



## **THE INTERNATIONAL DISORDERS OF SEX DEVELOPMENT REGISTRY**

### **I-DSD REGISTRY**

#### **PROTOCOL FOR A RESEARCH DATABASE**

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January 2015  
Version 4.0



## **Preface:**

The protocol for the I-DSD Registry describes the background, design and organisation of the study. The protocol will be maintained by the I-DSD Project Management Group at the University of Glasgow over the course of the project through new releases of the entire protocol, or issues of updates either in the form of revisions of complete chapters or pages thereof, or in the form of supplemental protocol memoranda. The I-DSD Registry is host to the I-CAH Registry and this protocol applies to both registries.

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## **1. Background**

The I-DSD Registry is used by a group of clinicians and scientists who are involved in performing research as well as delivering clinical care in the field of differences or disorders of sex development (DSD). Most people affected by DSD are identified in childhood and often present in early infancy with atypical development of the external and/or internal reproductive organs. There is a large amount of variation in how children and adults with these conditions are cared for across the world. In addition, there are enormous gaps in our knowledge about the aetiology of these conditions and the long-term outcome in adults with these conditions.

Until quite recently, there was little consensus about data collection in people with a DSD. In 2006, a group of international experts attempted to reach a consensus on terminology and which has now been adopted by many professional groups including the European Society of Paediatric Endocrinology, ESPE<sup>1</sup>, the Accord Alliance<sup>2</sup> and the EuroDSD project<sup>3</sup> – a programme of research between 2008 and 2011 funded by the EU Framework Project 7 grant, dsd-LIFE and DSDnet. As part of the EuroDSD programme, the core dataset was transformed into an electronic web based registry and subsequently transformed into an international DSD Registry. The primary goal of the Registry is to act as a source of observational data that will facilitate audit and research in the field of DSD. The Registry has also become an international database of professionals with an interest in DSD. These goals are compatible with the recommendations of the EU Committee of Experts on Rare Diseases<sup>4</sup> that were published in 2011.

## **2. Eligibility of Users of Registry**

### **2.1. Clinical users**

Clinical users shall be eligible to enter data into the Registry and will seek approval from the I-DSD Project Management Group to have this privilege. Only members of a national or international clinical professional society can become a clinical user and will need to show proof of membership. Application for more than one clinical user to act as a lead from the same institution shall be discouraged but not barred. Each clinical lead can identify other members of their team who will require access also as clinical users. Thus, the clinical lead will remain responsible and accountable for data entry. The clinical lead and approved members of the team shall be able to enter, search, edit, and delete data on all the cases that are entered under that clinical lead. Details of the clinical lead and their local institution should be entered on the participant information sheet. Details of the clinical lead and their centre shall also be available on the Registry.

### **2.2. Research users**

Research is a vital role of this research database and research users from commercial and non-commercial organisations are encouraged to apply to I-DSD. Research users shall need to apply to the I-DSD Project Management Group with details of their proposed study. Research users are required to demonstrate that they have obtained relevant national ethics approval for the proposed study. Research studies will be approved by the Project

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<sup>1</sup> [www.eurospe.org/about/workinggroups/DSD.html](http://www.eurospe.org/about/workinggroups/DSD.html)

<sup>2</sup> [Accordalliance.org](http://Accordalliance.org)

<sup>3</sup> [www.euordsd.eu](http://www.euordsd.eu)

<sup>4</sup> [nestor.orpha.net/EUCERD/upload/file/EUCERDRecommendationCE.pdf](http://nestor.orpha.net/EUCERD/upload/file/EUCERDRecommendationCE.pdf)

Management Group. In case of conflict with existing studies, investigators shall be asked to liaise with each other and the proposal discussed with the I-DSD steering committee. Brief details of the research study shall be posted on the Registry. In addition, any form of research output that results from the use of the Registry shall acknowledge its use using the standard sentence:

“This research study was conducted through access to data held in the I-DSD registry (<http://www.i-dsd.org>) originally supported by funding from EuroDSD (in EC FP7/2007–2013 under grant agreement no.201444) and currently supported by MRC award G1100236.”

Each research user can identify other members of their team who will require access for that same period. The research user and approved members of the team shall be able to search data on all the cases that can be shared by the clinical user. Access to patient's samples etc will be through the patient's local health professional only. Details of the research user and their centre shall also be available on the Registry. The use of the Registry by the research user will be approved for a fixed period of time. Research partners shall need to submit a 6-monthly report of their project for continued access to the Registry.

### 2.3. Joint Clinical & Research users

Some partners may have joint clinical and research user status. These users shall need to continue renewing their research user status.

### 2.4. Other users

Other users with no requirement for clinical or research access to the Registry will be able to search the User database to contact other users in a networking capacity. Clinical or Research users who have been inactive in the Registry for 12 months or more will have their access converted to Other user. Users who have been inactive in the Registry for 24 months shall have their access suspended.

### 2.5 Participant Access

Participants in the Registry are able to access a portion of their own record. A secure login link is sent from the system under the authorisation of the lead clinician at the centre where the participant is registered.

### 2.6. UKCRN Portfolio

The project is registered on the UK Clinical Research Network Study Portfolio with UKCRN ID 12729.

### 2.7. Authorship

Research groups using the Register are advised to follow the recommendations issued by the ICJME<sup>5</sup> which has recommended that the following 3 criteria should be met for authorship:-

1. substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. drafting the article or revising it critically for important intellectual content; and
3. final approval of the version to be published.

Activities such as collection of data, acquisition of funding, obtaining local approvals for data entry or general supervision of those entering data do not by themselves qualify for authorship but can be included in addition to the statement which should as a minimum include the three criteria above. If there are/were others in the group who contributed to any of these activities, then they can be acknowledged at the end but the lead will need to highlight their contribution.

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<sup>5</sup> <http://www.icmje.org/recommendations/>

### 3. Eligibility of Cases in Registry

#### 3.1. Eligibility Criteria

Any adult or a child with a condition that is associated with a DSD at a centre with an approved clinician is eligible to be included in the Registry. Conditions which may present as a DSD in one sex but not the other (eg congenital adrenal hyperplasia) are also eligible. Participating clinicians shall be informed about new approved studies, this will encourage them to approach and register suitable cases.

#### 3.2. Provision of Information

Participants and their legal guardians (if patient less than 16yrs old) shall be approached by the clinical lead or a member of their team for approval to include the participant's details on the Registry. Information and the approval form can be provided at the clinic.

#### 3.3. Obtaining Consent

Although the Registry contains exclusively non-identifiable data and there may be no need to obtain informed consent in the UK to share data with EEA and International members, it is recognised that some countries may have different national regulations which require opt-in. For uniformity as well as to comply with the feedback received from patient and user support groups and guidance from the EU Rare Diseases Task Force<sup>6</sup>, it is felt that the opt-in system should be adhered to as a basic minimum standard of consent.

#### 3.4. Minor Assent

As the Registry includes children, it is recommended that an information sheet should be provided for those under the age of 14 years. Over the age of 14 years, these young adults should be provided with the adult information sheet. The minor (under 16 years) may only participate if the minor and a parent or legal guardian both do not raise any objections. If either the parent/legal guardian or the minor declines participation, the minor shall not be enrolled into the Registry. If the minor lacks the capacity to provide assent, parent or legal guardian permission is sufficient. On turning 16 years old, the participant who is already on the Registry should be advised of their participation in the Registry. The Registry will remind the clinical user to do this. The adult information sheet can be used for this purpose.

#### 3.5. Participant Withdrawal from Registry

At any time a participant and/or a participant's legal guardian may request that his or her data or the affected child's data no longer be made available in the Registry. The participant and/or a participant's legal guardian shall make this request to their local clinician who is the clinical lead and who can delete the case. The participant and/or a participant's legal guardian can also make the request directly to the I-DSD Project Management Group. In the case of the latter, a confirmation of withdrawal shall be sent by the I-DSD Project Management Group to the clinical lead.

### 4. Approvals

The I-DSD Registry has been approved by the NHS Information Governance Body that oversees issues related to patient data protection in Glasgow (Caldicott Guardian) and has also been approved by the UK Research Ethics Committee and the Ethics Committee of the EuroDSD programme. All information stored in the Registry, and access to that information, conforms to the UK Data Protection Act (1998). However, all participating clinical users and research users should also follow their own national regulations and provide assurance to the I-DSD Project Management Group that national regulations are being followed for data handling as well as research. The information sheet and consent forms should include the name of the local clinical lead, local institution and local institutional contact. The CAH

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<sup>6</sup> [http://ec.europa.eu/health/rare\\_diseases/publications/index\\_en.htm](http://ec.europa.eu/health/rare_diseases/publications/index_en.htm)

(Congenital Adrenal Hyperplasia) support group and the AIS (Androgen Insensitivity Syndrome) Support Group in the UK have also been consulted on the development of the Registry.

## 5. Using The Registry

### 5.1. Flow of Information

Appendix 1 summarises how information shall flow in the Registry as well as the checks that will be employed for the purpose of security.

### 5.2. The Core Dataset

The core dataset is restricted to a set of identifiers and diagnostic classification. Those marked with an asterisk are mandatory. A local identifier should be stored in a separate database held locally with the clinical user. Further details about the dataset can be obtained by visiting [www.i-dsd.org](http://www.i-dsd.org)

### 5.3. Accessing and Navigating the Registry

Every approved user shall be provided with a unique log in and choose their own password. Users shall only log on with their username. For research users, the log in shall be time limited. Further details of how to access and use the Registry in general can be obtained by visiting [www.i-dsd.org](http://www.i-dsd.org). All users can access user registration information on other users. All clinical and research users shall be able to access the core dataset for those participants where the latter have approved the level of access. Research users will be able to access all the data of these participants for a fixed period.

### 5.4. User Tracking

Audit tracking software monitors access patterns, machine locations and user IDs. With this information, it is possible to accurately track and identify any illegal usage. The Registry shall store some user information so that it can act as a register of users, and will log the user's IP address, which is automatically recognised by the web server. The website and server logs are hosted by the IT Services at the University of Glasgow using private, TLS-encrypted web browser sessions, and the IP information is accessed through tools provided by Google Analytics. We shall not use cookies for collecting user information from the site and will not collect any information about users except that required for conducting research within the consortium, enforcing consortium privacy rules, or for system administration of the registry.

## 6. Registry Governance

### 6.1. Data Access:

Access to all information in the Registry will be tightly controlled with passwords and logins set at multiple levels. User passwords are acquired and stored encrypted using a one-way hash function, ensuring that passwords cannot be extracted from the password database. Access to the Registry is limited to named people who have specific job responsibilities related to the Registry. The identity of participants in the database will be kept confidential at all times. The Registry is housed within the University of Glasgow IT services and all project staff within the organization undertake training in the protection of data confidentiality. UK participants will be informed that a paper copy of their data will be stored in accordance with the Data Protection Act 1998.

Every data record in the Registry shall have a unique identifier. The I-DSD unique identifier contains no identifying information within it. This number is used to track all information about the participant in the Registry. This unique identifier will have a link local ID which is not entered on the Registry. This local ID links the clinical user to the data record and shall be kept by the clinical user, physically and electronically, separately to the Registry. The local

clinical user at each centre will keep a participant identification list in a locked office to link study records with hospital records.

With the participant's consent, data will be shared with approved research partners. Where these partners are based outside of the EEA, data will be shared on the agreement that data will be processed in line with the principles outlined in the EU Data Protection Directive (95/46/EC) or their equivalent national legislation.

#### 6.2. Data Access for Research Purposes:

Data released to research users does not include any personal identifiers. Data records will be known only by the unique identifier. The only way for research users to approach participants is through the clinical users. Research that is performed on the data that already exist in the Registry is considered 'Secondary Research' and is approved under its current ethics approval and has been mentioned in the participant information sheet.

#### 6.3. Ownership of Data

- The participant and/or the legal guardians, in case the participant is under the age of 16, is/are the primary owner(s) of the data, and will grant each of the users and UOG a non-exclusive licence to use such data for research purposes.
- The sponsor (University of Glasgow) is the owner of the database
- The institution of the clinical or research user who has entered the data is the owner of the aggregated data of that participant.
- When processed, the data become research data and is then the intellectual property of the research user who needs to pay due consideration to the benefits of sharing
- Prof. Faisal Ahmed, the principal investigator of the I-DSD project is the custodian of the data and is responsible for the protection of the data, its storage, use and access.

### 7. Project Management

#### 7.1 I-DSD Project Management Group

The I-DSD Project Management Group will coordinate the Registry. The PMG will be comprised of a Registry Panel (currently JB and FA) and a Business Operating Group. The Business Operating Group is comprised of the coinvestigators, the project manager and the database engineers. This group will have a remit to coordinate the network, organize meetings, assess data quality, prepare reports and perform other tasks related to the administration of I-DSD (project manager role).

#### 7.2 Steering Committee

The primary function of the Steering Committee is to participate in the planning and oversight of the I-DSD Registry and to advise its project management group. The I-DSD Registry Steering Committee will monitor and review the project status, as well as provide suggestions on its future plans.

The advice of the Steering Committee will also be sought on research proposals and to make recommendations for projects to support to the Project Management Group.

Research proposals requiring access to the database are made to the Project Management Group which will review them for operational feasibility and to set priority level for access. The Project Management Group will monitor the access to researchers and cohort usage and will also act as custodians of the clinical data and be responsible for quality control.

### 8. Funding

The I-DSD Registry is currently funded by a network project grant by the Medical Research Council (Award: G1100236).

Next Revision Date:01/01/16