EuRREB Coordinator
Prof. Faisal Ahmed

University of Glasgow & Leiden University Medical Center

‘Rare Disease Registries – seeing the forest for the trees’

EuRREB
European Registries for Rare
Endocrine and Bone conditions

University of Glasgow

Universiteit Leiden

Rare Disease Registries

Seeing The Forest For The Trees

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Disclosures

Research Collaboration Grants – GenSci, Novo Nordisk A/S, Pfizer

Why Develop A Rare Disease Registry

- Collection of standardised clinical information on rare conditions:
    - Understand pathogenesis & natural history
    - Improve diagnostic yield
    - Understand short-term and long-term outcome
    - Assess quality of care
    - Improve the case for service development

- To support research – epidemiology, genetic, molecular

- Establish a platform for evaluating drugs & devices

- To connect patients, families, clinicians and scientists

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- Unsustainable
- Poor quality
- Devaluation
- Disaffection with stakeholders

Plan

- The range of registries
- Sustainability is key
- Quality
- The Registry Ecosystem

Overview Of Registry Projects

2000 2005 2010 2015 2020 2025

Cambridge DSD Database

Phenotypic Features, Androgen Receptor Binding, and Mutational Analysis in 278 Clinical Cases Reported as Androgen Insensitivity Syndrome*

Scottish Audit of Genital Anomalies

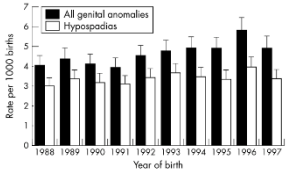
SDSD MCN Clin Audit System

Scottish Linked Genital Anomaly Database

SGAN / SDSD Register

Chief Scientist Office Of Scotland

Prevalence of hypospadias and other genital anomalies among singleton births, 1988–1997, in Scotland



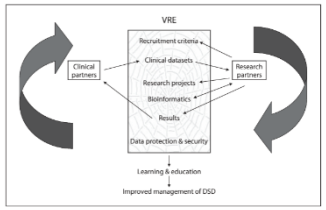
ESPE DSD

Euro-DSD

The European Disorder of Sex Development Registry: A Virtual Research Environment

S.F. Ahmed[a] M. Rodie[a] J. Jiang[b] R.O. Sinnott[b]

Sex Dev 2010;4:192–198



BSPED GH Audit

NHS Scotland Linked Datasets

Scottish Audit of Atypical Genitalia

I-DSD

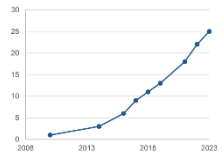
I-CAH

I-TS

I-HH

SDMregistries

Cumulative outputs – original data publications



EuRRECa (e-REC & Core Registry)

EuRR-Bone

EuRRE B

EU4health

HaDEA

The current landscape of European registries for rare endocrine conditions

GloBE-Reg

Different Types Of Registries

Type Of Registry	Example	Pro	Cons
Data Linkage	- SGA Linked database - NHS Scotland databases	- Data collected 'automatically' with no participant burden - Epidemiology and public health utility - Independent of health care providers - Generates hypotheses - Outcomes that may matter most for public health	- Outcomes limited to available datasets - Requires rigorous infrastructure and governance - Expense in setting up - Limited experience of longitudinal studies - Rare conditions – limited value unless coverage very wide
Surveillance Systems	- SAAG - EuRRECa e-REC - BPSU	- Information obtained from health care providers - Targeted information with low participant burden - Can provide epidemiological data - Non-personally identifiable data - No need for informed consent - Data can be used by networks to capture activity - Agile and versatile	- Limited information - Requires combining to a secondary survey - Secondary surveys can include personally identifiable data - Reporter bias - Cross-verification of returns to check reporting bias - Grey area between service provision and research
National Clinical Audit Systems	- SDSD - SPEG	- NHS systems so do not require opt-in consent - Can support networks esp for benchmarking	- Data entry, data access and re-use - Process for change - One size fits all; region not large enough for rare conditions
Natural History Registries	- I-DSD/I-CAH/I-TS - EuRRECa	- Focus on natural history of specific conditions - Support networks (local, regional or international) - Research utility - Patient and Clinician focused - Suited for outcome-based research for rare conditions - Can be used for benchmarking	- Initial set up - Long-term sustainability - May suffer from selection bias - Temporal and geographical confounders
Study Registries	- GloBE-Reg	- Focus on specific interventions - Clear aim from the start, eg PAS - Clear awareness of strengths and weaknesses - Clear design with limited dataset - Likelihood of achieving outcome	- Limited scope - Requires quality assurance protocols esp if PAS - Managing expectations of stakeholders

University of Glasgow

Natural History vs A Study Registry

Universiteit Leiden

	Natural History Registry	Study Registry
Definition	Data collection system on a group of people defined by a particular condition and used to conduct a study.	Investigation of a research question or hypothesis using data from an existing patient registry or from a new registry set up for the study
Timelines	Generally planned to be long-term	Timelines driven by the collection and analysis of the data relevant for the specific study
Patient enrolment	Aimed at wide enrolment	Defined by research objectives
Data collection	Wide range of data may be collected depending on the purpose of the registry; with an agreed core set of data elements	Restricted to what is needed for the research question including data on potential confounders and effect modifiers
Analysis plan	Statistical analysis usually descriptive	Specific analytical considerations may be required for the study objectives
Data quality control	Data systems ensure data integrity and quality check performed when investigators use data	Quality assurance to be performed for the study data; quality control to be prospectively defined and monitored

And Then There Are Several Shades Of Registries

Pharma-Led

- Conflict of Interest
- Lack of Transparency & Data Access
- Data Integrity and Reliability
- Patient Privacy Concerns
- Regulatory and Ethical Issues
- Public Trust and Credibility
- Marketing disguised as research
- Cost
- Specificity &

Patient-Led

- Lack of Expertise
- Bias and Advocacy Influence
- Inconsistent Data Collection
- Conflicts with Healthcare Providers, Researchers, Other Groups
- Data Governance & Access
- Limited Independence
- Scientific Rigour
- Limited Scalability and Interoperability

Public-Funding Led

- Data Access - cumbersome
- Privacy & Ethical issues
- Data Standardization & Quality
- Granularity and specificity of outcomes, esp for rare conditions
- Restrictions on commercial use
- Public Distrust
- Political sensitivity
- Coverage – too wide

Professional/Academic

- Data Access
- Data Quality
- Confidentiality & Ethical Concerns
- Conflict of Interest
- Regulatory & Legal barriers
- Mismatch in research priorities
- Sustainability

The Proliferation, Awareness & Participation In Registries

Orphanet Report Series
Rare Diseases collection
December 2021

COVERAGE	NUMBER OF REGISTRIES*
European	97
International**	76
National	561
Regional	78
TOTAL	**812**

Public Health Genomics

Public Health Genomics 2013;16:288–298
DOI: 10.1159/000355934
Published online: February 3, 2014

The Current Situation and Needs of Rare Disease Registries in Europe

D. Taruscio[a] S. Gainotti[a] E. Mollo[a] L. Vittozzi[a] F. Bianchi[b, c] M. Ensini[d] M. Posada[e, f]

Table 1. Number (percentage) of registries stratified by disease scope and registered cases

Disease scope (RDs included)	Registered cases (registries in the disease scope category)				Total
	10–200	201–1,000	1,001–5,000	>5,000	
Just one	34 (45.3)	29 (38.7)	8 (10.7)	4 (5.3)	75 (100)
A group of related RDs	22 (21.8)	38 (37.6)	27 (26.7)	14 (13.9)	101 (100)
Several RDs (or group of RDs) not related among them	5 (19.2)	4 (15.4)	7 (26.9)	10 (38.5)	26 (100)
All RDs	2 (12.5)	2 (12.5)	3 (18.8)	9 (56.3)	16 (100)
Total	63 (28.9)	73 (33.5)	45 (20.6)	37 (17.0)	218 (100)

The current landscape of European registries for rare endocrine conditions

S R Ali[1,2], J Bryce[2], M Cools[3,4], M Korbonits[5], J G Beun[6], D Taruscio[7], T Danne[8], M Dattani[9], O M Dekkers[10], A Linglart[11], I Netchine[12], A Nordenstrom[13], A Patocs[14], L Persani[15,16], N Reisch[17], A Smyth[2], Z Sumnik[18], W E Visser[19], O Hiort[20], A M Pereira[21] and S F Ahmed[1,2] on behalf of Endo-ERN

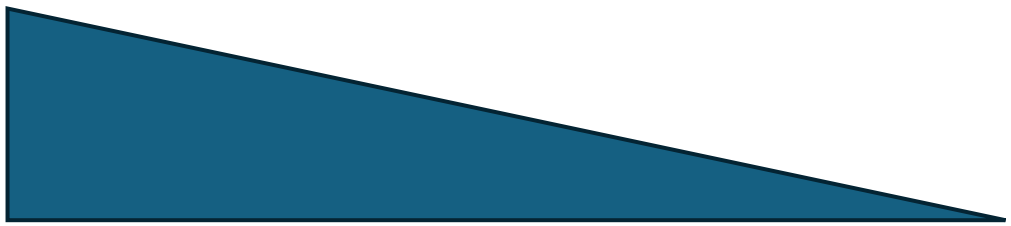
- There are over 600 specific rare endocrine diagnoses
- Even for the small proportion of conditions covered by Endo-ERN
  - There are several registries
    - International
    - National
    - Local
- For 75% of conditions in Endo-ERN, an international registry already existed in 2016
- Awareness and participation in existing registries was suboptimal but the desire to have a registry was high

European Journal of Endocrinology
(2019) **180**, 89–98

Sustaining Registries

Clear Vision & Purpose At Start, eg

- **Care Quality Improvement**
- **Research**



Likelihood of Failure

- **Evidence of activity**
- **Benefit to stakeholders and wider community**

Sustaining Registries

Likelihood of Failure

Clear Vision & Purpose At Start, eg
- Care Quality improvement
- Research

- Governance
- Ethics overview
- Legal support

- Long-term Funding
- Business model & economies of scale
- Independence from a single source

- Data quality & integrity
- Data standardization

- Data Security & Privacy
- Infrastructure
- Development & Maintenance

- Stakeholder involvement
- Data sharing & re-using
- Training & education

- **Evidence of activity**
- **Benefit to stakeholders and wider community**

Sustaining Registries = Quality Of Registries

International Journal of Environmental Research and Public Health

MDPI

Review

Recommendations for Improving the Quality of Rare Disease Registries

Yllka Kodra [1,*], Jérôme Weinbach [2], Manuel Posada-de-la-Paz [3], Alessio Coi [4,5], S. Lydie Lemonnier [6], David van Enckevort [7], Marco Roos [8], Annika Jacobsen [8], Ronald Cornet [9], S. Faisal Ahmed [10], Virginie Bros-Facer [11], Veronica Popa [12], Marieke Van Meel [13], Daniel Renault [14], Rainald von Gizycki [15], Michele Santoro [4,5], Paul Landais [2,16], Paola Torreri [1], Claudio Carta [1], Deborah Mascalzoni [17], Sabina Gainotti [18], Estrella Lopez [3], Anna Ambrosini [19], Heimo Müller [20], Robert Reis [20], Fabrizio Bianchi [4,5], Yaffa R. Rubinstein [21], Hanns Lochmüller [22,23] and Domenica Taruscio [1]

Int. J. Environ. Res. Public Health **2018**, *15*, 1644; doi:10.3390/ijerph15081644

Clear Vision & Purpose At Start, eg
- **Care Quality improvement**
- **Research**

- **Governance**
- **Ethics overview**
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- **Data Security & Privacy**
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- **Data sharing & re-using**
- **Training & education**

- **Evidence of activity**
- **Benefit to stakeholders and wider community**

Assessing The Quality Of A Registry

Int. J. Environ. Res. Public Health **2021**, *18*, 11968. https://doi.org/10.3390/ijerph182211968

International Journal of *Environmental Research and Public Health*

MDPI

The Quality Evaluation of Rare Disease Registries—An Assessment of the Essential Features of a Disease Registry

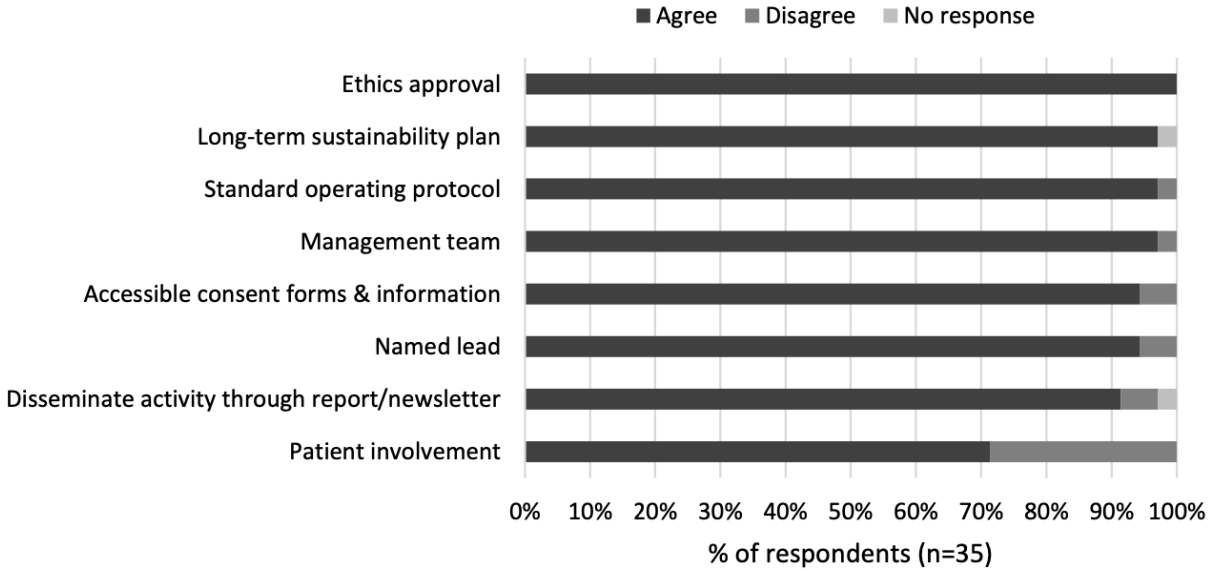
Salma Rashid Ali [1,2], Jillian Bryce [2], Yllka Kodra [3], Domenica Taruscio [3], Luca Persani [4,5] and Syed Faisal Ahmed [1,2,6,*]

Survey Domain	Item
Contact details for respondent	Name Email Institution Registry/Registries [a]
Governance	The registry should have a named lead The registry should have a management team Patients should be involved in the governance of the registry The registry should have a long-term sustainability plan The registry should have ethics approval The registry should have publicly accessible consent forms and participant information sheets The registry should have a document outlining its standard operating protocol The registry should disseminate its activity through a report or a newsletter If you disagree with any of the above criteria, please comment:
Data quality	The core data elements in the registry should have a clear definition and coded values The registry should specify who is responsible for entering the clinical data The registry should have procedures for checking data quality The registry should provide training to all users If you disagree with any of the above criteria, please comment:
IT infrastructure	The registry should have a web interface The web-interface should allow uploading and downloading of data The registry should have data breach procedures in place The registry should have clear procedures for erasing personal data when requested The registry should have clear procedures that only allow authorized users to have 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?

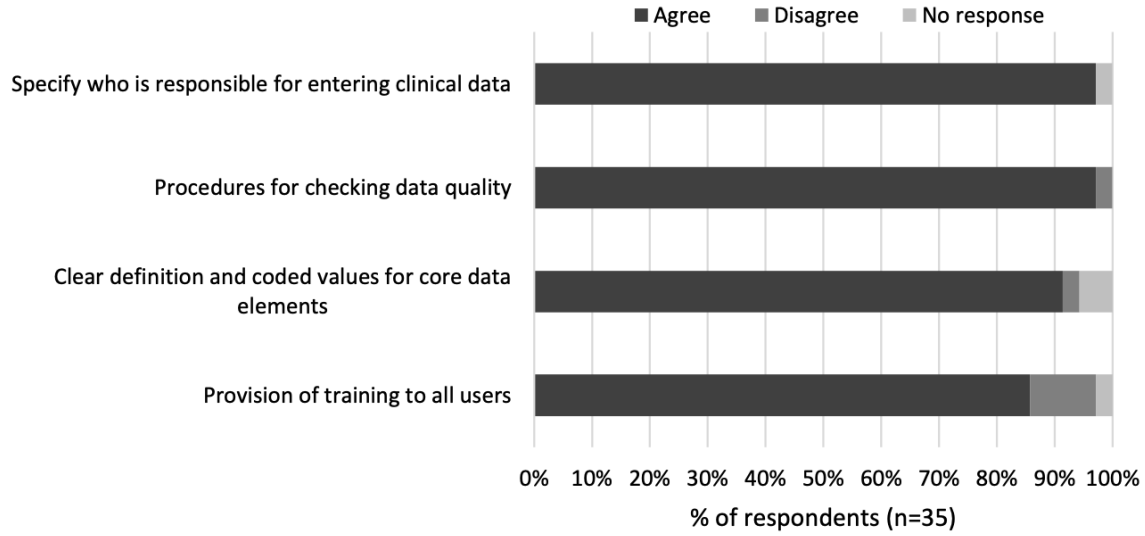
EuRRECa European Registries For Rare Endocrine Conditions

Level Of Consensus On Quality Criteria

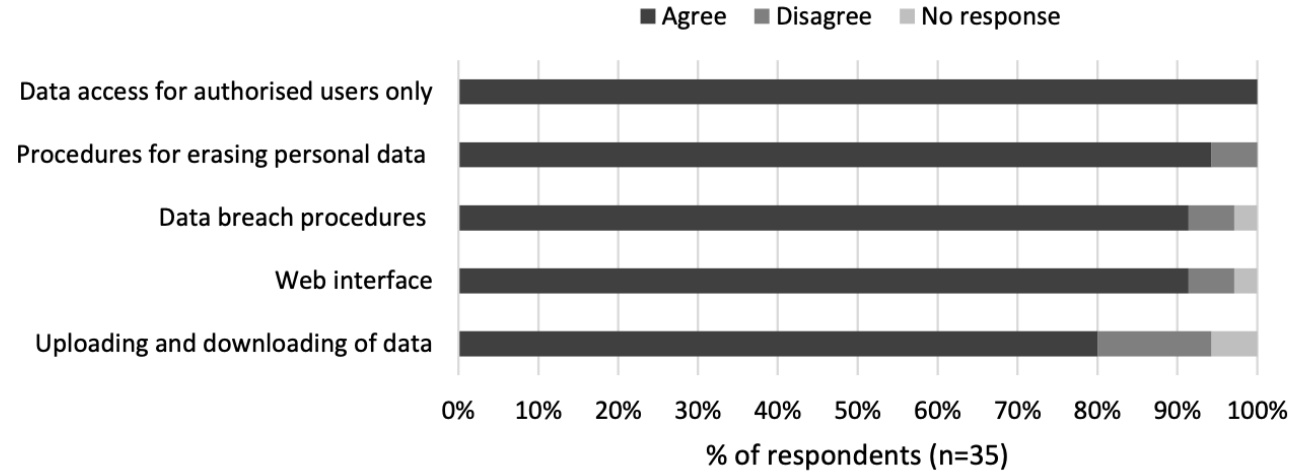
Governance



Data Quality

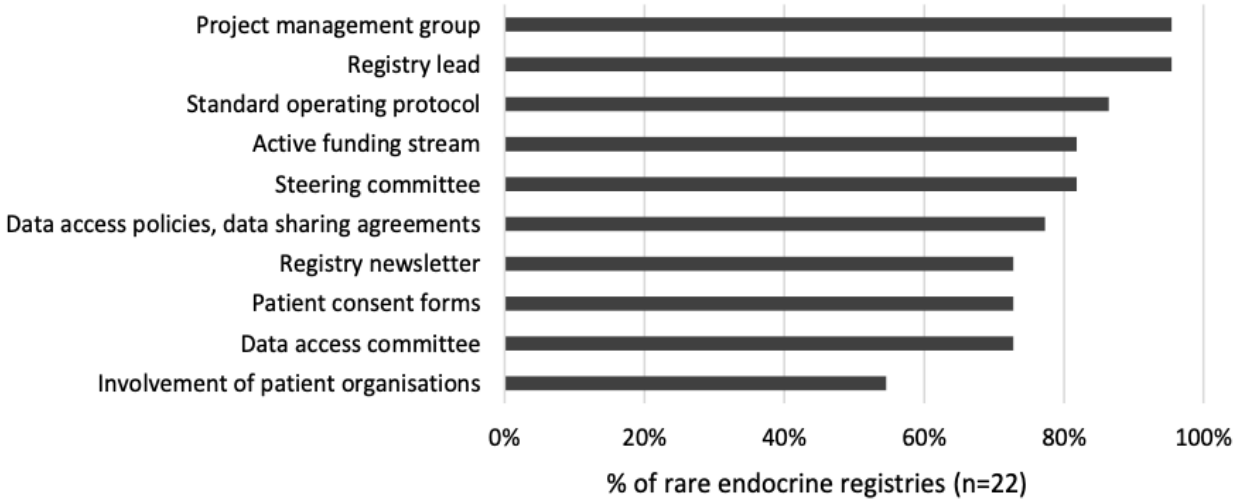


IT Infrastructure

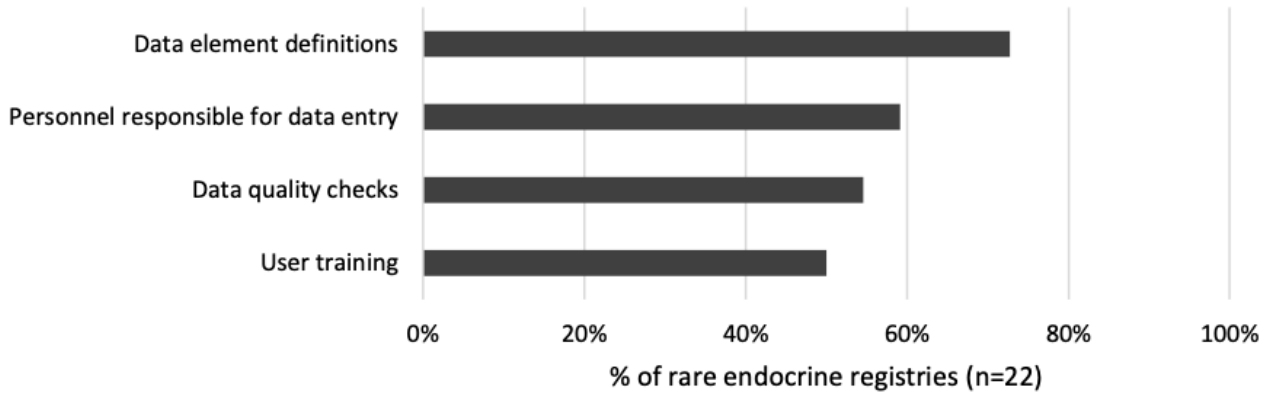


Evidence Of Complying With Quality Criteria

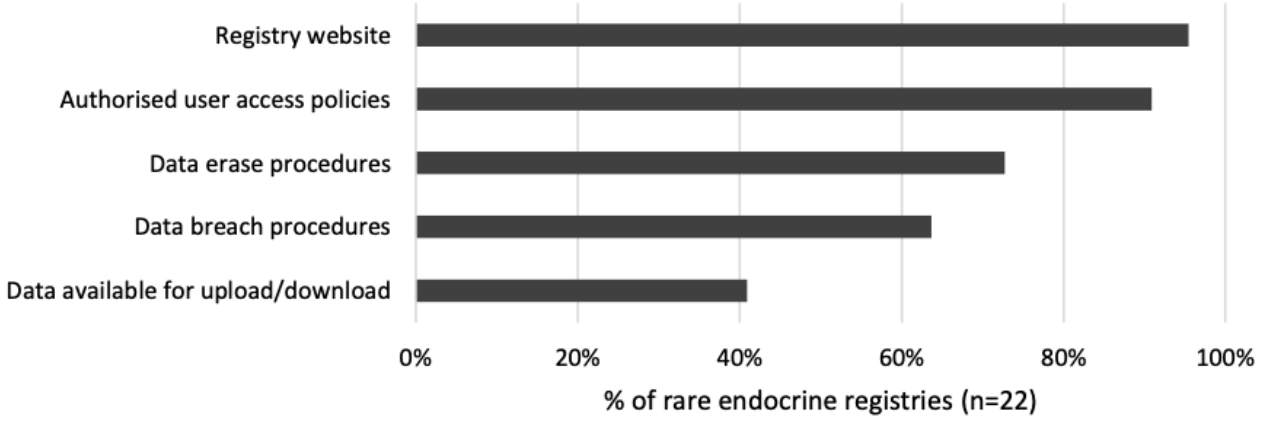
Governance



Data Quality



IT Infrastructure



Data Quality In The Eyes of GDPR

Article 5(1)(d) of the GDPR states that personal data shall be:

"accurate and, where necessary, kept up to date; every reasonable step must be taken to ensure that personal data that are inaccurate, having regard to the purposes for which they are processed, are erased or rectified without delay."

In practice, this means that organizations that collect and process personal data under GDPR are required to ensure that the data they hold is accurate, relevant, and current.

- Data minimisation
- Quality assurance
- Data Protection Impact Assessment
- Privacy notices (for all subjects, ie participants, users)
- Data sharing – EU 'adequacy' vs 'non-adequacy'

The Minimum Dataset

Hormone Research in Paediatrics

Horm Res Paediatr , DOI: 10.1159/000533763
Received: May 2, 2023
Accepted: July 31, 2023
Published online: September 13, 2023

Development of A Minimum Dataset for the Monitoring of Recombinant Human Growth Hormone (rhGH) Therapy Use in Children with Growth Hormone Deficiency (GHD) – A GloBE-Reg Initiative

Chen SC, Bryce J, Chen M, Charmandari E, Choi J-H, Dou X, Gong C, Hamza R, Harvey J, Hoffman AR, Horikawa R, Johannson G, Jorge AADL, Miller BS, Roehrich S, Sävendahl L, Tseretopoulou X, Vitali D, Wajnrajch M, Ahmed SF

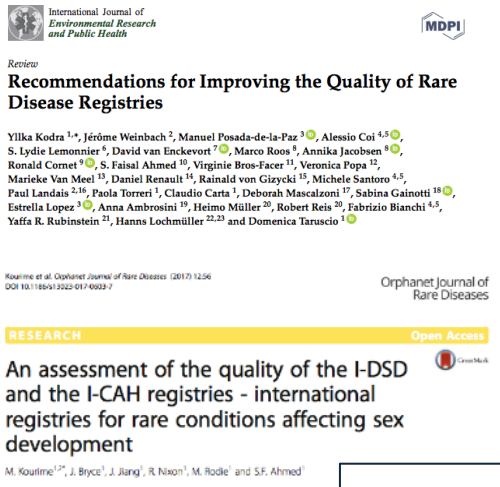
GloBE-Reg

Describes a methodology that has been developed to define a minimum dataset that is important and easy to collect.

The Registries 'Ecosystem'

Care Quality

Data Quality


International Journal of Environmental Research and Public Health

MDPI

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Kourime et al. Orphanet Journal of Rare Diseases (2017) 12:56
DOI 10.1186/s13023-017-0603-7

Orphanet Journal of Rare Diseases

RESEARCH Open Access

An assessment of the quality of the I-DSD and the I-CAH registries - international registries for rare conditions affecting sex development

M. Kourime[1,2*], J. Bryce[1], J. Jiang[1], R. Nixon[1], M. Rodie[1] and S.F. Ahmed[1]

SDM Registries

Research Awards

Bern, 2022

Stockholm, 2024

Postgraduate Courses

Stakeholder Involvement


Sexual Development

Original Article

Involving Individuals with Disorders of Sex Development and Their Parents in Exploring New Models of Shared Learning: Proceedings from a DSDnet COST Action Workshop

Sanders C.[a-c] · Hall J.[c] · Sanders C.[d] · Dessens A.[f] · Bryce J.[e] · Callens N.[h] · Cools M.[i] · Kourime M.[e] · Kyriakou A.[e] · Springer A.[j] · Audi L.[l] · Balsamo A.[n] · Iotova V.[o] · Mladenov V.[o] · Krawczynski M.[p] · Nordenskjöld A.[q] · Rozas M.[m] · Claahsen-van der Grinten H.[g] · Hiort O.[r] · Riedl S.[k] · Ahmed S.F.[e]

Author affiliations

Keywords: Communication · Disorders of sex development · Research · Support group

Sex Dev 2018;12:225-231
https://doi.org/10.1159/000490081


NATURE REVIEWS | ENDOCRINOLOGY

Addressing gaps in care of people with conditions affecting sex development and maturation

Olaf Hiort, Martine Cools, Alexander Springer, Ken McElreavey, Andy Greenfield, Stefan A. Wudy, Alexandra Kulle, S. Faisal Ahmed, Arianne Dessens, Antonio Balsamo, Mohamad Maghnie, Marco Bonomi, Mehul Dattani, Luca Persani and Laura Audi, on behalf of COST Actions DSDnet and GnRH Network as well as the European Reference Network for Rare Endocrine Conditions (Endo–ERN,

VOLUME 15 | OCTOBER 2019 | 615

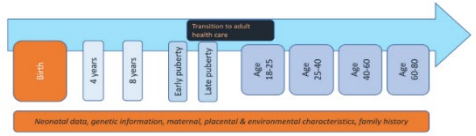

EJE Clinical & translational endocrinology from around the globe

Standardised data collection for clinical follow-up and assessment of outcomes in Differences of Sex Development (DSD): Recommendations from the COST Action DSDnet

in European Journal of Endocrinology

Authors: Christa Flueck [1], Anna Nordenstrom [2], S. Faisal Ahmed [3], Salma Rashid Ali [4], Marta Berra [5], Joanne Hall [6], Birgit Koehler [7], Vickie Pasterski [8], Ralitsa Robeva [9], Katinka Schweizer [10], Alexander Springer [11], Puck Westerveld [12], Olaf Hiort [13] and Martine Cools [14]

View Less



Management & Support

I-DSD/I-CAH/I-TS Steering Committee
Anna Nordenstrom, Stockholm

Data Access
Jeremy Tomlinson, Oxford

Learning & Training
Sabine Hannema, Amsterdam

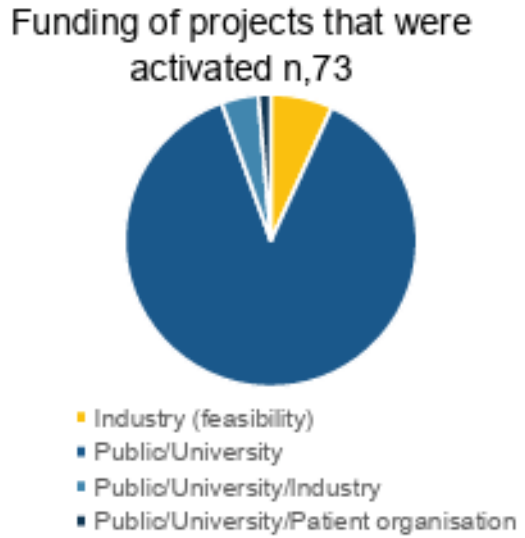
Care Quality Improvement
Justin Davies, Southampton

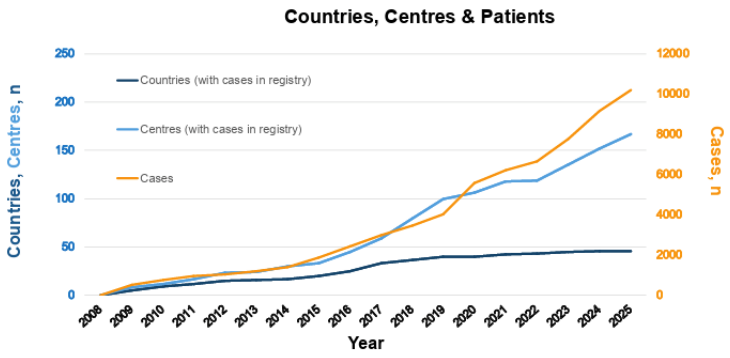
Project Support (Glasgow)
Administrative - Jillian Bryce, Minglu Chen, Martin McMillan
Data & Clinical Scientist - Malika Alimussina, Salma Ali, Sanhita Koley, Angela Lucas-Herald, Xanthippi Tserotopoulou
UofG Services – Admin, Human Resources, IT Services, Legal & Contracts, External Contractors

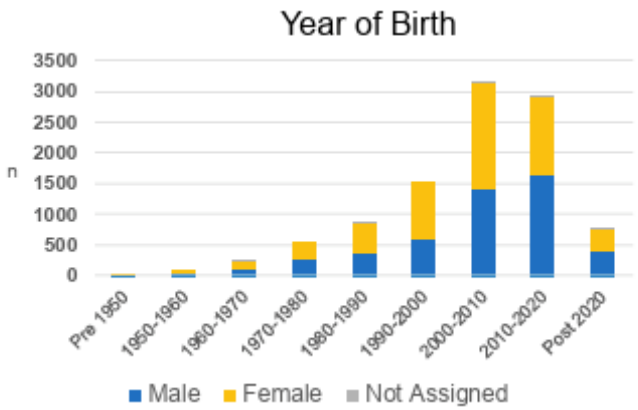
SDMregistries - Opportunities

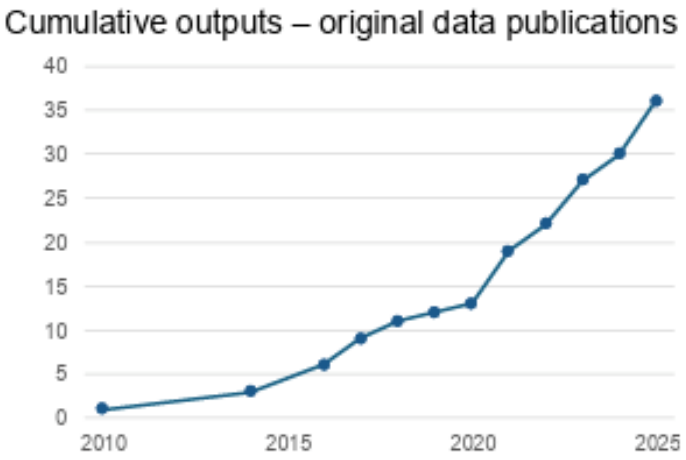
June 2025 – 10,179 cases
167 centres from 46 countries with cases
Additional 72 centres from 37 countries in dissemination list

https://sdmregistries.org/



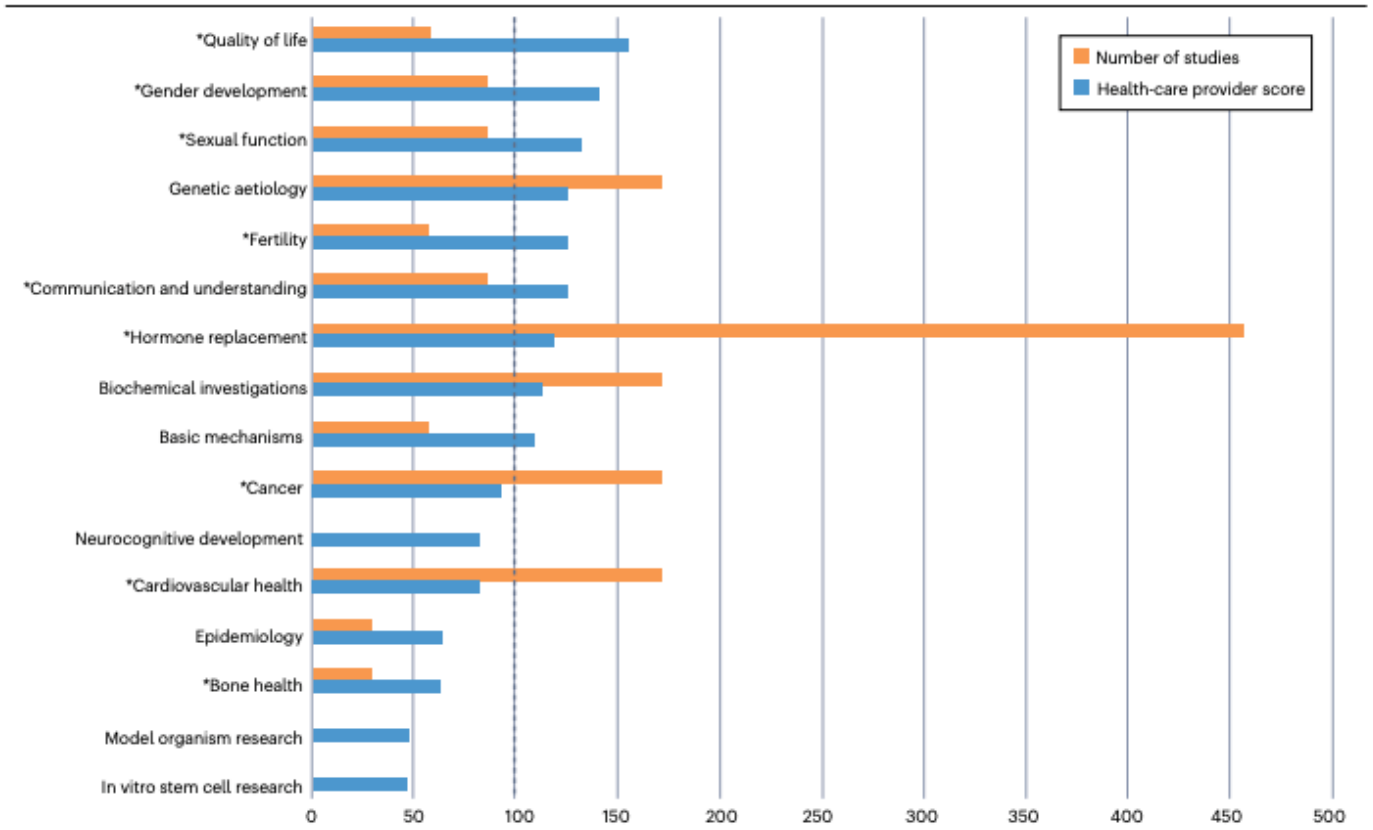






Stakeholder Priorities & Current Research

Survey of patients, parents, healthcare professionals and researchers



- Match research to areas of priority
- Researchers need to continue engaging with patients and health care providers
- Provide incentives for data access in high priority, low activity fields

Ahmed et al, Nat Rev Dis Primers 2025

Summary

- Rare disease registries come in all shapes and sizes
- Need to reduce the number of rare disease registries while increasing their versatility
- For long-term outcomes, sustainability is key, and this can be achieved through:-
  - Low-cost platforms with wide applicability
  - Transparent governance structure with a strong emphasis on data governance
  - Understanding the needs of a diverse range of stakeholders
  - An ‘ecosystem’ with visible outputs that are relevant to its stakeholders
  - Reducing reliance on a single funder or organisation

Thanks

Registries Team, Glasgow

Karyn Cooper
Admin Support

Jillian Bryce
Project Manager

Faisal Ahmed
Project Lead

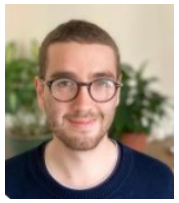
Malika Alimussina
Senior Clin Scientist

Chris Smythe
Registry Development

Yolanda Johnson
Finance Admin

Minglu Chen
Project Support

Jessica Anderson
PhD Student



Joseph McElvaney
Clin Res Fellow

Sanhita Koley
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Registries Team, Leiden

Dec 2016, Pre-EndoERN/EuRRECa

Paul Ellis, Claire Munro & Louise Andrew - Legal
Iain Sim & Paul McLaughlin – IT Services
Gemma Tougher – Data Protection Office

Abi Adewumi-Ogunjobi – REC4 Manager
Judith Godden – WoSREC Scientific Officer
Stewart Whyte – Data Protection Officer