RESEARCH PROTOCOL

Quality of life and organization of care for children and adolescents with spina bifida: a European study.

Full title of protocol	Quality of life and organization of care for children and adolescents with spina bifida: a European study.
Short title or Acronym	QoL in patients with spina bifida
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Sponsor (in Dutch: verrichter/opdrachtgever)	*European Association for Urology and International Federation for Spina Bifida and Hydrocephalus*
Subsidising party	*None*

Name	**Signature**	**Date**
Head of Department of Urology: *Dr. J.L. Boormans*		
Coordinating Investigator/Project leader/Principal Investigator: *Dr. L. 't Hoen*		

- *Coordinating investigator: Investigator who bears the responsibility for the coordination of investigators operating in the various centers participating in multicenter research. Not all multicenter research will have a coordinating investigator. There is no requirement to appoint one. A project leader has the responsibility to develop a research protocol and to complete the study within the predefined goals.*
- *Principal investigator: Investigator who has the overall responsibility to comply and to complete the study within the predefined goals.*
- *Only for multicenter research: as an alternative only the sites could be mentioned here, investigator names and contact data could be included in an appendix*
- *Sponsor: The party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or the investigator's employee. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.*
- *Subsidising party: A party that provides funding for a study but does not commission it*

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS*

CTA	Clinical Trial Agreement
De novo biobank	The information of a new data, human material or imaging collection
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
DTA	Data Transfer Agreement
EAU	European Association for Urology
Exception consent	Form Care for data Template , in Dutch: Formulier uitzondering toestemming
FSFI-6	Female Sexual Function Index – 6
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation in Dutch: Algemene Verordening Gegevensbescherming
IC	Informed Consent
IFSBH	International Federation for Spina Bifida and Hydrocephalus
IFU	Instruction For Use
IIEF-5	International Index of Erectile Function – 5
MTA	Material Transfer Agreement
NWTC	Non-WMO Review Committee; in Dutch: Niet WMO Toetsingscommissie
QUALAS	QUAlity of Life Assessment in patients with Spina bifida
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet Algemene Verordening Gegevensbescherming
WMO	Medical Research Involving Human Subjects Act, in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

**Please delete abbreviations/definitions that are not applicable and add any new ones that are used in the research protocol*

PROTOCOL SUMMARY

Children with spina bifida require care from various medical and paramedical specialists throughout their life. The availability and organization of the care needed differs between the European countries. The EAU and IFSBH are both organizations with the aim to improve patient care and clinical outcomes for children with spina bifida.
We have set up a collaboration to evaluate the differences in organization of care and clinical treatment received and how this affects outcomes with regard to quality of life and sexuality.
A digital survey has been constructed which will be distributed among children and adolescents with spina bifida and their caregivers. The IFSBH and national patient organizations will send out invitations to their members. Children and adolescents from 8 – 18 years of age with spina bifida are eligible for inclusion.
The survey includes a primary survey developed in collaboration between panelmembers of the EAU pediatric urology guidelines and patient representatives. The second part includes validated questionnaires to evaluate Quality of life with the QUALAS and sexual function with the IIEF-5/FSFI-6 for boys/girls respectively.
Primary outcome will be the quality of life in children and adolescents with spina bifida. We will evaluate if their demographic differences influence the quality of life and if differences are seen between the different European countries. Secondary outcomes include differences in sexual function, organization of care, treatment received, treatment options available, with also a focus on differences between the different European countries.
The results of this survey will be evaluated and interpreted within a sounding board group consisting of children/adolescents/adults with spina bifida, patient representatives from IFSBH and panel members of the EAU Pediatric Urology guidelines panel. Finally, the interpreted results will be used to update the EAU Pediatric Urology guidelines to make these more patient centered.
There are no known risks of participating in the study given the fact that participation includes only completion of questionnaires and data about standard of care. Furthermore, the study is completely voluntary and the results will be completely anonymous.

1. Introduction and rationale

Children with spina bifida require care from various medical and paramedical specialists throughout their life. The availability and organization of the care needed differs between the European countries. It can be expected that this variety results in differences in outcome of care.
Children with spina bifida have stated that for future research they feel it is important that quality of life and sexuality are investigated. **[1]**
The EAU Pediatric Urology guidelines panel wants to ensure that patients with spina bifida receive the best possible care based on the best available clinical evidence. **[2]** Additionally, we want to improve the clinical guidelines by including patients perspectives. The IFSBH represents patients with spina bifida and values the promotion and protection of the human rights of patients with spina bifida thereby improving quality of life.
Together with the IFSBH we have set up a collaboration to investigate how we can make the guidelines more patient centered and thereby improve quality of care and quality of life.
For this aim we have developed a survey to evaluate the current organization of care, demographic features and received treatment. The outcome of this survey will show the exact differences in care between European countries. We have included two validated questionnaires to measure the effect this has on quality of life and sexuality. The information gathered will be used to adapt the clinical EAU Pediatric Urology guidelines.

2. Objective(s)

The main objective is to improve the quality of life of patients with spina bifida by updating the guidelines according to the differences found in care and how this impacts patients outcomes.
We will evaluate the difference in organization of care between different European countries based on the outcomes of the primary survey. The baseline quality of life and sexuality reported will be evaluated with the QUALAS and the IIEF-5/FSFI-6 questionnaires **[3-6]**. We will then explore the relationship between how care is organized and how this affects quality of life and sexuality. The results of this study will be used to update the EAU Pediatric Urology clinical guidelines. Also, it will highlight the direction for future research to improve patients care and thereby quality of life and/or sexuality, which patients with spina bifida have stated they themselves find important.

3. Study type

3.1 Study type:

☐ Retrospective
☒ Prospective
☐ Combination Retrospective/Prospective

3.2 Check all the applicable boxes:

☐ Medical records (re-use of data from healthcare, including AI)
☐ Case report
☐ Re-use data from research
☐ Evaluations of quality of healthcare (retrospective)

- ☐ Research with additional use of residual material from regular healthcare
- ☐ Research with re-use of human materials from research or existing biobank
- ☐ Research with human materials without biobank
- ☐ De novo biobank (human material obtained without burdensome or invasive procedures)
- ☐ Post marketing survey research with medical devices
- ☐ Phase IV research
- ☑ Healthcare evaluation research (prospective)
- ☐ Medical devices
- ☐ In Vitro Diagnostic Tests
- ☐ Other research, *describe*

4. Study population

4.1 Population (base)

Children with spina bifida aged between 8 and 18 years old.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Must have spina bifida
- Must be able to complete the digital survey, with help of caregivers allowed.
- Speak one of the nine available languages:
  - English,
  - Spanish,
  - German,
  - Italian,
  - French,
  - Danish,
  - Greek,
  - Turkish,
  - Dutch

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Aged over 18 years or under 8 years of age
- Does not have spina bifida

4.4 Sample size calculation

Since this is a descriptive study no minimal sample size is required.

However, our aim is to include 500 patients.

4.5 (Planned) start date

Depending on the approval of the NWTC.

Start date 01.01.2023.

4.6 (Planned) end date

The digital questionnaire will be available for 3 months.

5 Methods

5.1 A digital survey has been created on Surveymonkey: https://www.surveymonkey.com/r/7WSB9S9

This digital survey includes a primary survey regarding basic demographic features, medical treatment and organization of care. This survey was constructed by the EAU guidelines panel and the IFSBH patient representatives. The second part of the digital survey includes two validated questionnaires. The QUALAS is a validated questionnaire regarding quality of life in patients with spina bifida. There are two different versions for the ages 8-12 and 13-18 years. To evaluate sexuality the IIEF-5 (for boys) and the FSFI-6 (for girls) are used. These questionnaires are validated and are used in patients with spina bifida to evaluate sexual function as standard of care. Only children aged 13 years or older will be asked if they want to answer questions about sexuality and if they answer yes they will be asked for which gender they want to answer questions about their sexuality. After this they'll get the IIEF-5 or FSFI-6 questionnaire.
This digital survey is available in nine languages: English, Spanish, German, Italian, French, Danish, Greek, Turkish and Dutch.
The link to surveymonkey will be distributed by the IFSBH and local patient organizations among their members.

After the data have been collected, the general results of the survey will be evaluated and interpreted with a sounding board group. When patients participate with the digital survey they will not be involved in the sounding group. This sounding board group will consist of children/adolescents/adults with spina bifida who are representatives from the patient organization IFSBH and panel members of the EAU. This sounding board group will meet for a day. Finally, the results will be used to update the EAU Pediatric Urology guidelines.

5.2 This is a demographic study. Patients will not receive any difference in treatment.

5.3 The survey only has to be completed once and is completely voluntary. The questionnaire will take around 15 minutes to complete. It will not influence their own treatment.

5.4 There are no known risks of participating in the study given the fact that involves only the completion of questionnaires and data about standard of care. Also, all responses will be anonymous and completely voluntary. No personal identifying information will be used when reporting the data.

6 Unexpected discoveries

6.1 Is there a chance of unexpected discoveries?

☐ Yes

☒ No

7 Exchange, sharing or transfer of data and/or human material and/or images outside Erasmus MC

The data will be collected and stored within the Erasmus MC in the Castor program. Only anonymous data will be collected and shared with collaborating colleagues from the EAU Pediatric Urology guidelines panel from their respective institutions outside the Erasmus MC. The institutions are:

- University of Leuven, Leuven, Belgium

- Medical University of Innsbruck, Innsbruck, Austria
- Hacettepe University, Ankara, Turkey
- University Medical Center Groningen, Rijks University Groningen, Groningen, The Netherlands
- Istanbul Biruni University, Istanbul, Turkey
- East of England Deanery, Urology, Cambridge, United Kingdom
- University of Medical Center Mannheim, Heidelberg University, Mannheim, Germany
- Aarhus University, Aarhus, Denmark
- Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy
- Pediatric Hospital Bambin-Gesù, Rome, Italy
- Radboud University Medical Center, Nijmegen, The Netherlands
- University of Zurich, Zurich, Switzerland
- Beacon Hospital, Dublin, Ireland

8 Statistical analysis

8.1Main study parameter/endpoint:

The primary parameter is to evaluate quality of life in children with spina bifida using the QUALAS questionnaire. We will evaluate the differences in quality of life between European countries. Also, we will evaluate which demographic parameters are of influence on quality of life.
Descriptive statistics will be used.

8.2Secondary study parameters/endpoints:

Secondary parameters will include sexual function using the outcomes of the IIEF-5/FSFI-6 questionnaires, also in relation to differences between European countries. Other parameters include organization of care, treatment received, treatment options available, which will all be extracted from the primary survey. Again descriptive statistics will be used.

9.Recruitment and consent

9.1 Will the subjects be asked for informed consent?

☐ Yes *(Upload Patient Information Letter and Informed Consent)*

☒ No, only anonymous data is used, i.e. the data can never be traced back to an individual subject

☐ No, this research will be performed under the exception consent
(Upload form Care for data Template, in Dutch: Formulier uitzondering toestemming)

☒ Other (e.g. partly, indirectly) *Please describe the situation*

The digital survey that has been constructed by the EAU and IFSBH will be distributed through the IFSBH and local patient organizations to their members by email and newsletter. A link to the digital survey can be found in this correspondence.

A short introduction with the purpose of the survey and a question whether patients agree that their data will anonymously be used for research is the start of the digital survey. When patients answer no to this question, the digital survey is immediately ended. The data gathered cannot be traced back to the individual respondents.

9.2 If no, exception consent: Participation is voluntary, people that do not want to participate will not complete the questionnaire. They can withdrawal at any time and the responses will be deleted.

10. Handling and storage of data and images

10.1 The data is collected anonymous and it will not be possible to trace back to one specific patient.

10.2 The data will be stored in the Castor information system. Only anonymous data will be used, so it will not be possible to trace back to an individual patient.

11. Amendments

Amendments are changes made to the research after a favourable opinion by the NWTC has been given. All amendments will be submitted to the NWTC that gave the favourable opinion.

Substantial amendments must be approved by the NWTC before they can be implemented.

12. Publication

Do you have the intention to submit the study results in a manuscript for publication in a journal:

☒ Yes
☐ No, *please motivate*

13. References

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2. Radmayr C, et al: EAU Pediatric urology guidelines, EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022. ISBN 978-94-92671-16-5
3. Szymanski KM, Misseri R, Whittam B, Yang DY, Raposo SM, King SJ, Kaefer M, Rink RC, Cain MP. Quality of Life Assessment in Spina Bifida for Children (QUALAS-C): Development and Validation of a Novel Health-related Quality of Life Instrument. Urology. 2016 Jan;87:178-84. doi: 10.1016/j.urology.2015.09.027.
4. Szymański KM, Misseri R, Whittam B, Casey JT, Yang DY, Raposo SM, King SJ, Kaefer M, Rink RC, Cain MP. Validation of QUALAS-T, a health-related quality of life instrument for teenagers with spina bifida. Cent European J Urol. 2017;70(3):306-313. doi: 10.5173/ceju.2017.1195.

5. van Kollenburg RAA, de Bruin DM, Wijkstra H. Validation of the Electronic Version of the International Index of Erectile Function (IIEF-5 and IIEF-15): A Crossover Study. J Med Internet Res. 2019 Jul 2;21(7):e13490. doi: 10.2196/13490.
6. Isidori AM, Pozza C, Esposito K, Giugliano D, Morano S, Vignozzi L, Corona G, Lenzi A, Jannini EA. Development and validation of a 6-item version of the female sexual function index (FSFI) as a diagnostic tool for female sexual dysfunction. J Sex Med. 2010 Mar;7(3):1139-46. doi: 10.1111/j.1743-6109.2009.01635.x.

14. Attachments

☐ Patient information letter and Informed consent document

☐ Care for data Template – Formulier uitzondering toestemming

☒ Questionnaires

☐ Data Management Plan

☐ Data Transfer Agreement

☐ Material Transfer Agreement

☐ Clinical Trial Agreement

☐ Other, *please describe*