TEMPLATE RESEARCH PROTOCOL
for non-WMO-applicable research

18-07-2024, versie 2

Full title of protocol	**'Validation of the Quality of Life Assessment in Spina Bifida for Children and Adolescents in Dutch'**
Short title or Acronym	**QUALAS validation in Dutch**
Protocol ID / Panama number	
Version	1
Date	**January 4th, 2024**
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Sponsor[4] (in Dutch: verrichter/opdrachtgever)	**Department of Urology, Erasmus MC**
Subsidizing party[5]	**None**

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

1. *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.*
2. *Principal investigator: Investigator who has the overall responsibility to comply and to complete the study within the predefined goals.*
3. *Multicenter research: as an alternative you can also state that these are specified in the list with participating centers including principal investigator. This separate document with version date must be uploaded under category I1.*
4. *Sponsor: The party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization 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 subsidizing party.*

5. *Subsidizing party: A party that provides funding for a study but does not commission it*

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List of abbreviations and relevant definitions*

CTA	Clinical Trial Agreement
De novo biobank	A new data, human material or imaging collection
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
DTA	Data Transfer Agreement
ENT	Ear Nose Throat
Exception consent	Form Care for data Template, in Dutch: Formulier uitzondering toestemming
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation in Dutch: Algemene Verordening Gegevensbescherming
IC	Informed Consent
ICC	Intraclass Correlation Coefficient
ICIQ	International Consultation on Incontinence Questionnaire
IFU	Instruction For Use
LOA	Limits of Agreement
MTA	Material Transfer Agreement
NWTC	Non-WMO Review Committee; in Dutch: Niet WMO Toetsingscommissie
QUALAS-A	QUAlity of Life Assessment in Spina bifida in Adults
QUALAS-C	QUAlity of Life Assessment in Spina bifida in Children
QUALAS-T	QUAlity of Life Assessment in Spina bifida in Teenagers
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
WHOQOL-BREF	World Health Organization Quality of Life instrument

Summary

Rationale
Patients with spina bifida often experience a decreased quality of life compared to patients without spina bifida. The Quality of Life Assessment for Spina Bifida (QUALAS) is a validated questionnaire to assess the quality of life in children, teenagers and adults with spina bifida, accounting for specific factors, such as bladder and bowel dysfunction. This questionnaire enables us to assess the current spina bifida related quality of life and identify if bladder and bowel dysfunction is of influence.

Objective(s)
To validate the Quality of Life Assessment for Spina Bifida in Children, Teenagers and Adults in Dutch.

Study type
A multicenter prospective validation cohort study.

Study population
Children aged 8 – 17 years and adults who are diagnosed with spina bifida. As a control group children aged 8 – 17 years and adults without spina bifida will be approached at the Ear-Nose-Throat (ENT) and paediatric clinics.

Methods
The main study parameter is the validation of the Dutch version of the questionnaire. Patients with spina bifida are asked to fill out the QUALAS at two time-points. They are also asked to fill out an extra questionnaire at two time-points, in order to validate the QUALAS. Children and adults in the control groups are asked to fill out the two questionnaires only once.

Burden and risks
No (extra) outpatient visit is required. The questions in the questionnaires are similar to the medical history during an outpatient visit. The burden is therefore minimal for these patients. Participation in this study will not influence patient treatment.

Recruitment and consent
Parents of children and children and adults who meet the inclusion criteria and none of the exclusion criteria will be informed orally about this study by their treating urologist during a regular visit. A patient information and consent form will be handed over to the parents and children over eight years of age and adults. Parents of children and children and adults at the ENT clinic will be approached by the local urologist for participation for this study. If they are willing to participate they will be asked to sign informed consent and fill out the questionnaire.

Introduction and rationale

Patients with spina bifida often face challenges in different areas. It is common to have a dedicated team of medical specialists for yearly follow-up [1]. This team includes paediatricians, neurosurgeons, orthopaedics, urologists and rehabilitation specialists. Patients with spina bifida may experience symptoms in each of these areas which will have an impact of these patient's quality of life [2]. From the urologist perspective urinary incontinence and faecal incontinence have a high impact on quality of life [3].

1. Questionnaires to evaluate quality of life in patients with spina bifida do not incorporate these specific symptoms. The QUAlity of Life Assessment in Spina bifida in Children (QUALAS-C), QUAlity of Life Assessment in Spina bifida in Teenagers (QUALAS-T) and The QUAlity of Life Assessment in Spina bifida in Adults (QUALAS-A) have been developed to take these symptoms into account when assessing quality of life. These questionnaires are validated in the United States [4,5]. For children aged 8-12 years the QUALAS-C version is available. For children between 13-17 years of age the QUALAS-T version is available. For adults the QUALAS-A version is available.

Currently, no versions of the QUALAS-C, QUALAS-T, QUALAS-A questionnaires are available in Dutch.

With the QUALAS-C, QUALAS-T and QUALAS-A we will be able to assess spina bifida related quality of life and monitor the development over time. This will enable clinicians to offer improved standardized care.

Objective(s)

2. The aim of this study is to validate the QUALAS questionnaire for children, teenagers and adults in Dutch.

3. **Study type**

3.1. **Study type**

☐ Retrospective
☒ Prospective
☐ Combination Retrospective/Prospective

3.2. **Single center / Multicenter**

☐ Single center
☒ Multicenter

3.3 **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 material from research or existing biobank

- ☐ De novo biobank
- ☐ Phase IV research
- ☒ Healthcare evaluation research (prospective)
- ☐ Research with medical devices
- ☐ Research with In Vitro Diagnostic Tests
- ☐ Other research, describe

4. Study population

4.1. Study population

☒ Adults (16 years and older)
☒ Minors (younger than 16 years)
☐ Incapacitated adults (16 years and older)
☐ Incapacitated minors (younger than 16 years)

4.2. Population (base)

Parents of children and children and adults with spina bifida that are patients at the Urology department of the two hospitals will be approached to participate.
This questionnaire quantifies the quality of life in patients with spina bifida, with a special interest in bladder and bowel dysfunction.
A group of children and adults without spina bifida will function as a control group. These children and adults will be approached at the ENT and paediatric clinics.

4.3. Inclusion criteria

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

Patient group:

- Male or female patients aged 8 -12 years (QUALAS-C)
- Male or female patients aged 13 – 17 years (QUALAS-T)
- Adult patients (QUALAS-A)
- Has spina bifida
- Adult or child and at least one parent fluent in the Dutch language
- Signed informed consent

Control group:

- Male or female children aged 8 -12 years (QUALAS-C)
- Male or female adolescents aged 13 – 17 years (QUALAS-T)
- Adults (QUALAS-A)
- Has no spina bifida
- Adult or child and at least one parent fluent in the Dutch language
- Signed informed consent

4.4. Exclusion criteria

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

- Has a neurogenic disease other than spina bifida
- Has had surgery in the last month

4.5. **Sample size calculation**

A minimum of 50 patients and 50 controls is recommended for reliable validation criteria of a questionnaire per group [6].

Methods

5.1. Research methods

5. This is a multicenter prospective cohort validation study of the QUALAS questionnaire. This is a spina bifida related quality of life questionnaire. We will validate the QUALAS using the validated KIDSCREEN-27 for children 8-17 years of age and the World Health Organization Quality of Life instrument (WHOQOL-BREF) and (International Consultation on Incontinence Questionnaire) ICIQ for adults [7]questionnaires to determine spina bifida related quality of life in a standardized manner.

All patients are subject to treatment at the department of Paediatric Urology in Erasmus MC–Sophia or University Medical Center Groningen. Participation in this study will not interfere with their treatment.

For this study two different phases are distinguished:

- Phase 1: The QUALAS will be translated following a standardized translation process [8]. This includes three forward translations by Dutch native speakers, one backward translation by a English native speaker and face-to-face testing in the target population.

- Phase 2: Children of 8 years and older and adults are asked to fill out the questionnaires, QUALAS and KIDSCREEN for children 8-17 years of age and the WHOQOL-BREF and ICIQ for adults, and repeat filling out the QUALAS questionnaire one week later. We ask all parents to fill out the questionnaire in order to secure a constant answer during the study. Children of 8 years and older and adults in the control group are asked to fill out the QUALAS and KIDSCREEN-27 for children 8-17 years of age and the WHOQOL-BREF and ICIQ for adults. Internal consistency, criterion validity, construct validity an reproducibility will be determined.

5.2. Standard clinical care versus extra for research

Participation in the study will mean that at two timepoints questionnaires need to be completed to no completion of questionnaires when there is no study participation.

5.3. Burden and risks

Given the nature of the questions in the questionnaires, which is similar to a regular medical history during an outpatient visit, the risks of participation is negligible and burden minimal. Incidental findings of low quality of life in the control group will not be followed up.

5.4. Medical device(s) / In vitro diagnostic tests

Not applicable

Incidental findings

6. 6.1. **Chance of incidental findings**
Is there a chance of incidental findings?

☐ Yes

☒ No

6.2. **Procedures**
Not applicable

Statistical analysis

7. 7.1 **Main study parameters/endpoints**
Internal consistency is the main study endpoint. Total scores of the patient and control group will be used to determine this endpoint.

7.2 **Secondary study parameters/endpoints**
For the following secondary endpoint scores from patient and control group will be used:

- Construct validity

For the following secondary endpoints scores from the patient group will be used:

- Reproducibility
- Content validity
- Interpretability

7.3 **Analysis**

Primary study parameter

Internal consistency is the main study endpoint. This will be calculated with Cronbach's alpha. Values between 0.70 and 0.95 reflect good consistency.

Secondary study parameters

Reproducibility will be determined to assess the ability to reproduce similar answers during the retest period. This will be calculated using Intraclass Correlation Coefficient (ICC), where ICC scores over 0.7 are acceptable. The limits of agreement (LOA), which is calculated by mean change in scores ± 1.96 SD are determined as well.

Content validity is subjectively determined by examining whether the questionnaire is measuring the quality of life related to spina bifida.

Construct validity is determined by testing the following hypotheses:

- The control group will have higher scores in the QUALAS than patients with spina bifida.

- Patients who score higher in the KIDSCREEN-27 or WHOQOL-BREF/ICIQ will have higher scores in the QUALAS.

8 Ethical considerations

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version, date, see for the most recent version: www.wma.net), Gedragscode Gezondheidsonderzoek 2022 and in accordance with other guidelines, regulations and Acts (if applicable, please specify).

8.2 Informed consent

Will the subjects be asked for informed consent?

☒ Yes

☐ No, consent already given in previous study *(Upload Participant Information Letter and Informed Consent previous study)*

☐ 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.*

8.3 Recruitment and informed consent procedures

Adults, parents of children and children who meet the inclusion criteria and none of the exclusion criteria will be informed orally about this study by their treating urologist during a regular visit. A patient information and consent form will be handed over to the adults, and parents and children over eight years of age. The two questionnaires are included in this package as well. When adults, parents and children are willing to participate adults or parents and children over twelve years of age are asked to sign the consent form, and sent it in through the post, along with the first questionnaire and voiding diary in the following week. For children of the ages 16 and 17 only the consent form signed by them is necessary. For all the children of the other age groups a signed consent by the parents is necessary.

Adults, or parents of children and children at the ENT and paediatric clinics will be approached by the local urologist for participation for this study. If they are willing to participate they will be asked to sign informed consent and fill out the questionnaire.

9 Handling and storage of data / images / sound recordings / photos / film recordings

9.1 Data / images / sound recordings / photos / film recordings

Data will be handled confidentially. Only the members of the study team will be able to access the clinical records and data resulting from this study. Patients will not be identified by personal information in any publication following this study.

9.2 Privacy protection

The data will be stored in the Castor information system. A key will be used so that individual data cannot be traced back to the individual patient. Only the local investigators at the Erasmus MC will have access to the key. The researcher analyzing the data will not have the key to track the data back to an individual patient.

9.3 **Handling and storage of data**
The data will be stored in the Castor information system. A key will be used so that the individual data cannot be traced back to the individual participant.
In line with Erasmus MC guidelines, data will be kept 10 years after it is collected.

9.4 **Handling and storage of images / sound recordings / photos / film recordings**
Not applicable

9.5 **Approval of access to data / images / sound recordings / photos / film recordings**
This study will be performed at the Erasmus Medical Center and University Medical Center Groningen. The PI's of both centers will have access to the anonymous data.

10 Handling and storage of human material

10.1 **Human material**
Not applicable

11 Exchange, sharing or transfer of data and/or human material and/or images

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 University Medical Center Groningen. A DTA is attached.

12 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

Non-substantial amendments will not be notified to the accredited METC , but will be recorded and filed by the sponsor.

13 End of study report

Within one year after the end of the study a final study report will be submitted with the results of the study, including any publications/abstracts of the study.

14 Publication

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

☒ Yes

☐ No, *please motivate*

When the required number of participants has been reached, the results will be analysed and a manuscript will be drawn up for publication. A final study report will be written after submission.
The expected duration of the study is 1 year.

15 References

1. Van Speybroeck A, Beierwaltes P, Hopson B, McKee S, Raman L, Rao R, Sherlock R. Care coordination guidelines for the care of people with spina bifida. J Pediatr Rehabil Med. 2020;13(4):499-511. doi: 10.3233/PRM-200738.

2. Koch VH, Lopes M, Furusawa E, Vaz K, Barroso U. Multidisciplinary management of people with spina bifida across the lifespan. Pediatr Nephrol. 2023 Jul 28. doi: 10.1007/s00467-023-06067-w.

3. Sawin KJ, Brei TJ, Houtrow AJ. Quality of life: Guidelines for the care of people with spina bifida. J Pediatr Rehabil Med. 2020;13(4):565-582. doi: 10.3233/PRM-200732.

4. 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.

5. 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. Epub 2017 Jun 23.

6. Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L., et al. (2010). The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: An international Delphi study. Quality of Life Research, 19, 539–549

7. U. Ravens-Sieberer, P. Auquier, M. Erhart, et al. The KIDSCREEN-27 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries Qual Life Res, 16 (2007), pp. 1347-1356

8. Guillemin, F., C. Bombardier, and D. Beaton, Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Epidemiol, 1993. 46(12): p. 1417-32.

16 Attachments

☒ Participant 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 (Site) Agreement

☐ Other, *please describe*