ERN eUROGEN registry Protocol
Retrospective inclusion of missed patients

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

EA Expertise Area
ERN European Reference Network
HCP Healthcare provider
ICF Informed Consent Form

INVITING MISSED PATIENTS RETROSPECTIVELY

Ethical approval

The Principal Investigator should decide whether ethical approval is necessary to approach the patients that were missed for inclusion in the ERN eUROGEN registry. The patients will be contacted by regular post, which was described in the original ERN eUROGEN registry Protocol as the way retrospective patients would be included. Another option is to approach them via email, but this was not described before.

Identification of patients

The treating physician, other member of the treatment team, or someone else on their behalf should perform the selection of missed patients for retrospective inclusion.

1. Select eligible patients:
    - patients treated at your Healthcare Provider (HCP) for the ERN eUROGEN Expertise Areas (EAs) that your HCP covers,
    - who first visited your HCP in 2022 (which is when the ERN eUROGEN registry started) or later,
    - who are alive,
    - who are not participating in the ERN eUROGEN registry yet, and
    - who did not object to being approached for research participation.
2. Ask the medical registry department for a list of these patients, including:
    - hospital number,
    - name,
    - address (or email address),
    - date of birth, and
    - patient status (dead or alive).

Invitation of patients

The treating physician, other member of the treatment team, or someone else on their behalf should invite the patients. If necessary, you can register in the patient file that the patient is invited for the ERN eUROGEN registry.

1. Use the date of birth of the patient to identify which letter to send to the patient (see page 5, 6 and 7).
    - There is one version for adult patients
    - There is one version for parents of child patients (changes with adult version in grey shading)
    - There is one version for youngsters, which should be added to the version for parents
2. Translate the letter to your own language
3. Replace the parts in blue shading
4. Add the Informed Consent Form (ICF) that your HCP uses.
    - Please note that we made some changes and we suggest you to do the same:
        - On page 7 and 10 we added the QR code to the video
        - On page 9, we replaced “Wout Feitz” with “Peter Mulders”
        - On page 11, we added the option to participate in the registry in general
        - and we added room for both parents and youngsters to sign (use only if applicable)
    - Please note you should **add at least 2 copies of the signature page**, as patients should be able to keep one copy themselves.
5. Make sure the **hospital number (or other identifying information) is on the signature pages** of the ICF.

Regular post:

6. Make envelopes to send to the patients including:
    - The information letter
    - The ICF (with at least 2 signature pages with the hospital number or other identifying information)
    - A return envelope
7. Send the envelopes to the patients identified via regular mail.
8. After four weeks, send a similar envelope via regular mail to the non-responders as reminder.

Email:

9. To approach patients via email, first ask the ethical committee whether a return email is enough to obtain Informed Consent for participation in the ERN eUROGEN registry.
    - Another option is to ask patients to sign digitally.
    - Another option is to ask patients to print the signature page, sign it, and send a photo or scan back via email.
    - Another option is to ask patients to print the signature page, sign it, and send it back via regular post.
10. Send the patients an email with the text from the information letter in the email and the ICF attached.
    - Please adjust the text from the information letter to explain patients how they can participate (by a reply mail / printing the signature page / …)
11. After four weeks, send a reminder email to the non-responders.

Registration of patients

If the patient and/or the parents/legal representatives want to participate in the ERN eUROGEN registry, make sure that everyone who should sign the ICF, signed it. If not everyone did, collect the missing signatures.
The Data manager will add the patients who provided informed consent to the ERN eUROGEN registry. Instructions:

1. If necessary: Register in the patient file that the patient consented for the ERN eUROGEN registry.
2. Store the signed ICF at the usual location.
3. Create a new record in Castor for the ERN eUROGEN registry (see ERN eUROGEN registry Castor Manual).
    - If the patient first visited your HCP more than 1 year ago, select “retrospective” at the first question (more than 2 years ago for EA 1.2, Bladder exstrophy / epispadias)
    - Otherwise, select “prospective” at the first question
4. Add the patient to the key file with the Castor ID number as usual.

INFORMATION LETTER – ADULT PATIENT

European Reference Network | eUROGEN *Urogenital Diseases*

Dear <name patient>,

In our hospital, we treat patients with rare and complex urogenital conditions. In Europe, the European Reference Networks (ERN) were established, which are networks of professionals providing care to patients with rare or complex conditions. ERN eUROGEN is the European Reference Network focusing on rare and complex urogenital conditions.

To understand the course of a disease and investigate new diagnostic procedures and treatments in order to improve patient care, ERNs need databases (also known as "registries") for research and knowledge development. To build such registries, data from many patients must be combined. We ask for your consent to include your data in the ERN eUROGEN registry.

The booklet attached contains more information about the ERN eUROGEN registry and what it means to participate. The English-language video that you can watch via the QR code also explains what participation entails. You can turn on <language> subtitles by using the gear icon.

We hope that you will decide to participate in the registry, which will help research into rare and complex urogenital disorders. Participation is voluntary and if you decide not to participate, this will not influence your treatment in any way.

Please indicate on the informed consent form attached, whether you want to participate in the ERN eUROGEN registry. You can sign two copies and keep one copy for your own reference and to know what you consented for. Please send the other copy within two weeks back to us with the free return envelope.

If you have any questions, you can contact your treating physician or <…>.

Best regards, on behalf of all urologists,

<SIGNATURE>

<name physician>

PATIENT INFORMATION LETTER – CHILD PATIENT

European Reference Network | eUROGEN *Urogenital Diseases*

Dear parent(s) / legal representative(s) of <name patient>,

In our hospital, we treat patients with rare and complex urogenital conditions. In Europe, the European Reference Networks (ERN) were established, which are networks of professionals providing care to patients with rare or complex conditions. ERN eUROGEN is the European Reference Network focusing on rare and complex urogenital conditions.

To understand the course of a disease and investigate new diagnostic procedures and treatments in order to improve patient care, ERNs need databases (also known as "registries") for research and knowledge development. To build such registries, data from many patients must be combined. We ask for your consent to include your child's data in the ERN eUROGEN registry.

The booklet attached contains more information about the ERN eUROGEN registry and what it means to participate. The English-language video that you can watch via the QR code also explains what participation entails. You can turn on <language> subtitles by using the gear icon.

We hope that you will decide to participate in the registry, which will help research into rare and complex urogenital disorders. Participation is voluntary and if you decide not to participate, this will not influence the treatment of your child in any way.

Please indicate on the informed consent form attached, whether you want to participate in the ERN eUROGEN registry. You can sign two copies. This holds for both parents (if both alive and having parental authority) and for patients who are 12 years of age or older. You can keep one copy for your own reference and to know what you consented for. Please send the other copy within two weeks back to us with the free return envelope.

If you have any questions, you can contact your treating physician or <…>.

Best regards, on behalf of all urologists,

<SIGNATURE>

<name physician>

PATIENT INFORMATION LETTER – YOUNGSTER

Dear <name patient>,

In our hospital, we treat patients with rare and complex urogenital conditions. To understand the course of a disease and investigate new diagnostic procedures and treatments in order to improve patient care, we need databases (also known as "registries") for research. To build such registries, data from many patients must be combined. We ask for your consent to include your data in a European registry.

The booklet attached contains more information about the registry and what it means to participate. Please read this booklet together with your parents and ask them to explain things you don't understand. The English-language video that you can watch via the QR code also explains what participation entails. You can turn on <language> subtitles by using the gear icon. If you have questions that your parents cannot answer, you can contact <…>.

We hope that you will decide to participate in the registry, which will help research into rare and complex urogenital disorders. Participation is voluntary and if you decide not to participate, this will not influence your treatment in any way.

Please indicate on the informed consent form attached, whether you want to participate in the ERN eUROGEN registry. You can sign two copies and keep one copy for your own reference and to know what you consented for. Please send the other copy within two weeks back to us with the free return envelope.

If you have any questions, you can contact your treating physician or <…>.

Best regards, on behalf of all urologists,

<SIGNATURE>

<name physician>

PATIENT INFORMED CONSENT FORM

Dear parent(s)/legal representative,
We invite your child/the patient[1] to take part in a patient registry for rare urogenital diseases. Participation

[1] Adult for whom you are legal guardian

is voluntary and requires your written consent as a legal basis to use the data of your child/the patient. Please read this information carefully and ask the medical doctor of your child/the patient for explanation if you have any question.

EUROPEAN REFERENCE NETWORK REGISTRIES

- Rare and complex urogenital conditions may require surgical correction or other therapy, often during the neonatal period or in childhood. Individuals affected require life-long care provided by multidisciplinary teams of experts who plan and perform surgery and provide post-operative long term multidisciplinary care.
- European Reference Networks (ERNs) are networks of healthcare professionals for rare diseases across Europe working together to support patients with rare and complex diseases.
- ERN eUROGEN is the ERN for rare urogenital diseases and complex conditions (https://eurogen-ern.eu/for-patients/).
- To understand the course of a disease and investigate new diagnostic procedures and treatments in order to improve patient care, ERNs need databases (also known as "registries") for research and knowledge development.
- To build such registries, data from many patients must be combined. We ask for your consent to include the data of your child/the patient in the ERN eUROGEN registry to perform research, as described below, in accordance with national and European data protection laws and ethics guidelines[2].
- Only the data required for such research will be recorded and may be shared with users as outlined below. Such data may include age, sex, the signs and symptoms of the disease, results of diagnostic procedures (e.g., laboratory test results, genetic information, imaging studies), as well as therapeutic interventions and their long-term outcomes.
- Your child/the patient's data privacy will be secured as described below in this form. Only the medical doctor of your child/the patient and the persons who will register your data will be able to link your child/the patient to your child/the patient. Therefore, the risk of re-identification by unauthorized persons is minimal.
- In the English-language video, which you can watch via the QR code below, an explanation of what participation entails is provided. You can turn on <language> subtitles by using the gear icon.

VALUE & BENEFITS

[2] including the European General Data Protection Regulation (GDPR), Reg. (EU) 2016/679; the Declaration of Helsinki 2013; the International Ethical Guidelines for Biomedical Research Involving Human Subjects CIOMS-WHO (2016); the Oviedo Convention and its Additional Protocol on human rights and biomedicine, concerning biomedical research (2005); the "standard contractual clauses for the transfer of personal data to third countries" (EU) 2021/914.

HOW WILL THE DATA BE USED?

The data collected in this registry is used to improve the delivery of healthcare, including the diagnosis, treatment and prognosis of patients with rare urogenital diseases and complex conditions.

Only users authorised by a special committee (consisting of the Project Steering Committee and Advisory Board) can use the data. This committee is composed of qualified health professionals, patients' representatives as well as members with legal and ethical expertise. It ensures that the request for data use aligns with the purposes of the registry and its policy.

The committee may provide data access to **clinical researchers from within or outside ERN eUROGEN, patient organisations, and the pharmaceutical industry** in order to develop projects, policies or studies aimed to improve the delivery of healthcare for rare diseases**.** Also, registry data may be shared with **health authorities, policy makers and regulators** to inform their decisions on rare disease health policy and approval of medicines.

Data use for commercial purposes

Companies might request access to data stored in the registry to perform research aimed to develop new therapies for your child/the patient's condition. For example, the registry can inform companies how many patients live with a certain disease and help find patients in clinical trials of new therapies.

Typically, the results of this research will become property of the company that may also use them for further **commercial purposes** and to patent. Your child/the patient will not acquire any rights over these results, own them in any way, or be entitled to share any future financial benefit derived from this research.

You may choose if you want to allow the use of the data of your child/the patient for commercial research.

Data transfers outside the EU

Data without any personally identifiable information may also be forwarded to researchers working in countries outside the EU, where the General Data Protection Regulation (GDPR) does not apply. In this case, a written agreement will be set up to ensure that the data is processed in compliance with the GDPR. Data will only be transferred if the project adheres to the goals of the registry and was approved by the special committee. You may choose if you want to allow the transfer of the data of your child/the patient to non-EU countries.

Future changes in data collection

To gain more insight on the condition of your child/the patient we may need additional data in the future. Which information we collect will be published on the registry website https://eurogen-ern.eu/what-we-do/the-eurogen-registry/.

In the event a disease-specific subregistry exists for your rare urogenital disease or complex condition, more detailed clinical data will be collected. Such subregistries are of great importance to better understand the precise nature of rare diseases. More information on the available subregistries can be found on the registry website.

Furthermore, we may request additional data from existing databases/registries, such as ARM-Net or registries from other ERNs. You may choose if you want to allow the linking of the data of your child/the patient with additional data as described above.

Re-contacting to participate in research projects

In the future, research projects on the diseases and conditions covered by this registry may be proposed. You may choose if you want to be re-contacted by the medical doctor of your child/the patient to participate in such studies. If you agree to be contacted, you are free to refuse, without any prejudice, participation in the proposed studies after you have been fully informed. The current care of your child/the patient will not change in any way if you choose not to give your consent.

WHAT ARE THE BENEFITS?

While there is no direct benefit from participating in this registry, the knowledge about the disease will be improved. This may benefit your child/the patient and other patients suffering from the same disease.

The participants may benefit by facilitated access to clinical studies aimed to prevent and treat the disease.

Communication of research results

The information about projects given access to registry data is publicly available on the registry website. The results of the research will be shared with the scientific community by publications in scientific journals where personal data are not provided. In addition, results will be communicated through the ERN eUROGEN website. The privacy of the data your child/the patient's data will always be protected as described below.

PROTECTION

WHAT ARE THE RIGHTS OF THE REGISTRY PARTICIPANT?

- You decide whether to let your child/the patient participate in the registry. Please take as much time as you need to make this decision. Participation is voluntary. You can decline participation without giving any reasons. Your child/the patient will receive the same treatment irrespective of whether or not you agree to participate in this registry.
- You have the right to give or withhold your consent at any time. If you consent today, you may modify or withdraw your consent later, without any prejudice. The medical doctor of your child/the patient will explain how your consent can be modified and how the data can be removed from the registry if you wish so. Please be informed that, to guarantee the validity of any research performed, data already processed cannot be deleted. However, this data will not be used in new research projects after withdrawal.
- You are entitled to receive further information about the purposes for which the data of your child/the patient will be processed and who will have access to it. You can also request to access the data of your child/the patient at any time.
- The hospital where your child/the patient is treated is the "data controller" responsible for the **local protection** of confidential patient data. If you have any concerns about the way in which the data of your child/the patient is processed, you would like more information or to exercise your rights, you may contact the Data Protection Officer (<please replace with contact details (postal address and email address) of your local Privacy Officer>), or you may raise a complaint to the <please replace with the name of your national privacy authority>.They have the duty to ensure the data is processed safely and to notify you if a breach of data security occurs. Any inquiries should be addressed by the Data Protection Officer within 30 days.
- For all data submitted to the **central registry database**, the Radboud university medical centre, Nijmegen, The Netherlands and its principal investigator Peter Mulders is responsible for the protection of the data, its storage, use and access: Peter Mulders, Radboudumc, internal postal number 610, POobox 9101, 6500HB Nijmegen, The Netherlands, secretariaat.uro@radboudumc.nl.
- When your child will reach legal majority, the hospital will approach your child again to check whether he/she wishes to stay in the registry.

HOW WILL DATA BE SECURED?

- Participation in the registry will be kept strictly confidential and all information will be handled through very secure electronic systems. As the registry involves collecting information from many centres, the system will be password protected and only persons specifically involved with the registry will have access.

- The registry users and administrators will not be able to contact you because the name of your child/the patient, address and hospital number will not be recorded. All your child/the patient's data will be pseudonymised before being stored in the registry. This means that all identifiers that relate to your child/the patient will be removed and replaced by a pseudonym[3]. Only the medical doctor of your child/the patient and the persons who will register your data can link the pseudonym to your child/the patient. Therefore, the risk of re-identification by unauthorized persons is minimal.
- A pseudonymisation service will be used for this purpose. It allows to identify duplicate registration of patients, linkage between registries and other data resources, keep data protected and preserve the possibility of re-contacting by the medical doctor in charge.
- In all publications emerging from the registry, it will be ensured that it is not possible to identify an individual patient, e.g., by providing data in tables or presenting age categories rather than the real age.
- The registry data will be stored on a secure server in The Netherlands. As the registry is designed to look at long term outcomes, the data will be stored for at least 25 years. After this period, the need for keeping the stored data in the registry will be reviewed every 10 years by the ethical committee of the Radboudumc.

COULD PARTICIPATION IN THE REGISTRY CAUSE ANY HARMS?

- Participating in this observational registry will not cause any health risks.
- Even though the registry has processes in place to ensure your child/the patient's personal information is protected, there is a remote risk the data could be matched with information you have already authorized in publicly available databases such as ancestry websites or public rare disease registries with identifiable information. To minimize this risk, researchers asking for access to registry data will confirm in writing not to try to identify you by any means, applying their duty of professional secret.

ADDITIONAL INFORMATION

Costs

Participation in this registry will not entail any costs for your child/the patient.

Ethics Committee Approval

This Informed Consent Form has been reviewed and approved by CMO Radboudumc

In the English-language video, which you can watch via the QR code, an explanation of what participation entails is provided. You can turn on <language> subtitles by using the gear icon.

More information is available on the website https://eurogen-ern.eu/what-we-do/the-eurogen-registry/ (in English). If you have any other question about the registry, please

INFORMED CONSENT

Patient First and Last Name:……..……..

Date of Birth (dd/mm/yyyy):: .. .. / .. .. / .. .. E-mail address:……

Parent/ Legal Representative First and Last Name: ……

contact: <please fill out the name and e-mail address of the local Principal Investigator>

I have read the information sheet about the ERN eUROGEN registry. I have been given the time and opportunity to ask questions about the objectives of the registry and the use of the data of my child/the patient and that I have solved all my doubts with the medical doctor. I understand that the participation of my child/the patient is voluntary

[3] A pseudonym is a sequence of letters and numbers that replaces all identifiers that relate to a patient; the data of the patient is then called "pseudonymised data". These identifiers can only be retrieved, from the pseudonym, by the authorised health care professionals enrolling the patient in the registry.

and that I can withdraw the consent at any time without the need of justification and without affecting the future medical care of my child/the patient. I approve that the data of my child/the patient will be stored in the ERN eUROGEN registry, used for non-profit purposes and shared with approved users to improve the delivery of healthcare as described above. I consent to the processing of my child/the patient pseudonymized data for the purposes described above.

YES	NO
☐	☐

The following consent conditions are optional. Please indicate your preferences by writing your initials in the relevant box. If you leave the boxes empty, we assume you agree to the statements.

YES	NO	
☐	☐	**I CONSENT** that the pseudonymized data of my child/the patient may also be **used to support commercial projects** aimed to improve healthcare.
☐	☐	**I CONSENT** that the pseudonymized data of my child/the patient **may be transferred to non-EU countries, in compliance with GDPR,** to support projects aimed to improve healthcare.
☐	☐	**I CONSENT** that the pseudonymized data of my child/the patient may be **linked to existing databases/registries** to improve healthcare.
☐	☐	**I WOULD LIKE TO BE CONTACTED** by the medical doctor of my child/the patient about any **research project and/or clinical study related to my child/the patient's condition.**
☐	☐	**I CONSENT** to receive in the future, if applicable, a **link to an online questionnaire** on the email address above.

PARENT(S) / LEGAL REPRESENTATIVE(S)

First and last names:	Signature:	Signature date:
Parent 1	.....	__-__-____
Parent 2	.....	__-__-____
Child	.....	__-__-____

DOCTOR / WITNESS

Name:

Function:

Date and signature:

Please keep one copy of this Informed Consent Form in case records and hand one copy to the person who has signed this form.

European Reference Networks

European Reference Network
for rare or low prevalence complex diseases
Network Urogenital Diseases (ERN eUROGEN)

http://eurogen-ern.eu/

Funded by the European Union

ERN eUROGEN is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are funded by the European Commission. For more information about the ERNs and the EU health strategy, please visit http://ec.europa.eu/health/ern