**Memorandum of Understanding**

**Development and Implementation of Clinical Practice Guidelines / Clinical Decision Support Tools for the Urological Care of Patients with Spinal Dysraphism**

v 2022-08-11 (FINAL)

1. introduction

The European Reference Network (ERN) for rare urogenital diseases and complex conditions, ERN eUROGEN, was launched with support from the European Association of Urology (EAU) in 2016. The European Commission approved the network in 2017. The EAU is a Supporting Partner of ERN eUROGEN, and an agreement has been signed to facilitate collaboration on issues of strategic importance between the two organisations.

After initial contact from ERN eUROGEN and ERN ITHACA, the EAU Guidelines Office took the initiative to arrange a meeting with the representatives of the relevant parties to discuss potential collaborations concerning urological care for Spinal Dysraphism.

Following a virtual meeting on 24 February 2022, the organisations below agreed to collaborate specifically to standardise the care approach where possible, exchange knowledge and work on a coordinated joint Guidelines Development Group for the creation of Clinical Practice Guidelines (CPGs) and/or Clinical Decision Support Tools (CDSTs) for the Urological Care of Patients with Spinal Dysraphism.

2. Purpose

The purpose of this memorandum of understanding (MoU) is to state the parties' intentions in standardising the care approach for adult and paediatric patients with Spinal Dysraphism, exchange knowledge, and collaborate in CPG/CDST development. The collaboration aims to facilitate research and improve care for patients with Spinal Dysraphism. The parties have common clinical, scientific, and research interests and will cooperate in performing the activities stated below.

3. memorandum of understanding - terms and conditions

The agreement is made on this day, 11 August 2022, between:

The **European Association** **of Urology (EAU),** a charitable foundation registered In the Netherlands with its office at Mr. E.N. van Kleffensstraat 5, NL 6842 CV Arnhem, The Netherlands and represented by Prof. Dr. M. Ribal, EAU Guidelines Office Chair.

**and**

The **ERN eUROGEN**, the European Reference Network for Rare Urogenital Diseases and Complex Conditions, is one of the 24 ERNs established following Article 13 of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients’ rights in cross-border healthcare. The coordinating healthcare provider of the ERN is Radboud university medical center, P.O. Box 9101, 6500 HB Nijmegen, The Netherland and represented by Prof. Dr. W.F.J. Feitz. Dr G Mosiello will lead the work on guidelines for the urological care of patients with spinal dysraphism.

**and**

The **ERN ITHACA**, the European Reference Network for Intellectual disability, TeleHealth, Autism and Congenital Anomalies, is one of the 24 ERNs established following Article 13 of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients’ rights in cross-border healthcare and represented by Prof. Alain Verloes. Dr A Manunta will lead the work on guidelines for the urological care of patients with spinal dysraphism.

* The representatives of the above organisations have resolved to collaborate in a joint Guidelines Development Group for creating CPGs and/or CDSTs for the Urological Care of Patients with Spinal Dysraphism. The collaborative effort will proceed with the agreed timelines described in Appendix A. All collaborative party representatives must agree to any extension or modification of the timeline in writing.
* All parties agree to follow the methodology as specified in Appendix B. The methodology used aims to, where possible, meet the standards set by the European Commission as provided by the Aragon Health Sciences Institute (IACS) on behalf of the European Reference Networks. By attempting to do so, it should then also meet the minimum requirements set by the EAU Guidelines Office. The scientific reasoning behind any deviation from the methodology will be extensively recorded and submitted to all parties for review during the endorsement process. ERN ITHACA, ERN eUROGEN, EAU, ESPU and IFSBH will be approached for their endorsement of the final guideline. The language used will be UK English.
* Promptly, upon execution of this agreement, each party will appoint up to a minimum of three (3) members to each of the two working Groups on Paediatric and Adult Spinal Dysraphism to review literature for clinical importance, to review methodological analysis of the data, to participate in discussion and consensus building and the drafting of the publication and actionable recommendations.
* Any joint publication by the two Working Groups on paediatric and adult Spinal Dysraphism Urology should be in accordance with established publication rules. The Working Groups will produce one scientific publication of a summary document on Paediatric Spinal Dysraphism and one scientific publication of a summary document on Adult Spinal Dysraphism. For each of these guidelines, an ERN version will be produced on the official ERN templates provided by the European Commission and made available through appropriate communication and dissemination channels (such as the ERN websites and ERN Academy). The same will apply to the EAU, with the guidelines being incorporated into the EAU guidelines and distributed through the appropriate communication and EAU dissemination channels.
* Any publication/abstract/poster or other derivative publications, including the incorporation of the full-text guidelines in the relevant EAU Guidelines (Neuro-Urology and Paediatric Urology), arising from initiatives by the working groups, shall be jointly owned by all parties and must include relevant authorship. Relevant authorship would relate to those having contributed to the development of the data. The list must be agreed upon before the commencement of projects and recorded in the minutes of the group meetings.
* If for any reason, the collaboration between the parties should end before the completion of the CPGs/CDSTs, then the components of the uncompleted work (or work in progress) shall be made available to and owned by the remaining parties.

3. Participants and duties

Prof Dr. Giovanni Mosiello will serve as Chair of the Trans ERN Working group, Prof Dr Kate Abrahamsson as coordinator of the Paediatric CPG/CDST Working Group and Dr. Andrea Manunta as coordinator of the Adult CPG/CDST working group. The remaining representatives and their affiliations:

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| --- | --- |
| Paediatric CPG/CDST | Adult CPG/CDST |
| Dr. Giovanni Mosiello - ERN eUROGEN/ITHACA | Dr. Andrea Manunta - ERN ITHACA |
| Prof.Dr. C. Radmayr – EAU | Dr. Benoit Peyronnet - ERN ITHACA/EAU |
| Prof.Dr Rien Nijman Netherlands, EAU | Prof. Dr. Bertil Blok - EAU |
| Prof .Dr. Guy Bogaert Belgium | Dr Giovanni Mosiello, ERN EUROGEN/ITHACA |
| Prof Kate Abrahamsson Sweden - ERN eUROGEN | Yuan Cathi (Ca) – methodologist |
| Prof .Michaela Dellenmark Bloom Sweden - ERN eUROGEN | David Castro Diaz (Sp) General Secretary of ICS |
| Magdalena vu Minh Sweden | John Heesakkers (Ne) |
| Dr. Sylvia Roozen – IFSBH | Dr. Sylvia Roozen - IFSBH |
| Ms. Julie Darraugh - EAU GO | Mrs. Natasha Schouten - EAU GO |
| Dr Ingrid Olsen (Sweden ) | Jan Krhut (Cz) |
| Dr Anju Goyal (UK) | Rizwan Hamid (UK) |
| Dr Michael Maternik (Poland ) | Frank Van der Aa (Be) - ERN eUROGEN |
| Prof Dr Alexander Von Gontard (Switzerland) | Tufan Tarcan (Tur) |
| Prof Dr Johan VandeWalle ( Belgium) | Xavier Gamé (Fr) |
| Dr Lisette t’Hoen (Netherlands) | Gerard Amarenco (Fr) |
| Prof Dr Raimund Stein (Germany) | Giulio Del Popolo (It) |
| Rianne Lammers | Salvador Arlandis (Sp) |
| Prof Dr Wout Feitz (Netherlands) | Thomas Kessler (Ch) |
|  | Ferdinand Dhombres (Fr) ITHACA) |

* Each member of the panel is expected to attend at least one meeting in-person each year, at a location to be determined by the Coordinators, and to attend up to six (6) telephone or video conference calls each year - with adequate preparation before each meeting and prompt and diligent follow-up after each meeting.
* Beforehand, at least one staff member from each of the participating parties will be assigned to complete administrative functions, including preparation and shipping of literature, and other materials, co-ordination of panel meetings, liaison with consultants, ensuring adherence to the timeline and providing draft guideline materials to panel members promptly.
* In addition, all meetings, paediatric or adult, will be attended by the coordinators of both groups to ensure uniformity.

4. funding

The costs of the project will be divided into eligible and non-eligible expenses.

* The non-eligible costs include the costs of the staff in each organisation helping to coordinate the work, time contributed by the clinical experts, and overheads from the respective parties, ERN eUROGEN, ERN ITHACA and the EAU.
* The eligible costs shall include all travel and accommodation expenses and other meeting-related costs where face-to-face meetings are necessary, materials and supplies, data work search costs, database costs, meeting site and communication costs.

When a final consensus is reached for the guidelines, the conditions above regarding eligible and non-eligible costs are maintained.

The ERNs receive funding from the European Commission (EC), some of which may be allocated by the individual ERNs to support work on guidelines and other CDSTs which may be needed where the evidence is lacking. The current funding period for ERN ITHACA and ERN eUROGEN runs from 1 March 2022 until 31 August 2023. However, the current proposals are still under evaluation by the EC. Therefore, it is not possible to fully commit to the funding listed below until the grants have been signed. It Is, however, a realistic indication of the level of resources currently expected to be available.

If consensus meetings are required, and for a contribution towards the other eligible costs, ERN eUROGEN will contribute up to a maximum amount of €25,000, which must be spent, and Invoices sent to Radboudumc as the coordinating Institution for the ERN before 1 August 2023. Where possible, the preferred option would be for the EAU to lead on meeting organisation and running consensus processes etc., when needed and for the EAU to invoice Radboudumc for their contribution towards these eligible costs. This can be arranged within the EC financial rules, which all ERNs must comply with as a subcontracting arrangement and which has worked well In the past.

ERN eUROGEN will continue the fruitful discussions with the EAU and other Supporting Partners to plan what funding should be Included In future grants to ensure future work on guidelines development.

ERN eUROGEN has agreed to a contribution of up to a maximum of €5000 toward the EJP RD workshop in Rennes as the budget allocation was insufficient. Upon receiving the program's total budget and final financial overview of the meeting, an Invoice can be sent to Radboudumc within the time limits of the EU grant related to the meeting and reporting period. If the provided information and timeline are not In accordance with the EU financial requirements for the specific grant, Radboudumc cannot provide the requested financial support from other sources, and the organising party must take over the responsibility.

ERN ITHACA also has some funding available to support this work on guidelines; however, they prefer to keep the agreement general for the time being from their perspective until the precise levels of financial support available to the ERNs are known.

ERN ITHACA has agreed to a contribution of €3800 toward the EJP RD workshop in Rennes (March-April 2022) as the budget allocation was insufficient. The travel agency that works with the coordinating HCP of ERN ITHACA has already issued and invoiced the incurred expenses.

In addition, ERN ITHACA has reinforced its coordination team with a specialised methodologist dedicated to drafting ERN ITHACA Guidelines for methodological support for all ERN ITHACA working groups whose mission is to prepare de novo CPGs and/or CDSTs or to adopt and endorse existing high-quality guidelines.

In the ERN ITHACA project proposal and within the time limits of the aforementioned ERN coordinating grants, a budget of around 9600 EUR is allocated to the organisation of final consensus meetings of the Paediatric and Adult guidelines on Spinal Dysraphism.

5. Support

This MoU binds the supporting parties, ensuring:

* Any data shared can only be utilised solely for the purpose of this project, as listed In the MoU. Any deviation must be discussed, agreed upon by all parties and minutes within the group meetings and in accordance with the EU regulations.
* The MoU shall remain in force for three (3) years from the date it has been signed. An individual party may terminate the MoU by providing all other parties a 60-calendar day written notice. Termination or expiration of the MoU does not terminate the agreement or initiatives already in place before expiration.
* Each party is liable for its own acts and omissions under this MoU, which, for the prevention of doubt, does not include any liability based on the acts or omissions of a third party.

6. Meeting Schedule

TBC

7. Signatures

**Signed for on behalf of ERN eUROGEN**

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Signature

Prof. Dr. Wout F.J. Feitz

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Signature

Dr. Giovanni Mosiello

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Name

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| Signed for on behalf on ERN ITHACA  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Signature  Prof. Alain Verloes  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Name  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Title  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Date | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Signature  Dr. Andrea Manunta  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Name  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Title  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Date |
| **Signed for on behalf of EAU**  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Signature  Prof. Dr. Maria Ribal  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Name  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Title  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Date | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Signature  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Name  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Title  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Date |

Appendix A: Timeline of actions and deliverables

Graphical user interface, application, Word

Description automatically generated

\* The timetable will be adjusted If a formal or informal consensus finding exercise is required.

Appendix B

# Proposal of Methodology for Clinical Practice Guidelines / Clinical Decision Support Tools for the Urological Care of Patients with Spinal Dysraphism

## Terminology

Whilst the term “spina bifida” is used colloquially and is easily understood by the public, “spinal dysraphism” is the more appropriate term as it includes all spinal malformations related to abnormal closure of the neural tube.

Therefore, **spinal dysraphism** is preferred and should be used in all documentation.

## Objectives

The objectives of the Spinal Dysraphism Guidelines Development Group are to improve the health status of patients affected by spinal dysraphism and decrease the variability among clinicians relating to diagnosis and therapeutic approach.

## Working Groups and Coordinators

The European guidelines on the urological management of spinal dysraphism will be divided into a paediatric CPG/CDST and an adult CPG/CDST. Therefore, the Spinal Dysraphism Guidelines Development Group will be divided into two Working Groups:

* Working Group on Paediatric CPG/CDST: coordinated by Kate ABRAHAMSSON (Sweden), Christian Radmayr (Austria), Rien Nijman (Netherlands)
* Working Group on Adult CPG/CDST: coordinated by Andrea MANUNTA and Benoit PEYRONNET (France)

The Coordinators of each group will identify a panel of relevant experts to be involved in writing their section of the CPG/CDST taken from within and when needed outside the Spinal Dysraphism Guidelines Development Group members.

The Coordinators of each section will divide their section into different chapters, further subdivided into structured clinical questions. The coordinators will call a working group meeting and delegate each chapter's creation to a different expert.

Because the two Working Groups may work at different paces, each CPG/CDST should be written as an independent “stand-alone” document that can be published as soon as completed, thereby avoiding any potential delay in achievements caused by waiting to publish the two sections simultaneously. That said, the two working groups will collaborate on the transitional sections from paediatric to young adult, avoiding duplication of work.

The chapters, structures, and clinical questions of the two documents will be compared to eliminate duplications and redundancies. Chapters common to both documents (e.g., definition and classification of spinal dysraphism, epidemiology, transitional care of spinal dysraphism, etc.) will be published unchanged in each document.

The two Working Groups must include:

* A paediatrician in the paediatric group
* A general practitioner in the adult group
* Any other professionals usually involved in the care of patients with rare conditions (e.g., a psychologist)
* Patient advocates
* A methodologist

The Coordinators will:

* Divide their sections of the CPG/CDST into chapters, avoiding overlap and repetition in the two documents, albeit bearing in mind that some chapters may need to be reproduced in both documents (e.g., epidemiology, classification of spinal dysraphism, etc.)
* Define the method for the literature search, which the content experts must validate.
* Identify an expert responsible for each chapter who will coordinate and devise relevant recommendations.

## Structured clinical questions

The chapters will be subdivided into structured clinical questions; however, using an adapted PICO format as a referral method.

## Search and selection of the scientific evidence

Databases searched

EBM Reviews - Cochrane Central Register of Controlled Trials <March 2021>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 14, 2021,>, Embase <1974 to 2021 April 20>, OVID Medline, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 2005 to Present.

A bibliographic search of PubMed and Embase databases will be carried out, seeking all relevant articles in the English language published up to 28 February 2022.

Systematic reviews will be included in the search, provided they comply with the PRISMA statement (however, there may not be any systematic reviews of this kind on the urological management of spinal dysraphism).

Currently, at least two systematic reviews on urological management of spinal dysraphism are available. PRISMA statement Is more of a quality Indicator here. Existing reviews can be used when of high quality and meeting the questions the groups have for this project. Otherwise, reviews can help Identify relevant papers for consideration or used differently.

Evaluation of the bibliographic search results will be carried out as a two-step approach by two reviewers:

* Review round no. 1: Based on reading titles and abstracts only, to determine if the articles appeared to address inclusion criteria.
* Review round no. 2: Full texts will be retrieved for all unclear and selected papers, and the full-text article will be read to determine if the articles meet inclusion criteria.

There will be no search for grey literature.

Electronic records of the references retrieved by searches will be stored using the ZOTERO reference management software. This will provide a platform for the panel to review titles, abstracts, and full-text articles.

The headings and keywords used in the search and the number of references retrieved, the number of abstracts examined, the number read, and the number finally retained will be recorded.

When searching PubMed for "spinal dysraphism" with the filter “RCT”, 38 references are returned, of which only three concern urological management and two of these relate to the same study published twice (and with only 10 patients in each group). Therefore, because the published literature on spinal dysraphism is frequently very scanty, with a limited level of evidence, if required, the literature search regarding general topics such as intermittent catheterisation and pharmacological or surgical treatment could be expanded to include articles on neurological bladder dysfunction related to traumatic spinal cord lesions.

General Inclusion criteria

Time frame: The timeline for publications and their inclusion criteria may be adapted as necessary following the progress of the guidelines' work.

Patient groups: paediatric group, up to 18 yrs, or 16 yrs - keeping In mind that not all datasets allow for this difference (when selecting papers, set aside papers for the transition groups, dealing with mixed groups of patients (adults/paediatric): If results are presented separately, papers can be utilised.

General Exclusion criteria

Incomplete articles, abstracts without full text, duplicates, case reports, dissertations, theses, conference presentations, newsletters, letters to the editor, and animal studies, republications of the same patient groups.

Appraisal and synthesis of the scientific evidence

The main problem with rare diseases is the absence of high-level evidence. It Is therefore impossible to strictly apply the usual evidence-based approaches. However, the GRADE approach will be conformed as far as possible, knowing that most evidence will come from observational studies or expert opinion.

Decisions will be reached through informal consensus; however, the Delphi method may be used for controversial issues.

The GRADE Evidence to Decision (EtD) framework will be used to evaluate the level of evidence and to determine the strength of the recommendations.

External review group

The external review group will be composed of the working group of the section not involved in the creation of the CPG/CDST under review, i.e.:

* The adult working group will be the external review group for paediatric guidelines
* The paediatric working group will be the external review group for adult guidelines

Guideline reporting format

The CPGs/CDSTs will be published in two different formats:

1. A full version of the CPGs/CDSTs will be published on the ERN ITHACA, ERN eUROGEN, EAU and IFSPH websites.
2. Two short versions of the CPGs/CDSTs will be published as two separate articles in peer-reviewed journals. The acknowledgement sections of the articles should state that the recommendations were coordinated by the European Spinal Dysraphism Guidelines Development Group within the European Reference Networks on rare diseases ERN ITHACA and ERN eUROGEN.