RESEARCH PROTOCOL

for non-WMO-applicable research:

Signaling Instrument Stuttering – development, standardization and validation

11-10-2023, version 2

Table of Contents

List of abbreviations and relevant definitions*

DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IC	Informed Consent
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
SIS	Signaling Instrument Stuttering
SLS	Screening List Stuttering
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. 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.
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

**Please add any new definitions that are used in the research protocol*

Summary

Rationale: Stuttering usually starts in children from 3 to 5 years old and it occurs in about 8% of children. Approximately 60% of these children will recover from stuttering within 3 years post onset. There are known risk factors for persistent stuttering, such as male gender and family history of stuttering. Since many upgrowing children regularly experience disfluencies in their speech, a stuttering signaling tool is a useful tool for parents who have noticed disfluency in their child's speech. With such a tool they can determine whether they should see a speech therapist or not.
30 years ago, a screening tool for stuttering was developed in the United States for paediatricians who could complete the questionnaire together with parents. At the time, the instrument was translated into Dutch as the ScreeningsList Stuttering (SLS). The SLS has fulfilled the described need for a long time. However, this instrument is now very outdated because the policy has changed on the basis of studies on recovery and persistence of stuttering that have been published over the past 20 years. The revised Stuttering Guideline (2020), therefore recommends updating the instrument so that an up-to-date checklist becomes available again that gives parents something to hold on to: 1) the dysfluent speech will most likely go away on its own, 2) consult a speech therapist to assess/monitor treatment or start treatment.
Objective: The primary objective is to develop, standardize and validate a new signaling tool for stuttering, to be used by parents for children aged 2-5 years, which includes all known risk factors for persistent stuttering and requirements for intervention by a speech therapist.
Study type: Observational cross-sectional study.
Study Population: In the first phase of the study n=150 children will be assessed: All children will be aged 2-5 years. In the second phase a new group of children will be included, to validate the developed and normed questionnaire and determine sensitivity and specificity. The size of this group will be based on the outcomes of the first phase.
Methods: First, a candidate version of the new Signaling Instrument Stuttering (SIS) will be developed, based on literature research and presented to a group of parents and professionals to attain sufficient face validity. Second, the SIS will be normed and standardized. To this end, 150 parents who have noticed disfluencies in their toddler or preschooler (aged 2-5 years) are asked to complete the SIS. All 150 children will be examined by a speech therapist as well, to asses a child's speech fluency, attitude towards speaking and sound production skills. Third, the SIS and according scoring system will be validated on the basis of a new group of children. Based on the SIS outcome, the developed standards and the clinical judgment of the speech therapist, the relationship between sensitivity and specificity (Receiver Operating Curve) and the accuracy of the Signaling Instrument is determined.
Burden and risks: Parents will be requested to complete a 5 minute questionnaire once. The children's assessments will take 15 minutes for the children recruited through schools. These children can be assessed at school. The children recruited through the speech therapists will already be assessed for clinical reasons by the speech therapist. Only a 5 minute additional assessment (non-word repetition task) will be done extra for research purposes. The assessments are not invasive, not cognitively difficult and not social-emotionally burdensome. Therefore, the risks of this study are negligible and the burden will be minimal.
Recruitment and consent: Participants will be recruited via our network of peripheral speech therapists and via kindergartens and schools. Speech therapists and kindergartens and schools in the neighborhood of participating speech therapists will be contacted and requested to assist in the recruitment of parents in our study. Speech therapists will be requested to verbally inform parents who have attended to them regarding beginning stuttering of their child about the study, supported by the PIF. Kindergartens and schools we be requested to reach out to parents with a letter about the study. Parents who hear disfluencies in their child's speech will be requested to participate in the study. Parents who are interested can react by sending their contact information to us via a Limesurvey form of Erasmus MC. The parents who give their contact information, will be called or emailed to inform them about the study and send the PIF. Informed consent letters will be send to the parents home addresses or digitally through Limesurvey (based on parents' preference). Parents can take as much time as needed (at least 2 weeks) to decide about participation.

1. Introduction and rationale

Stuttering usually starts in children from 3 to 5 years old and it occurs in about 8% of children (1, 2). Approximately 60% of children will recover from stuttering within 3 years post onset (1, 3). There are known risk factors for persistent stuttering, such as male gender and family history of stuttering. In addition, it is known that the chance of recovery without treatment decreases the longer children stutter without the stuttering severity decreasing. In the absence of recovery, stuttering can develop into a disability that seriously impedes social development and personal well-being. If children still stutter when they are 7-8 years old, full recovery is rare. Treatment at this age and older is no longer aimed at recovering from stuttering, but at daring to talk and talk as easily as possible. Starting treatment at a young age if there is an increased risk for persistent stuttering is therefore of great importance for the best chances of full recovery. At the same time, many children recover spontaneously or only have normal disfluencies, appropriate for the developmental phase of young children.

A stuttering signaling tool is a useful tool in determining whether parents should see a speech therapist if they have noticed disfluency in their child's speech. Many upgrowing children regularly experience disfluencies in their speech. It is often difficult for parents (but also for doctors) to assess whether the speech disfluencies are typical/normal or not and when help from a speech therapist is required.

30 years ago, a signaling tool for stuttering was developed in the United States for paediatricians who could complete the questionnaire together with parents (4). At the time, this instrument was translated into Dutch as the ScreeningsList Stuttering (SLS)(5). Parents can complete the screening tool themselves (online). Care providers to whom parents raise the issue of stuttering (general practitioner, social nurse at the consultation centre, the paediatrician) can complete the instrument together with the parents. It is therefore a handy checklist that can be used to determine whether it is necessary for parents to consult a speech therapist or whether this is not (yet) necessary.
The SLS has fulfilled the described need for a long time. However, this instrument, which was published in 1989, is now outdated. This questionnaire only contains questions about stuttering symptoms. However, several studies published over the last 25 year, have resulted in risk factors for stuttering persistence, such as sex and stuttering running in the family. These and other factors are not included in the old instrument. Therefore, the current SLS is obsolete. Since the decision of starting therapy depends on the risk on persistency of stuttering, these known risk factors should be included in the instrument, In line with this, the revised Stuttering Guideline (2020)(6) recommends updating the SLS . An up-to-date checklist , aiming for a more accurate signaling list, will assist parents and physicians something to hold on to: 1) the dysfluent speech will most likely resolve naturally 2) consult a speech therapist to start monitoring the dysfluent speech 3) consult a speech therapist to start treatment without any delay.

2. Objective(s)

The primary objective is to develop, standardize and validate a new signaling tool for stuttering, to be used by parents for children aged 2-5 years, which includes all known risk factors for persistent stuttering and requirements for intervention by a speech therapist.

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)**

In the first phase of this study 150 children will be included, to norm and standardize the questionnaire. All children will be aged 2-5 years. Half of the children (N=75) will be recruited through peripheral speech therapists. Parents who just have reached out to a speech therapist regarding the beginning of stuttering in their child will be requested to participate. The other 75 children will be recruited at kindergartens, where parents who noticed disfluencies in their child's speech will be requested to fill in the questionnaire since they have (light) concerns about the speech of their child. They will do an additional assessment of 15 minutes.
N.B.: only parents that have already signaled (some) fluencies in their child's speech and have (mild) concerns about this will participate in the study.
In a second phase, the normed and standardized questionnaire will be validated based on a new group of children. Based on the sensitivity and specificity that were found in the first phase a new power analysis will be done to calculate the number of participants that will need to be included in this phase.

4.3. **Inclusion criteria**

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- aged 2;0–5;0 years, and;
- parents noticed speech disfluencies in their child's speech and/or are concerned about their child's speech fluency.

4.4. Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- both parents have insufficient proficiency in Dutch.
- the child has insufficient access to spoken language due to hearing disorder, which had been diagnosed by an audiologist.

4.5. Sample size calculation

Our sample size for the first phaseis based on the prediction model that we will use to determine the cut-off value of the questionnaire to predict the dichotomous outcome of the speech therapist (treatment or no treatment). Each question of the questionnaire will be included as a possible predictor variable, the dichotomous outcome of the speech therapist will be the dependent variable to predict. Based on estimated numbers of speech therapists, we expect that 90% of the group that already have reached out to a speech therapist and 50% of the group that is recruited through kindergartens will need treatment. For the total group, consequently, we expect 70% will be treated. The questionnaire will consist of 9 questions. For each of these 9 variables in the prediction model, 10 patients (children that will need treatment) need to be included, resulting in n=90 children (=70%). Consequently, the other 30%, who is expected to need no treatment refer to a group of n=38 children. Therefore, the total number of participants will need to be n=128. To allow for some leeway, we will recruit 20% extra participants, which result in a total number of n=150 children. .
The sample size for phase two will be determined based on the found sensitivity and specificity score in phase 1. If we allow 5% more or less specificity and sensitivity in the second phase, we will use the following formula to calculate the sample size: $0.10=2x1.96 \sqrt{(p(1-p)/n)}$, where p is the sensitivity or specificity value.

5. Methods

5.1. Research methods

First, the development of the new Stuttering Signaling Tool (SIS), the items of the existing SLS (Stuttering Screening List) are assessed for topicality based on the most recent literature. Based on this, we will compile a candidate questionnaire for the SIS, that we will present to 10 parents (3 with low, 4 with middle and 3 with high socio-economic status) and 10 professionals (speech therapists, general practitioners and doctors of children's health centers) to assess the content, comprehensibility, ambiguity and clarity of the questions (face validity). We will adjust the list based on this review. The final questionnaire is aimed to consist of 9 questions.
The second step is to norm and standardize this questionnaire. To this end, 150 parents who have noticed a lack of fluency in their toddler or preschooler (aged 2-5 years) are asked to complete the SIS. All 150 children will be examined by the speech therapist (duration of this examination is approximately 15 minutes):
- Recording of 5-10 minutes of spontaneous speech to assess objective stuttering severity using the Stuttering Severity Instrument (SSI-4, Riley). The percentage of stuttered syllables, the average duration of the stutters and the additional behaviors are analyzed.
- Administration of a short questionnaire, Kiddy-CAT (Van Rijckeghem & Brutten), to assess the child's attitude towards speaking.
- Administration of a Nonword Repetition Test as an indication of the child's speech skills and to discriminate against fluency problems as a result of multilingualism.
- Qualitative judgment of the speech therapist of the fluency of speech on an 8-point scale [0= normal fluency, 7= very severe stuttering].

We will analyze the relationship between the scores on SIS, the raw scores on the above reference tests and the clinical decision of the speech therapist: (1) discharge because there is no stuttering (2) monitor because treatment can be postponed (3) start with treatment because of high-risk stuttering. Based on this analysis, standards (criteria) are formulated for the interpretation of the results of the SIS: 1. normal disfluencies - no stuttering - consultation of a speech therapist is not necessary; 2. stuttering and monitoring by a speech therapist; 3. stuttering and starting treatment.

The third step is the validation of the compiled and standardized questionnaire on the basis of a new group of children. Based on the SIS outcome, the developed standards and the clinical judgment of the speech therapist, the relationship between sensitivity and specificity (Receiver Operating Curve) and the accuracy of the SIS is determined.

N.B.: If children reject to participate at any time during the 15 minutes examination, the examination will be stopped. The speech therapist will in no way insist or force the child to participate.

1.2 Standard clinical care versus extra for research

Half of the participants (n=75) will be children who stutter whose parents attended a speech therapist already. For these children speech assessments are part of their standard clinical procedures. The other half of the participants (n=75) will be children whose parents did not attend a speech therapist, but hear disfluencies in the speech of their child. These children will be assessed extra for research, by a speech therapist at their school (during school time), which will cost 15 minutes.

1.3 Burden and risks

Parents will be requested to complete a 5 minute questionnaire once, including questions about speech development and stuttering onset of their child, stuttering occurrence in the family and educational level of the parents. The children's assessments will take 15 minutes for the children recruited through schools. These children can be assessed at school. The children recruited through the speech therapists will already be assessed for clinical reasons by the speech therapist. Only a 5 minute additional assessment (non-word repetition task) will be done extra for research purposes. The assessments are not invasive, not cognitively difficult and not social-emotionally burdensome. Therefore, the risks of this study are negligible and the burden will be minimal.

1.4 Medical device(s) / In vitro diagnostic tests

Not applicable.

6. Incidental findings

6.1. **Chance of incidental findings**

Is there a chance of incidental findings?

☐ Yes

☒ No

6.2. **Procedures**

Not applicable

Statistical analysis

Data will be analyzed with SPSS for Windows. All statistical tests will be 2-sided. A p-value <0.05 will be

considered significant. All statistical analyses will be performed after consultation and approval of a statistician of our department.

7.1 **Main study parameters/endpoints**
The main study parameters are the specificity and sensitivity of the main dichotomous outcome of the SIS: is consultation by a speech therapist required: (1) no, there are normal disfluencies (no stuttering), consultation of a speech therapist is not necessary (2) yes, the child stutters and consultation of a speech therapist is recommended, to assess, monitor and/or treat stuttering.

7.2 **Secondary study parameters/endpoints**
Not applicable.

7.3 **Other study parameters**
Not applicable.

7. Analysis

For the first phase a prediction model will be used, with the separate questions of the questionnaire as the independent variables and the outcome of the speech therapist as the dependent variable. The best cut-off score of the total questionnaire will be the outcome. In the second phase this cut-off score will be validated by calculating the specificity and sensitivity of the normed questionnaire.

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 *(Upload Participant Information Letter and Informed Consent)*

☐ 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**
Participants will be recruited via our network of peripheral speech therapists and via kindergartens and schools.

First, speech therapists will be contacted to request their commitment to the study. They will be requested to:

- Qualitatively judge the first candidate list of the questionnaire, to further develop the questionnaire in the first phase of the study.
- Verbally inform parents who have attended to them regarding beginning stuttering of their child about the study, supported by the PIF. Parents will be requested to give their contact

information when they are interested in participating in the study. Speech therapists will collect contact information through a Limesurvey form of Erasmus MC. The parents who give their contact information, will be called or emailed by the researchers of Erasmus MC to further inform them about the study. Informed consent letters will be send to the parents home addresses or digitally through Limesurvey (based on parents' preference). Parents can take as much time as needed (at least 2 weeks) to decide about participation.

Second, kindergartens and schools in the neighborhood of participating speech therapists will be contacted and requested to assist in the recruitment of parents in our study.

- When schools give permission, we will reach out to parents with a letter about the study. Parents who hear disfluencies in their child's speech will be requested to participate in the study. Parents who are interested can react by sending their contact information to us via a Limesurvey form of Erasmus MC. The parents who give their contact information, will be called or emailed to inform them about the study and send the PIF. Informed consent letters will be send to the parents home addresses or digitally through Limesurvey (based on parents' preference). Parents can take as much time as needed (at least 2 weeks) to decide about participation.

8.4 Exception consent

Not applicable.

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

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

Audio recordings of the speech assessment will be used. They will be recorded for research purposes for at least half of the group (recruited through schools). For the other half of the participants recordings will be made for clinical care. They will be saved at Erasmus MC for research purposes.

9.2 Privacy protection

Data will be coded, using anonymous coding (i.e. not based on initials or date of birth). The key to the code is safeguarded by the investigator. The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. (in Dutch: Uitvoeringswet AVG, UAVG)

9.3 Handling and storage of data

In line with Erasmus MC guidelines, data will be kept 10 years after it is collected. Questionnaire data will be collected through LimeSurvey. Audio data will be saved on an Isilon drive.

9.4 Handling and storage of images / sound recordings / photos / film recordings

In line with Erasmus MC guidelines, images / sound recordings / photos/ film recordings will be kept 10 years after it is collected.

9.5 Approval of access to data / images / sound recordings / photos / film recordings

Access to the data is granted by the Principal investigator of the data collection.

10. Handling and storage of human material

10.1 **Human material**
Not applicable.

10.2 **Check all the boxes which are applicable to the human material origin:**
Not applicable.

☐ Residual material from regular healthcare

☐ Research (material acquired from a previous study).
Add the reference of the study i.e., MEC-number Erasmus MC.

☐ Re-use of human material from existing biobank
Describe whether the human material originates from research into the same disease.

☐ Other, *please specify*

10.3 **Handling and storage of human material**
Not applicable.

☐ Anonymous, i.e. the material can never be traced back to an individual subject

☐ Pseudonymized/Coded

☐ Identifiable

10.4 **Biobank**
Not applicable.

10.5 **Approval of access to human material**
Not applicable.

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

Data will not be shared with others. Speech therapists will share their collected speech samples with Erasmus MC by using Surffilesender. A data transfer agreement will be used.

12. Amendments

Amendments are changes made to the research after a favorable opinion by the NWTC has been given.

All amendments must be submitted to the NWTC that gave the favorable opinion.

Substantial amendments must be approved by the Niet WMO Toetsingscommissie before they can be implemented.

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*

15. References

1. Mansson H. Childhood stuttering: Incidence and development. . Journal of Fluency Disorders. 2000;25(1):47–57.

2. Reilly S, Onslow M, Packman A, Cini E, Conway L, Ukoumunne OC, et al. Natural history of stuttering to 4 years of age: a prospective community-based study. Pediatrics. 2013;132(3):460-7.
3. Yairi E, Ambrose NG. Early childhood stuttering: For clinicians by clinicians. Austin, TX: Pro-Ed; 2005.
4. Reilly G, Reilly J. Physician's screening procedure for children who may stutter. Journal of Fluency Disorders. 1989;14:57-66.
5. Screeningslijst voor Stotteren [Available from: https://www.stotteren.nl/ouders/screeningslijst-voor-stotteren-sls.html.
6. NVLF. Richtlijn stotteren bij kinderen, adolescenten en volwassenen 2020 [Available from: https://www.nvlf.nl/kennis/inhoudelijke-richtlijnen/.

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*