

Validation of the lay-reported 5-Domain Niemann-Pick Disease Type C Clinical Severity Scale (NPCCSS)

Background

A lay-reported version of the 5-domain NPCCSS was developed by Orphazyme in 2019 to obtain a self-reported perspective on disease burden in persons with NPC. The lay-reported NPCCSS measures the same 5 symptoms (ambulation, fine motor skills, swallowing, cognition and speech) on a likert scale. However, a 0-10 rating scale was added to each symptom domain to assess the impact on the person with NPC's daily life (0= no impact; 10= completely impacts). Both self-report and caregiver-report forms were created. In 2021, NPUK shared a survey with the NPC community to collect data on the lay-reported NPCCSS. Preliminary analysis of the data indicated issues with discriminating ability between response options on some of the symptom domains. Additionally, there appeared to be no relationship between the impact and severity scores of each symptom. Therefore, a mixed methods study was conducted to examine the validity of the lay-reported NPCCSS.

Current study

Jackson Pountney, a PhD student at Aston University is currently running a study to validate the lay-reported NPCCSS. In the first phase, cognitive interviews were conducted with members of the NPC community (n=12) to obtain their perspective and feedback on the performance of the scale. Interview questions centred around the comprehension and clarity of the survey instructions as well as the wording of the items and response options. This information was used to suggest amendments the instructions and phrasing of the items. A total of 7 amendments were proposed.

1. Questionnaire instructions

The instructions for the NPCCSS ask respondents to think about their experience of symptoms during "a typical day over the past week". However, during interviews, participants would often cite experiences from earlier time periods when providing a rationale for their responses to the questions. Therefore, it was suggested that each question be made time bound, to ensure responses are contextualised to the desired time window.

Original Instruction	Suggested change following cognitive interview
Example from the 'walking' item: "This question relates to the person's ability to walk about from place to place. Please select the option that best describes how they are generally, considering their age and stage in development"	Example from the 'walking' item: "This question relates to the person's ability to walk about from place to place. Please select the option that best describes how they were generally on a typical day over the past week , considering their age and stage in development"

2. Impact on daily life scores

For each of the symptom items on the lay-reported NPCCSS, there is a 0-10 rating scale to capture the magnitude of impact that symptom has on the person with NPC's, or the family's daily life. During interviews with caregivers of persons with NPC, it became clear that the impact on the person with NPC and their family are two separate experiences. Since the NPCCSS is a patient-reported measure, the impact questions should focus on the effect of the symptom on the person with NPC's daily life, rather than that of their family.

3. Fine motor skills response options

On the fine motor skills item, participants found it difficult to discern a meaningful difference in severity between the terms "slight" and "mild", which denoted scores of 1 and 2, respectively. As a result, some alternate response options have been proposed below.

Original response options	Suggested changes following cognitive interview
"Normal, he/she has no problems coordinating hand movements"	"Normal, he/she has no problems coordinating hand movements"
"Slight difficulties coordinating hand movements, but he/she can handle objects without assistance"	" Mild difficulties coordinating hand movements, but he/she can handle objects without assistance"
"Mild difficulties coordinating hand movements, requiring little or no assistance and he/she is able to feed himself/herself without difficulty"	" Moderate difficulties coordinating hand movements, requiring little or no assistance and he/she is able to feed himself/herself without difficulty"
"Moderate difficulties coordinating hand movements such that he/she has difficulty feeding him/herself"	" Severe difficulties coordinating hand movements such that he/she has difficulty feeding him/herself"
"Severe difficulties coordinating hand movements, needing help for self-care"	" Very severe difficulties coordinating hand movements, needing help for self-care"

4. Swallowing response option

Some participants noted that they/the person they cared for also coughed whilst drinking as well as eating. The response option on the swallowing domain was altered to reflect this preference.

Original	Suggested change following cognitive interview
“He/she coughs while eating”	“He/she coughs while eating or drinking ”

5. Frequency of swallowing difficulty

When looking at frequency of swallowing difficulties, respondents felt the terms “occasionally” and “Frequently” should be quantified.

Original	Suggested changes following cognitive interview
Never	Never
Occasionally	Occasionally (once or twice a day)
Frequently”	Frequently (more than once or twice a day)

6. Cognition item instructions

The final two suggested changes to the NPCCSS are linked and refer to the cognition item. It was proposed that the item instructions be amended to ensure consistent use of the term “cognitive ability”. It also needs to be made clear that the question is asking about the effect of NPC on the person’s cognition and not other confounding factors such as age.

Original	Suggested change following cognitive interview
“This question relates to the person’s cognitive ability, for example, their ability to learn new skills, make decisions, follow instructions, or focus their attention. Please select the option that best describes how they are generally considering their age and stage of development.”	“This question relates to the effect of NPC on the person’s cognitive ability , for example, their ability to learn new skills, make decisions, follow instructions, or focus their attention. Please select the option that best describes how they were generally on a typical day over the past week , considering their age and stage of development.”

7. Cognition item response options

The definitions of “learning delay” and “cognitive function” and the inconsistency of the use of these terms throughout the response options contributed to confusion in some participants. The response options and instructions were amended to ensure the item reflected the effect of NPC on the person’s cognitive ability. The term “cognitive ability” is now used consistently in the phrasing of response options, ensuring clarity.

Original	Suggested changes following cognitive interview
“Normal for their age”	“Normal for their age”
“Mild learning delay but he/she can keep up with others his/her own age”	“Mild effect on cognitive ability but he/she can keep up with others his/her own age”
“Moderate learning delay, for example, requires an adjusted environment if in school or work”	“Moderate effect on cognitive ability , for example, requires an adjusted school, work or home environment”
“Severe learning delay, he/she is not progressing, or he/she can no longer attend school or work because of some loss of cognitive function (ability to learn new skills, make decisions, follow instructions, or focus their attention)”	“Severe effect on cognitive ability , he/she is not progressing, or he/she can no longer attend school or work”
“Minimal cognitive function e.g. very much limited in ability to learn new skills, make decisions, follow instructions, or focus their attention and/or is losing skills previously acquired”	“Minimal cognitive ability e.g. very much limited in ability to learn new skills, make decisions, follow instructions, or focus their attention and/or is losing skills previously acquired”

Next steps

In partnership with NPUK, NNPfD, the INPDA and the INPDR, quantitative data on the amended 5-domain NPCCSS will be collected. This will allow an examination of the validity and reliability of the scale. Once the lay-reported NPCCSS has been validated in English, it will be translated. Cultural adaptation and translation of the lay-reported NPCCSS will be performed across 6 languages: Portuguese, Spanish, Italian, German, Czech and Dutch. Once this work is completed, we will have robust measures of self-reported disease burden for people with NPC across multiple countries.