.

Thyen, U., Lanz, K., Holterhus, P. M. and Hiort, O. (2006). "Epidemiology and initial management of ambiguous genitalia at birth in Germany." Horm Res **66**(4): 195-203.

Timmermans, S., Yang, A., Gardner, M., Keegan, C. E., Yashar, B. M., Fechner, P. Y., Shnorhavorian, M., Vilain, E., Siminoff, L. A. and Sandberg, D. E. (2019). "Gender destinies: assigning gender in Disorders of Sex Development-Intersex clinics." Sociol Health Illn **41**(8): 1520-1534.

Torky, A., Sinaii, N., Jha, S., Desai, J., El-Maouche, D., Mallappa, A. and Merke, D. P. (2021). "Cardiovascular Disease Risk Factors and Metabolic Morbidity in a Longitudinal Study of Congenital Adrenal Hyperplasia." J Clin Endocrinol Metab.

Traino, K. A., Roberts, C. M., Fisher, R. S., Delozier, A. M., Austin, P. F., Baskin, L. S., Chan, Y. M., Cheng, E. Y., Diamond, D. A., Fried, A. J., Kropp, B., Lakshmanan, Y., Meyer, S. Z., Meyer, T., Buchanan, C., Palmer, B. W., Paradis, A., Reyes, K. J., Tishelman, A., Williot, P., Wolfe-Christensen, C., Yerkes, E. B., Mullins, L. L. and Wisniewski, A. B. (2022). "Stigma, Intrusiveness, and Distress in Parents of Children with a Disorder/Difference of Sex Development." J Dev Behav Pediatr **43**(7): e473-e482.

Tresoldi, A. S., Sumilo, D., Perrins, M., Toulis, K. A., Prete, A., Reddy, N., Wass, J. A. H., Arlt, W. and Nirantharakumar, K. (2020). "Increased Infection Risk in Addison's Disease and Congenital Adrenal Hyperplasia." J Clin Endocrinol Metab **105**(2): 418-429.

Tumiene, B. and Graessner, H. (2021). "Rare disease care pathways in the EU: from odysseys and labyrinths towards highways." J Community Genet **12**(2): 231-239.

van der Kamp, H. J. and Wit, J. M. (2004). "Neonatal screening for congenital adrenal hyperplasia." Eur J Endocrinol **151 Suppl 3**: U71-75.

van der Straaten, S., Springer, A., Zecic, A., Hebenstreit, D., Tonnhofer, U., Gawlik, A., Baumert, M., Szeliga, K., Debulpaep, S., Desloovere, A., Tack, L., Smets, K., Wasniewska, M., Corica, D., Calafiore, M., Ljubicic, M. L., Busch, A. S., Juul, A., Nordenström, A., Sigurdsson, J., Flück, C. E., Haamberg, T., Graf, S., Hannema, S. E., Wolffenbuttel, K. P., Hiort, O., Ahmed, S. F. and Cools, M. (2020). "The External Genitalia Score (EGS): A European Multicenter Validation Study." J Clin Endocrinol Metab **105**(3).

Varni, J. W., Limbers, C. A., Neighbors, K., Schulz, K., Lieu, J. E., Heffer, R. W., Tuzinkiewicz, K., Mangione-Smith, R., Zimmerman, J. J. and Alonso, E. M. (2011). "The PedsQL™ Infant Scales: feasibility, internal consistency reliability, and validity in healthy and ill infants." Qual Life Res **20**(1): 45-55.

Wallace, A. M., Beastall, G. H., Cook, B., Currie, A. J., Ross, A. M., Kennedy, R. and Girdwood, R. W. (1986). "Neonatal screening for congenital adrenal hyperplasia: a programme based on a novel direct radioimmunoassay for 17-hydroxyprogesterone in blood spots." J Endocrinol **108**(2): 299-308.

Weise, M., Drinkard, B., Mehlinger, S. L., Holzer, S. M., Eisenhofer, G., Charmandari, E., Chrousos, G. P. and Merke, D. P. (2004). "Stress dose of hydrocortisone is not beneficial in patients with classic congenital adrenal hyperplasia undergoing short-term, high-intensity exercise." J Clin Endocrinol Metab **89**(8): 3679-3684.

Werumeus Buning, J., Touw, D. J., Brummelman, P., Dullaart, R. P. F., van den Berg, G., van der Klauw, M. M., Kamp, J., Wolffenbuttel, B. H. R. and van Beek, A. P. (2017). "Pharmacokinetics of oral hydrocortisone - Results and implications from a randomized controlled trial." Metabolism **71**: 7-16.

White, E. K., Wagner, I. V., van Beuzekom, C., Iotova, V., Ahmed, S. F., Hiort, O. and Pereira, A. M. (2022). "A critical evaluation of the EU-virtual consultation platform (CPMS) within the European Reference Network on Rare Endocrine Conditions." Endocr Connect **11**(11).

White, K. and Arlt, W. (2010). "Adrenal crisis in treated Addison's disease: a predictable but under-managed event." Eur J Endocrinol **162**(1): 115-120.

White, P. C. and Speiser, P. W. (2000). "Congenital adrenal hyperplasia due to 21-hydroxylase deficiency." Endocr Rev **21**(3): 245-291.

Whittle, E. and Falhammar, H. (2019). "Glucocorticoid Regimens in the Treatment of Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis." J Endocr Soc **3**(6): 1227-1245.

Wijaya, M., Huamei, M., Jun, Z., Du, M., Li, Y., Chen, Q., Chen, H. and Song, G. (2019). "Etiology of primary adrenal insufficiency in children: a 29-year single-center experience." J Pediatr Endocrinol Metab **32**(6): 615-622.

Wilkinson, M. D., Dumontier, M., Aalbersberg, I. J., Appleton, G., Axton, M., Baak, A., Blomberg, N., Boiten, J. W., da Silva Santos, L. B., Bourne, P. E., Bouwman, J., Brookes, A. J., Clark, T., Crosas, M., Dillo, I., Dumon, O., Edmunds, S., Evelo, C. T., Finkers, R., Gonzalez-Beltran, A., Gray, A. J., Groth, P., Goble, C., Grethe, J. S., Heringa, J., t Hoen, P. A., Hooft, R., Kuhn, T., Kok, R., Kok, J., Lusher, S. J., Martone, M. E., Mons, A., Packer, A. L., Persson, B., Rocca-Serra, P., Roos, M., van Schaik, R., Sansone, S. A., Schultes, E., Sengstag, T., Slater, T., Strawn, G., Swertz, M. A., Thompson, M., van der Lei, J., van Mulligen, E., Velterop, J., Waagmeester, A., Wittenburg, P., Wolstencroft, K., Zhao, J. and Mons, B. (2016). "The FAIR Guiding Principles for scientific data management and stewardship." Sci Data **3**: 160018.

Wisniewski, A. B. (2017). "Psychosocial implications of disorders of sex development treatment for parents." Curr Opin Urol **27**(1): 11-13.

Wolfe-Christensen, C., Fedele, D. A., Mullins, L. L., Lakshmanan, Y. and Wisniewski, A. B. (2014). "Differences in anxiety and depression between male and female caregivers of children with a disorder of sex development." J Pediatr Endocrinol Metab **27**(7-8): 617-621.

Wolfe-Christensen, C., Wisniewski, A. B., Mullins, A. J., Reyes, K. J., Austin, P., Baskin, L., Bernabé, K., Cheng, E., Fried, A., Frimberger, D., Galan, D., Gonzalez, L., Greenfield, S., Kolon, T., Kropp, B., Lakshmanan, Y., Meyer, S., Meyer, T., Nokoff, N. J., Palmer, B., Poppas, D., Paradis, A., Yerkes, E. and Mullins, L. L. (2017). "Changes in levels of parental distress after their child with atypical genitalia undergoes genitoplasty." J Pediatr Urol **13**(1): 32.e31-32.e36.

Wolfe, B. L. (1985). "The influence of health on school outcomes. A multivariate approach." Med Care **23**(10): 1127-1138.

Yeatts, K. B., Stucky, B., Thissen, D., Irwin, D., Varni, J. W., DeWitt, E. M., Lai, J. S. and DeWalt, D. A. (2010). "Construction of the Pediatric Asthma Impact Scale (PAIS) for the Patient-Reported Outcomes Measurement Information System (PROMIS)." J Asthma **47**(3): 295-302.