



# Patient-reported measures of tinnitus for individuals with neurofibromatosis type 2–related schwannomatosis: Recommendations for clinical trials

Heather L Thompson<sup>1</sup>, Jane Grabowski<sup>2</sup>, Barbara Franklin<sup>3</sup>, Kimberley S Koetsier<sup>4</sup> and D Bradley Welling<sup>5</sup>; on behalf of the REiNS International Collaboration

## Abstract

**Background:** Neurofibromatosis type 2–related schwannomatosis is a genetic disease characterized by the development of bilateral vestibular schwannomas, ependymomas, meningiomas, and cataracts. Mild to profound hearing loss and tinnitus are common symptoms reported by individuals with neurofibromatosis type 2. While tinnitus is known to have a significant and negative impact on the quality of life of individuals from the general population, the impact on individuals with neurofibromatosis type 2 is unknown. Consensus regarding the selection of suitable patient-reported outcome measures for assessment could advance further research into tinnitus in neurofibromatosis type 2 patients. The purpose of this work is to achieve a consensus recommendation by the Response Evaluation in Neurofibromatosis and Schwannomatosis International Collaboration for patient-reported outcome measures used to evaluate quality of life in the domain of tinnitus for neurofibromatosis type 2 clinical trials.

**Methods:** The Response Evaluation in Neurofibromatosis and Schwannomatosis Patient-Reported Outcomes Communication Subgroup systematically evaluated patient-reported outcome measures of quality of life in the domain of tinnitus for individuals with neurofibromatosis type 2 using previously published Response Evaluation in Neurofibromatosis and Schwannomatosis rating procedures. Of the 19 identified patient-reported outcome measures, 3 measures were excluded because they were not validated as an outcome measure or could not have been used as a single outcome measure for a clinical trial. Sixteen published patient-reported outcome measures for the domain of tinnitus were scored and compared on their participant characteristics, item content, psychometric properties, and feasibility for use in clinical trials.

**Results:** The Tinnitus Functional Index was identified as the most highly rated measure for the assessment of tinnitus in populations with neurofibromatosis type 2, due to strengths in the areas of item content, psychometric properties, feasibility, and available scores.

**Discussion:** Response Evaluation in Neurofibromatosis and Schwannomatosis currently recommends the Tinnitus Functional Index for the assessment of tinnitus in neurofibromatosis type 2 clinical trials.

## Keywords

Neurofibromatosis type 2, tinnitus, tinnitus severity, tinnitus distress, hearing disorder, Tinnitus Functional Index

<sup>1</sup>Department of Communication Sciences and Disorders, California State University, Sacramento, Sacramento, CA, USA

<sup>2</sup>Mimi Hearing Technologies, Charité, Universitätsmedizin Berlin, Berlin, Germany

<sup>3</sup>REiNS Patient Representative for NF2, New York, NY, USA

<sup>4</sup>Otorhinolaryngology and Head & Neck Surgery, Leiden University Medical Center, Leiden, The Netherlands

<sup>5</sup>Harvard Department of Otolaryngology–Head and Neck Surgery, Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital, Boston, MA, USA

## Corresponding author:

Heather L Thompson, Department of Communication Sciences and Disorders, California State University, Sacramento, 6000 J Street, MS 6071, Sacramento, CA 95819, USA.

Email: heather.thompson@csus.edu

## Introduction

*NF2*-related schwannomatosis (NF2) is a genetic tumor predisposition syndrome characterized by a mutation of the *NF2* gene located on chromosome 22q.<sup>1,2</sup> A hallmark characteristic of NF2 is the development of bilateral vestibular schwannomas<sup>3</sup> resulting in progressive hearing loss most often associated with tinnitus. Hearing loss and tinnitus are often the earliest presenting complaints, although other tumors including ependymomas, meningiomas, cutaneous schwannomas, and retinal hamartomas may also be symptomatic.<sup>4</sup> Many individuals, including some with normal hearing, report disequilibrium or tinnitus.<sup>5</sup>

Tinnitus is the perception of sound without the presence of an external sound stimulus (American Academy of Audiology; AAA<sup>6</sup>). Tinnitus occurs in approximately 9.6% of the general population,<sup>7</sup> is sufficiently severe to lead to mental health and social concerns in 1%–2%,<sup>6</sup> and is a presenting symptom in 10% or more of patients with vestibular schwannomas.<sup>8,9</sup> Kentala and Pyykkö<sup>9</sup> evaluated 122 patients with vestibular schwannomas and found that 101 (83%) reported tinnitus and 44 (34%) reported that tinnitus and hearing loss were the presenting symptoms. Tinnitus may occur in many patients with NF2, which can cause significant distress for some patients.<sup>10</sup> Tinnitus has been shown to have a significant and negative impact on quality of life (QoL), resulting in increased stress and rates of depression, decreased sleep, and problems with concentration.<sup>11</sup> To further elucidate the patient experience, a case vignette is presented in Supplemental Appendix A.

While the exact cause of tinnitus in the general population is unknown, a recent systematic review reported several risk factors associated with tinnitus including high-frequency sensorineural hearing loss, noise exposure, presbycusis, excessive stress or depression, ototoxicity, neurologic diagnoses (e.g. traumatic brain injury, multiple sclerosis, vestibular schwannomas, or infection), or somatosensory concerns.<sup>12</sup> In patients with NF2, tinnitus is likely associated with the presence of vestibular schwannomas.<sup>13</sup>

Patients with NF2 face multiple deficits and challenges. Tinnitus may be just one aspect of many that affects an individual's QoL. While tinnitus may be bothersome, there may be other hearing-related concerns beyond tinnitus that impact patients with NF2, such as progression of vestibular schwannomas, reduced hearing ability, or dizziness and/or problems with balance. As a result, tinnitus may have a lower priority during patients' clinical visits. Therefore, it is important to consider the broader context of multiple challenges that patients with NF2 face when assessing tinnitus.

Tinnitus can occur in the right ear, left ear, bilaterally, or in an individual's head. Individuals can also experience tinnitus in the ear which is contralateral to

intervention. Surgical interventions for NF2 do not necessarily improve tinnitus, as patients have reported experiencing tinnitus even after the auditory nerve has been cut.<sup>14</sup> A study of 72 patients with unilateral (sporadic) vestibular schwannomas demonstrated that patients experienced tinnitus distress that was comparable to patients with primary tinnitus.<sup>13</sup> Future research is warranted to provide normative data on the Tinnitus Functional Index in NF2 patients specifically, as the impact of tinnitus on patients with NF2 may differ from other populations on which the tinnitus measures were normed.

Currently, there are no objective measures of tinnitus. Assessment of patients' experience coping with tinnitus generally involves the administration of questionnaires such as patient-reported outcome measures (PROMs). PROMs refer to measures of a patient's health status reported by patients directly without information or interpretation by others, including healthcare providers.<sup>15</sup> PROMs for tinnitus generally ask about characteristics of patients' tinnitus such as pitch and/or intensity, distress caused by tinnitus (e.g. Erlandsson et al.<sup>11</sup> and Wilson et al.<sup>16</sup>), and tinnitus intrusiveness<sup>11</sup> or annoyance.<sup>17</sup> Data from PROMs have shown that patients with tinnitus report a buzzing, humming, or ringing in the ears that can be intermittent or persistent. PROMs can be used as co-primary endpoints for both efficacy and safety for clinical trials.

There are several challenges associated with selecting PROMs to assess tinnitus in clinical trials in patients with NF2. Patients with NF2 may use a variety of hearing devices (such as hearing aids, cochlear implants, or auditory brainstem implants) at different stages in their lives. Devices may not be used all the time or consistently across activities. Devices may change after an intervention. As is the case for patients without NF2, individuals may have diagnoses unrelated to NF2 which may also require intervention (e.g. cancer or noise-induced hearing loss). Also, some interventions that are effective for assisting with hearing function may have a benefit of reducing tinnitus (e.g. Roberts et al.<sup>18</sup>). These diagnoses may result in the occurrence of tinnitus that is unrelated to their diagnosis of NF2, or the intervention itself might cause tinnitus. Finally, the progressive nature of NF2 means "no change" in terms of tumor growth may be a positive outcome (see Thompson et al.<sup>19</sup>). Challenges in the assessment of tinnitus across activities, devices, or patient factors suggest that additional research is needed.

There are also challenges related to the use of tools that truly capture patient experiences. Because there are several domains that a given PROM could assess (such as tinnitus severity, distress, interference, and which side the tinnitus is (left or right ear)), measures should be carefully selected based on the purpose of the given clinical trial. Careful consideration should

TINNITUS FUNCTIONAL INDEX		TINNITUS FUNCTIONAL INDEX	
Today's Date _____ Your Name _____		PAGE 2	
Month / Day / Year _____ Please Print _____		Please read each question below carefully. To answer a question, select ONE of the numbers that is listed for that question, and draw a CIRCLE around it like this: (10%) or (1).	
<b>I Over the PAST WEEK...</b>		<b>A Over the PAST WEEK, how much has your tinnitus interfered with...</b>	
1. What percentage of your time awake were you consciously <b>AWARE</b> of your tinnitus? Never aware ▶ 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◀ Always aware		13. Your ability to <b>HEAR CLEARLY</b> ? Did not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interfered	
2. How <b>STRONG</b> or <b>LOUD</b> was your tinnitus? Not at all strong or loud ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Extremely strong or loud		14. Your ability to <b>UNDERSTAND PEOPLE</b> who are talking? 0 1 2 3 4 5 6 7 8 9 10	
3. What percentage of your time awake were you <b>ANNOYED</b> by your tinnitus? None of the time ▶ 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◀ All of the time		15. Your ability to <b>FOLLOW CONVERSATIONS</b> in a group or at meetings? 0 1 2 3 4 5 6 7 8 9 10	
<b>SC Over the PAST WEEK...</b>		<b>R Over the PAST WEEK, how much has your tinnitus interfered with...</b>	
4. Did you feel <b>IN CONTROL</b> in regard to your tinnitus? Very much in control ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Never in control		16. Your <b>QUIET RESTING ACTIVITIES</b> ? Did not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interfered	
5. How easy was it for you to <b>COPE</b> with your tinnitus? Very easy to cope ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Impossible to cope		17. Your ability to <b>RELAX</b> ? 0 1 2 3 4 5 6 7 8 9 10	
6. How easy was it for you to <b>IGNORE</b> your tinnitus? Very easy to ignore ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Impossible to ignore		18. Your ability to enjoy <b>PEACE AND QUIET</b> ? 0 1 2 3 4 5 6 7 8 9 10	
<b>C Over the PAST WEEK...</b>		<b>Q Over the PAST WEEK, how much has your tinnitus interfered with...</b>	
7. Your ability to <b>CONCENTRATE</b> ? Did not interfere ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Completely interfered		19. Your enjoyment of <b>SOCIAL ACTIVITIES</b> ? Did not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interfered	
8. Your ability to <b>THINK CLEARLY</b> ? Did not interfere ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Completely interfered		20. Your <b>ENJOYMENT OF LIFE</b> ? 0 1 2 3 4 5 6 7 8 9 10	
9. Your ability to <b>FOCUS ATTENTION</b> on other things besides your tinnitus? Did not interfere ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Completely interfered		21. Your <b>RELATIONSHIPS</b> with family, friends and other people? 0 1 2 3 4 5 6 7 8 9 10	
<b>SL Over the PAST WEEK...</b>		22. How often did your tinnitus cause you to have difficulty performing your <b>WORK OR OTHER TASKS</b> , such as home maintenance, school work, or caring for children or others? Never had difficulty ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Always had difficulty	
10. How often did your tinnitus make it difficult to <b>FALL ASLEEP</b> or <b>STAY ASLEEP</b> ? Never had difficulty ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Always had difficulty		<b>E Over the PAST WEEK...</b>	
11. How often did your tinnitus cause you difficulty in getting <b>AS MUCH SLEEP</b> as you needed? Never had difficulty ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Always had difficulty		23. How <b>ANXIOUS</b> or <b>WORRIED</b> has your tinnitus made you feel? Not at all anxious or worried ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Extremely anxious or worried	
12. How much of the time did your tinnitus keep you from <b>SLEEPING</b> as <b>DEEPLY</b> or as <b>PEACEFULLY</b> as you would have liked? None of the time ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ All of the time		24. How <b>BOTHERED</b> or <b>UPSET</b> have you been because of your tinnitus? Not at all bothered or upset ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Extremely bothered or upset	
Copyright Oregon Health & Science University 2008 08.15.08		Copyright Oregon Health & Science University 08.15.08	

Figure 1. Tinnitus Functional Index.

also be given for the fact that patients may have multiple, simultaneous complications (e.g. conflicting or competing issues of tumor growth or stability, hearing loss, balance changes, facial weakness, fatigue, or facial pain) along with the increasing or decreasing tinnitus. Researchers also need guidance on how to score measures in the context of multiple concerns happening simultaneously.

As tinnitus is frequently associated with hearing loss, current treatments to address tinnitus in the general population often include those that address hearing-related concerns. Intervention for hearing concerns secondary to the progression of vestibular schwannomas in NF2 includes surgery, radiotherapy, pharmacological intervention (e.g. bevacizumab<sup>10</sup>) or use of auditory devices/technology such as hearing aids, cochlear implants, or auditory brainstem implants.<sup>18</sup> Aural rehabilitation may also be provided to not only assist patients with device usage and maintenance, but also to teach communication strategies for use with familiar and unfamiliar communication partners and to optimize communication in a variety of settings.

Pharmacological clinical trials are conducted with the goal of obtaining Food and Drug Administration (FDA) approval for preventing NF2-related tumors, reducing tumor size, and relatedly, preventing loss of hearing function, and reducing pain intensity and pain interference associated with trigeminal neuralgia or headache. Studies evaluating treatments for the

remediation of hearing loss in NF2 have largely focused on evaluating the outcomes of pharmacological interventions used to treat vestibular schwannomas. Pharmacologic interventions utilized to target tinnitus specifically have been shown to have limited success.<sup>20</sup> Tinnitus reduction has not been a primary endpoint of any NF2-related study to this point but may be an important secondary measure.

Bevacizumab, a vascular endothelial growth factor inhibitor, has demonstrated improved hearing for 35%–40% of NF2 patients.<sup>10,21</sup> At least one study has reported improvements in hearing and tinnitus using the Tinnitus Reaction Questionnaire.<sup>10,16</sup> Patients with improved hearing with bevacizumab may also experience decreases in tinnitus.<sup>22</sup> Additional pharmacological interventions may also reduce tumor size or positively impact hearing (e.g. Laraba et al.<sup>23</sup>).

Cognitive behavioral therapy and hearing aids, when indicated, have been the most successful in reducing tinnitus. Masking or sound therapy is also often employed to reduce the annoyance, if unsuccessful at reducing tinnitus (e.g. Bauer<sup>20</sup> and Hobson et al.<sup>24</sup>). Tinnitus retraining therapy in conjunction with hearing aids has shown some utility for patients with non-NF2 related tinnitus.<sup>25</sup> There is a paucity of research on PROMs used to assess these pre- to post-changes in tinnitus intervention, with no consensus on the most optimal measure to be used. Therefore, a PRO to assess tinnitus in patients with NF2 is indicated.

As observed in the general oncological population, one side effect of chemotherapy and radiotherapy is the occurrence of tinnitus following ototoxicity.<sup>26</sup> Given this unintended possible side effect, it is important for researchers to be able to identify tinnitus occurring as a result of the NF2 disease process as opposed to tinnitus caused by pharmacological interventions themselves. Regardless of the etiology of tinnitus in individuals with NF2, it is essential that there be consensus on assessments that can be utilized to assess the nature, severity, and impact of tinnitus on QoL for patients. Currently, the impact of tinnitus on QoL of individuals with NF2 is unknown as there is no consensus concerning which assessment measures are appropriate for the assessment of tinnitus in this patient population. Consensus regarding the selection of suitable outcome measures could advance research into tinnitus interventions for NF2 patients. Following conversations of clinicians, researchers, and patient representatives, this study was motivated by a need for additional guidance for the research community on the selection of PROMs for tinnitus interventions. The purpose of this project is to present current Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration recommendations for PROMs used to evaluate the domain of tinnitus for NF2 clinical trials.

## Methods

The REiNS International Collaboration is composed of more than 140 researchers, clinicians, and patient representatives who collaborate with the goal of achieving consensus on outcomes for clinical trials. For this work, REiNS clinician-researchers representing the disciplines of otology, otorhinolaryngology—head and neck surgery, audiology, speech-language pathology, as well as patient representatives, formed the PRO Communication subgroup. Following discussion by clinicians, researchers, and REiNS patient representatives, the PRO Communication subgroup sought to focus on identifying preferred PROMs used to assess tinnitus severity and associated QoL for use in clinical trials for NF2-related schwannomatosis.

Members of the PRO Communication Subgroup met monthly via videoconferencing from March 2020 to February 2022 to identify and prioritize PROMs for review. Methods used to identify and select PROM measures for tinnitus have been described previously by Wolters et al.<sup>27</sup> The bibliographic databases PubMed, Embase, and Google Scholar were searched for PROMs in April of 2020 using the keywords *tinnitus questionnaire*, *patient-reported outcome*, *neurofibromatosis type 2*, and *tinnitus outcome measure*. No time frame for publication was limiting. Additional terms identified by these searches were added to identify potential

inventories. Articles were also manually reviewed for other measures, resulting in two additional measures that were explored further and ultimately determined to be measures to be excluded from the review.

After compiling a list of measures, clinicians/researchers within REiNS with expertise in tinnitus and hearing health reviewed and provided input on the list of measures to ensure that no measures were missing from the list. Measures were subsequently evaluated for inclusion criteria, where included measures were required to be (1) a PROM, (2) published and validated in English, and (3) used to assess tinnitus.

A total of 19 PROMs for tinnitus were identified. Descriptions of identified PROMs were aggregated and provided to group members for initial review. Of the 19 identified PROMs, 2 were excluded because the measures were not validated as outcomes and/or had different items among forms translated into different languages.<sup>28</sup> One measure was excluded (i.e. the Client Oriented Scale of Improvement-Tinnitus)<sup>29</sup> because while it would be very useful for clinical settings as outcomes are selected by clinicians and patients collaboratively based on the patient's individual needs, this measure would not be feasible in the context of a clinical trial because theoretically there could be a unique outcome measure for each study participant, limiting the researcher's ability to draw conclusions from the entire sample of study participants on a single specific domain of interest.

The remaining 16 PROMs were submitted to a formal group review process using the Patient-Reported Outcomes Rating Acceptance Tool for Endpoints (PRO-RATE) form described and published previously.<sup>27</sup> The PRO-RATE form allowed for the numerical scoring and consequent comparison of the PROMs under evaluation. To summarize, PRO-RATE form scoring criteria includes (1) patient characteristics (age range assessed, availability of child self-report and/or parent proxy forms, published normative data from health and population of interest), (2) use in published studies (clinical trials and validation studies), (3) domains assessed and item content (thorough domain assessment, relevant to patients with NF, systematic item development), (4) scores available (response format, scoring, and standardization of scores), (5) psychometric properties (reliability, validity, sensitivity to change, factor analysis), and (6) feasibility for implementation (cost, length in terms of time required for completion, ease of administration, and language availability).

A score for each PRO-RATE form domain area was assigned for each PROM by individual reviews. Domain and total scores were then aggregated and averaged across all reviewers for inter-scale comparisons. Final meetings included re-reviews with side-by-side comparisons with group discussion on the strengths and limitations of top-rated measures.

**Table 1.** REiNS patient-reported outcomes rating and acceptance tool for endpoints criteria [PRO-RATE<sup>27</sup>].

Rating criteria	Rating (0–3)*
Patient characteristics:	
Age range (e.g., child, adolescent, and adult)	
Normative groups (e.g., general, NF, oncology, other, and # subjects)	
Used in published studies:	
Number and types of studies (e.g., descriptive and clinical trials)	
Domains assessed/Item content:	
Number/description (e.g., physical, social, emotional, and cognitive)	
Scores available:	
Item response format (e.g., Likert-type scale and visual analog scale)	
Types of scores (e.g., raw, standardized, domain, and total)	
Psychometric data:	
Reliability (e.g., internal consistency and test/retest)	
Validity (e.g., construct and discriminative)	
Factor analysis	
Feasibility:	
Cost	
Length (number of items)	
Ease of administration	
Recall period assessed (e.g., 1 week, 24 hours)	
Availability in different languages/international use	

\*0 = No/poor data/information, 1 = limited data but information suggests potential, 2 = good preliminary data and relevant information but needs more work, 3 = solid data and published information supporting its use in neurofibromatosis trials. Half ratings (.5, 1.5, 2.5) can be used if needed.

Throughout the process, clinician-researchers provided domain-specific knowledge, and patient representatives contextualized the relative importance and feasibility of completing tinnitus-specific PROMs during clinical trial participation.

## Results

Sixteen PROMs met inclusion criteria and were included in this study for extensive review according to our PRO-RATE procedures (Table 1). No pediatric measures were available at the time of review. The top three most highly rated measures included the Tinnitus Functional Index (Figure 1),<sup>30</sup> the Tinnitus Handicap Inventory,<sup>31</sup> and the Tinnitus Reaction Questionnaire.<sup>16</sup> These measures were later re-evaluated with side-by-side comparisons. Measures evaluated along with a summary of strengths and limitations are presented in Table 2.

After extensive review by the REiNS PRO Communication Subgroup, the Tinnitus Functional Index<sup>30</sup> is recommended for the assessment of tinnitus-related concerns or distress, including quantification of severity and QoL implications, specifically for use in clinical trials related to NF2. Table 3 provides a summary of the review for the Tinnitus Functional Index.

The Tinnitus Functional Index is a 25-item questionnaire developed for scaling the severity and negative impact of tinnitus. Items are rated on an 11-point Likert-type scale (ranging from 0 = did not interfere to 10 = completely interfered). Scores are summed and divided by the number of questions for which the respondent provided valid answers, yielding a score out

of a maximum of 250 points should all questions be answered with a maximum score of 10. The domains or subscales include *intrusiveness/persistence of tinnitus*, *overall quality of life*, and *tinnitus-related emotional distress, interference of cognition and relaxation, sleep disturbance, auditory difficulties*, and *reduced sense of control due to tinnitus*. The measure includes three to four items per domain and items have a recall period of 1 week. Clinical studies report good to excellent reliability and validity. For its development, expert judges surveyed the content of nine tinnitus questionnaires which led to two prototypes. These prototypes were (longitudinally) tested in a multicenter setting including >300 patients between 17 and 97 years of age. Consequently, the best-functioning items were included in the Tinnitus Functional Index.

Important advantages of the Tinnitus Functional Index included that the measure was validated to assess both intake assessments, as well as treatment-related changes in tinnitus (responsiveness) which enables it to be used in a wide range of studies, including trials. The Tinnitus Functional Index has clear instructions for both participants and researchers (i.e. how to deal with ambiguous answers, or the minimum number of items participants must complete to obtain total scores). A minimally clinically important difference (MCID) was established at a reduction of 13 points. In addition, the measure is free, easy to administer, and available in at least 14 languages. A limitation of this measure is that although it has been used in at least one study that included those with unilateral vestibular schwannomas, there is a current absence of data where the Tinnitus

**Table 2.** Overview of tinnitus questionnaires evaluated.

Name of measure (reference)	Domain area	Validated age range, in years	Strengths for use in NF2 clinical trials	Limitations for use in NF2 clinical trials
Tinnitus Handicap Inventory <sup>31</sup>	Impact of tinnitus on everyday life	10–12 years; 23–77 years	Used in VS and NF2 Used in clinical trials Good psychometric data Brief Available in multiple languages	No recall period Some items are lengthy
Tinnitus Reaction Questionnaire <sup>16</sup>	Psychological distress due to tinnitus	24–80 years	Recall period – 1 week 5-point Likert-type scale Available in multiple languages	Has not been used/validated in NF No MCID Good test-retest reliability Not validated as an outcome measure
Tinnitus Severity Questionnaire <sup>32</sup>	General tinnitus severity, QoL, psychological aspects	15–86 years	Quick, easy to complete Single factor scale	Has not been used/validated in NF No recall period Limited psychometric data Limited number of languages
Tinnitus Severity Index <sup>30</sup>	Negative impact of tinnitus on work and social activities	Unknown	5-point Likert-type scale Fast and easy to complete	Has not been used/validated in NF No recall period No age range specified Not validated as an outcome measure Limited psychometric data
Tinnitus Cognitions Questionnaire <sup>33</sup>	Positive and negative thoughts toward tinnitus	20–83 years	5-point Likert-type scale Positively and negatively worded items (positive items are reverse scored)	Only available in English Limited use in published studies Has not been used/validated in NF Many items Limited psychometric data
Subjective Tinnitus Severity Scale <sup>34</sup>	Classify tinnitus severity	Mean age 62 years	Free Fast and easy to administer Available in multiple languages (at least three)	Only available in English 2-point Likert-type scale No recall period Has not been used/validated in VS or NF2 No MCID; severe tinnitus seen as > 12 (out of 16) Limited psychometric data
Tinnitus Acceptance Questionnaire <sup>35</sup>	Activity engagement and tinnitus suppression	Adults	7-point Likert-type scale Developed from previously published questionnaires Good internal consistency Fast and easy to complete Available in multiple languages	Has not been used/validated in NF No recall period Limited psychometric data
Tinnitus Primary Functions Questionnaire <sup>36</sup>	To determine treatment efficacy of emotions, sleep, hearing and concentration affected by tinnitus	28–76 years	12-items Three factors Free Fast and easy to complete Available in multiple languages	No recall period Has not been used/validated in NF Limited psychometric data No data for use with children
Tinnitus Handicap/Support Scale <sup>11</sup>	Role of social support for an individual who experiences tinnitus	12–89 years	5-point Likert-type scale Free Easy to administer and score	Has not been used/validated in NF Limited psychometric data Limited published data Lengthy (26 items) No standard scores No recall period Only available in English

(continued)

Table 2. (continued)

Name of measure (reference)	Domain area	Validated age range, in years	Strengths for use in NF2 clinical trials	Limitations for use in NF2 clinical trials
Tinnitus Coping Style Questionnaire <sup>37</sup>	Coping strategies used by individuals with tinnitus	20–85 years	7-point Likert-type scale Free Available in multiple languages (at least three)	Lengthy (40 items) No recall period Has not been used/validated in VS or NF2 Items do not assess tinnitus impact, but is focused on coping style No MCID Limited psychometric data
Tinnitus Beeintraechtigungs Fragebogen (TBF-12/THI-12) <sup>38</sup>	To quantify tinnitus handicap in a typical clinical setting	Adults, mean age 52	12-items Free, easy to administer Quick and easy to complete Available in multiple languages (at least six) Excellent psychometric data Used in published studies and clinical trials	3-point Likert-type scale No recall period Has not been used/validated in VS or NF2 Items are worded negatively No MCID
Tinnitus Functional Index <sup>30</sup>	To assess tinnitus severity and tinnitus distress	17–97 years	11-point Likert-type scale Recall period assessed Free, easy to complete Has been used in VS research Available in multiple languages (at least fourteen) Available MCID (13 points) SR form available Developed as an outcome measure Extensive developmental phase with multiple prototypes Excellent psychometric data Eight domains assessed (intrusive, sense of control, cognitive, sleep, auditory, relaxation, quality of life, emotional)	Lengthy (25 items) Has not been used/validated in NF2
Tinnitus Questionnaire <sup>39</sup>	To assess tinnitus distress	20–93 years	Free Easy to score The mini-TQ-12 has been used in VS <sup>40</sup> Available in multiple languages (at least sixteen) Good psychometric data Subscales to assess emotional distress, auditory perceptual difficulties, intrusiveness, sleep disturbance, and somatic complaints	Lengthy (52 items) 3-point Likert-type scale No recall period Has not been used/validated in NF2 Only MCIDs available in German (12 points) and Mandarin (7.5) <sup>41</sup>

(continued)

**Table 2.** (continued)

Name of measure (reference)	Domain area	Validated age range, in years	Strengths for use in NF2 clinical trials	Limitations for use in NF2 clinical trials
Tinnitus and Hearing Survey <sup>42</sup>	To differentiate hearing problems from tinnitus problems	24–83 years	Nine items 5-point Likert-type scale Recall period assessed Free, easy to administer Available in multiple languages (at least four) Good psychometric data	Has not been used/validated in VS or NF2 Aim of measure not necessarily relevant to NF2 clinical trials No MCID
Tinnitus Coping Strategy Questionnaire <sup>43</sup>	To assess the use of cognitive and behavioral coping strategies in response to tinnitus	31–83 years	5-point Likert-type scale Two separate rating scales Free, easy to administer Excellent psychometric data	Lengthy (33 items) No recall period Has not been used/validated in VS or NF2 Only available in English Aim of measure not necessarily relevant to NF2 clinical trials (items do not assess tinnitus impact; focused on coping style) Descriptive data included in unpublished dissertation No MCID
Tinnitus Psychological Impact Questionnaire <sup>44</sup>	To broadly assess impact of tinnitus on everyday life	35–79 years	Variety of domain areas assessed	Has not been used/validated in VS or NF No normative data Lengthy (42 items)

VS = vestibular schwannoma, NF/SWN = neurofibromatosis and schwannomatosis, QoL = quality of life, SR = self-report, MCID = minimally clinically important difference.

**Table 3.** REiNS PRO RATE criteria for the Tinnitus Functional Index.

Criteria (ratings)	Tinnitus Functional Index
	Overall group rating = 2.73
Patient characteristics (2.5)	SR forms 17-97 years (sample 1) SR forms 22-90 years (sample 2) No SR forms for <17 Measure developed from a prototype Normative data included patients with severe tinnitus
Domains/item content (3)	25 items Items selected to avoid being overly negative and were deemed important by experts from the tinnitus research consortium Minimum of 3–4 items per domain; multiple domains
Psychometric data (3)	Test-retest reliability = 0.92 Internal consistency reliability = 0.99 Item-total correlations 0.56–0.91; 37 correlations 0.70 High correlation with the THI = 0.91; correlated with the VAS = 0.73 Discriminant validity 0.56 with the Beck DI MCID = 13-point reduction
Feasibility (2.75)	Free 25 items 1-week recall period Available in multiple languages

Functional Index was used in studies involving patients with NF2. At this time, there is no known published validated pediatric measure used to assess tinnitus severity or tinnitus distress.

## Discussion

The objective of this study was to use previously described procedures of the REiNS International Collaboration PRO Working Group to evaluate published PROMs for the assessment of tinnitus for patients with NF2. The primary goal was to obtain a measure of how patients perceive their tinnitus in terms of self-reported tinnitus severity and distress. In this study, published measures of tinnitus were reviewed and evaluated according to their patient characteristics, use in published studies, domains assessed/item content, available scores, psychometric data, and feasibility following the previously published REiNS PRO-RATE criteria.<sup>27</sup>

The Tinnitus Functional Index is currently recommended by the REiNS PRO Communication Subgroup as a PROM for assessing tinnitus severity and distress in patients with NF2. Strengths of the Tinnitus Functional Index include that it was developed as a self-report form and has excellent normative data, including from patients with a vestibular schwannoma. In addition, it has excellent psychometric data, excellent



feasibility, good item content, the availability of subscale or total scores, and evidence of prior use within the context of clinical trials. It is worth noting that a pediatric instrument is still needed, as the Tinnitus Functional Index is not currently validated for use with individuals under 17 years.

Throughout the review process, several limitations were identified in the non-selected tinnitus measures. Most commonly, there was a lack of data regarding the use of these measures in studies that included patients with NF2 or vestibular schwannomas. Only one measure was used in a study with NF2 patients (Tinnitus Reaction Questionnaire; Huang et al.<sup>45</sup>). Many of the measures had limitations in item construction in that they were not ideal for patients with NF2, had limited psychometric data available, or had not been used in the context of a clinical trial. Across measures, there was a great deal of variability in the area assessed (e.g. cognitive or behavioral coping strategies, or impact of tinnitus on everyday life). Finally, some measures were only available in English, which limited their ability to be used with a variety of patients with NF2 who may be involved in neurofibromatosis/schwannomatosis clinical trials in the United States and globally.

When evaluating measures used to assess tinnitus our group found that many measures have only a single published paper on them. Of the published measures with strong psychometric data, there were limitations including a lack of data for patients with NF2 or concerns with item content. Another challenge was that there were multiple instruments without manuals, or with limited instructions, making it challenging to ensure consistent administration by individuals carrying out clinical trials. In addition, because most tinnitus is experienced by individuals within an older age range, normative data often disproportionately include older adults. In the population of individuals with NF2, however, there is a need for outcome measures that can also be given to school-aged children, as genetic testing has resulted in the possibility of earlier diagnosis and subsequent enrollment of children in clinical trials. It is important to note that these children may exhibit a more severe presentation of the condition. In addition, as children are learning to read, there is a need for self-report measures that are easy to understand. Because individuals may enroll in a study for an extended period (such as in the case of natural history investigations), measures need to include items that are appropriate for use with many different ages of participants for repeated administrations.

As was demonstrated in the case vignette in Supplemental Appendix A, patients with NF2 may have significant concerns outside of tinnitus that could be addressed with healthcare providers. Therefore, it is important that medical team members have an effective and efficient way of addressing tinnitus-related concerns to provide optimal patient care. It is

recommended that researchers who conduct clinical trials in NF2 include direct assessments of hearing and the PROM Self-Assessment of Communication to evaluate hearing function and hearing-related QoL (see Thompson et al.<sup>19</sup>). Ideally, natural history studies should also include audiometric assessment, patient-reported evaluations of hearing functioning, and hearing-related QoL. Future research in this area could provide insight on our understanding into patterns of tinnitus development in patients with NF2 over time. Clinical trials should include diverse groups of patients, including younger adults with NF2 with varying levels of tinnitus severity. It is very important to note that these recommendations are based on current available literature and may change in the future. Finally, we think that even if objective measures of tinnitus are developed, they should complement, but not replace, PROMs evaluating tinnitus severity or distress.

## Conclusion

The REiNS International Collaboration recommends the Tinnitus Functional Index as a PROM for assessing tinnitus distress and severity in clinical trials involving individuals with NF2-related schwannomatosis.

## Acknowledgement

This manuscript is submitted on behalf of the REiNS International Collaboration, the full membership of which is listed in Supplemental Appendix B.


## Declaration of conflicting interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research is supported by the Intramural Research Program of the NIH, National Cancer Institute. The authors acknowledge the support of the Children's Tumor Foundation for publication of this manuscript. This study is not industry sponsored.

## ORCID iDs

Heather L Thompson  <https://orcid.org/0000-0002-4205-239X>

Kimberley S Koetsier  <https://orcid.org/0000-0002-2918-4750>

## Supplemental material

Supplemental material for this article is available online.

## References

- Rouleau GA, Merel P, Lutchman M, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. *Nature* 1993; 363: 515–521.
- Trofatter JA, MacCollin MM, Rutter JL, et al. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. *Cell* 1993; 72: 791–800.
- Plotkin SR, Messiaen L, Legius E, et al. Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: an international consensus recommendation. *Genet Med* 2022; 24(9): 1967–1977.
- Asthagiri AR, Parry DM, Butman JA, et al. Neurofibromatosis type 2. *Lancet* 2009; 373: 1974–1986.
- Parry DM, Eldridge R, Kaiser-Kupfer MI, et al. Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. *Am J Med Genet* 1994; 52: 450–461.
- American Academy of Audiology, <https://www.audiology.org/consumers-and-patients/hearing-and-balance/tinnitus/> (accessed 9 January 2023).
- Bhatt JM, Lin HW and Bhattacharyya N. Prevalence, severity, exposures, and treatment patterns of tinnitus in the United States. *JAMA Otolaryngol Head Neck Surg* 2016; 142: 959–965.
- Evans DGR, Huson SM, Donnai D, et al. A clinical study of type 2 neurofibromatosis. *Q J Med* 1992; 84: 603–618.
- Kentala E and Pyykkö I. Clinical picture of vestibular schwannoma. *Auris Nasus Larynx* 2001; 28(1): 15–22.
- Plotkin SR, Duda DG, Muzikansky A, et al. Multicenter, prospective, phase II and biomarker study of high-dose bevacizumab as induction therapy in patients with neurofibromatosis Type 2 and progressive vestibular schwannoma. *J Clin Oncol* 2019; 37: 3446–3454.
- Erlandsson SI, Hallberg LR and Axelsson A. Psychological and audiological correlates of perceived tinnitus severity. *Audiology* 1992; 31(3): 168–179.
- Makar SK. Etiology and pathophysiology of tinnitus—a systematic review. *Int Tinnit J* 2021; 25: 76–86.
- Kojima T, Oishi N, Nishiyama T, et al. Severity of tinnitus distress negatively impacts quality of life in patients with vestibular schwannoma and mimics primary tinnitus. *Front Neurol* 2019; 10: 389.
- Greene J and Al-Dhahir M. *Acoustic neuroma*. Treasure Island, FL: StatPearls Publishing, 2023.
- U.S. Department of Health and Human Services FaDA. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance, 2009, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1629006/#:~:text=Generally%2C%20findings%20measured%20by%20PRO,the%20specific%20concepts%20at%20issue.>
- Wilson PH, Henry J, Bowen M, et al. Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus. *J Speech Hear Res* 1991; 34(1): 197–201.
- Simons IA, Goderie T, Lissenberg-Witte BI, et al. The effects of tinnitus and tinnitus annoyance on need for recovery after work: results of the Netherland longitudinal study on hearing. *Ear Hear* 2023; 44(4): 768–775.
- Roberts DS, Otto S, Chen B, et al. Tinnitus suppression after auditory brainstem implantation in patients with neurofibromatosis type-2. *Otol Neurotol* 2017; 38(1): 118–122.
- Thompson HL, Blanton A, Franklin B, et al. Patient report of hearing in neurofibromatosis type 2: recommendations for clinical trials. *Neurology* 2021; 97: S64–S72.
- Bauer CA. Current validated medical treatments pharmacologic interventions. *Otolaryngol Clin North Am* 2020; 53(4): 617–626.
- Blakeley JO, Ye X, Duda DG, et al. Efficacy and biomarker study of bevacizumab for hearing loss resulting from neurofibromatosis type 2-associated vestibular schwannomas. *J Clin Oncol* 2016; 34: 1669–1675.
- Plotkin SR, Stemmer-Rachamimov AO, Barker FG, et al. Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. *N Engl J Med* 2009; 361: 358–367.
- Laraba L, Hillson L, de Guibert JG, et al. Inhibition of YAP/TAZ-driven TEAD activity prevents growth of NF2-null schwannoma and meningioma. *Brain* 2023; 146(4): 1697–1713.
- Hobson J, Chisholm E and El Refaie A. Sound therapy (masking) in the management of tinnitus in adults. *Cochrane Database Syst Rev* 2010; 11: CD006371.
- Bauer CA, Berry JL and Brozoski TJ. The effect of tinnitus retraining therapy on chronic tinnitus: a controlled trial. *Laryngoscope Investig Otolaryngol* 2017; 2: 166–177.
- Lee TF, Yeh SA, Chao PJ, et al. Normal tissue complication probability modeling for cochlea constraints to avoid causing tinnitus after head-and-neck intensity-modulated radiation therapy. *Radiat Oncol* 2015; 10: 194.
- Wolters PL, Martin S, Merker VL, et al. Patient-reported outcomes in neurofibromatosis and schwannomatosis clinical trials. *Neurology* 2013; 81: S6–S14.
- Vanneste S, To WT and De Ridder D. The psychometric properties of the tinnitus handicap questionnaire in a Dutch-speaking population. *Clin Otolaryngol* 2011; 36(1): 9–16.
- Searchfield GD. A client oriented scale of improvement in tinnitus for therapy goal planning and assessing outcomes. *J Am Acad Audiol* 2019; 30(4): 327–337.
- Meikle MB, Henry JA, Griest SE, et al. The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear Hear* 2012; 33(2): 153–176.
- Newman CW, Jacobson GP and Spitzer JB. Development of the tinnitus handicap inventory. *Arch Otolaryngol Head Neck Surg* 1996; 122: 143–148.
- Coles R, Lutman ME, Axelsson A, et al. Tinnitus severity gradings: cross-sectional studies. In: *Proceedings of the 4th international tinnitus seminar*, Bordeaux, 1 December 1992.
- Henry JL and Wilson PH. The psychological management of tinnitus: comparison of a combined cognitive educational program, education alone and a waiting-list control. *Int Tinnit J* 1996; 2: 9–20.
- Halford JBS and Anderson SD. Tinnitus severity measured by a subjective scale, audiometry and clinical judgement. *J Laryngol Otol* 1991; 105(2): 89–93.

35. Westin V, Hayes SC and Andersson G. Is it the sound or your relationship to it? The role of acceptance in predicting tinnitus impact. *Behav Res Ther* 2008; 46: 1259–1265.
36. Tyler R, Ji H, Perreau A, et al. Development and validation of the tinnitus primary function questionnaire. *Am J Audiol* 2014; 23(3): 260–272.
37. Budd RJ and Pugh R. Tinnitus coping style and its relationship to tinnitus severity and emotional distress. *J Psychosom Res* 1996; 41(4): 327–335.
38. Greimel KV, Leibetseder M, Unterrainer J, et al. Ist Tinnitus messbar? Methoden zur Erfassung tinnituspezifischer Beeinträchtigungen und Präsentation des Tinnitus-Beeinträchtigungs-Fragebogens (TBF-12). *HNO* 1999; 47: 196–201.
39. Hiller W and Goebel G. A psychometric study of complaints in chronic tinnitus. *J Psychosom Res* 1992; 36(4): 337–348.
40. Klersy PC, Arlt F, Hofer M, et al. Quality of life in patients with unilateral vestibular schwannoma on wait and see—strategy. *Neurol Res* 2018; 40(1): 34–40.
41. Hall DA, Mehta RL and Argstatter H. Interpreting the Tinnitus Questionnaire (German version): what individual differences are clinically important? *Int J Audiol* 2018; 57(7): 553–557.
42. Henry JA, Griest S, Zaugg TL, et al. Tinnitus and hearing survey: a screening tool to differentiate bothersome tinnitus from hearing difficulties. *Am J Audiol* 2015; 24(1): 66–77.
43. Henry J. *Psychological management of tinnitus: an evaluation of cognitive interventions*. Sydney, NSW, Australia: University of Sydney, 1992.
44. Philippot P, Nef F, Clauw L, et al. A randomized controlled trial of mindfulness-based cognitive therapy for treating tinnitus. *Clin Psychol Psychother* 2012; 19(5): 411–419.
45. Huang V, Bergner AL, Halpin C, et al. Improvement in patient-reported hearing after treatment with bevacizumab in people with neurofibromatosis type 2. *Otol Neurotol* 2018; 39(5): 632–638.