

Interpreting Treatment-Related Changes Using the Tinnitus Questionnaire in Argstatter H, Grapp M, Plinkert PK, Bolay HV. Heidelberg Neuro-Music Therapy for Chronic-tonal Tinnitus - Treatment Outline and Psychometric Evaluation. *Int Tinnitus J* 2012;17(1):31-41

There is little evidence-based guidance to facilitate design decisions for definitive trials that evaluate treatment efficacy for adults with tinnitus. Our recent systematic review of intervention studies for tinnitus determined the current status of trial designs by identifying and evaluating the reporting of outcome domains and instruments for publications between 1st July 2006 and 12th March 2015¹. Eight studies published in *International Tinnitus Journal* contributed to the systematic review, from a total of 228. Two were designated as randomised controlled trials^{2,3}, four were controlled but not fully randomised^{4,7}, and two had a non-randomised before-and-after design^{8,9}. Patient groups and interventions were diverse, as were the tinnitus-related outcome measurements, precluding direct comparison across findings. For example, main patient-reported outcome measures across the eight studies were Tinnitus Handicap Inventory, Tinnitus Questionnaire (TQ, English and German versions), the Klockhoff assessment, Tinnitus Handicap Questionnaire and visual analogue scales of tinnitus loudness and annoyance. All studies reported the treatment-related change on these measures according to whether or not they reached statistical significance, but only Argstatter et al.⁴ sought to additionally interpret whether or not the observed treatment related improvements were clinically significant. They reported that neuro-music therapy is statistically significant and clinically effective, with 85% of patients having improved at the end of about 8 hours of neuro-music therapy. Reporting of clinical significance is welcomed because findings can be statistically significant, without being clinically significant. Clinical significance usually means that a treatment-related change corresponds to a noticeable, appreciable difference that is of value to the patient and healthcare professional, and cannot be attributed to chance. Clinical significance is thus important because it tells us whether a trial finding is meaningful to patients, and also helps healthcare professionals to interpret the research data in order to inform their evidence-based practice.

My co-authors and I learned a lot of valuable lessons about trial design during the process of systematic review process. Some of these reveal a few uncomfortable truths about how the concept of clinical significance has been handled by tinnitus investigators. In this letter, I explain what these uncomfortable truths are and I also suggest a further incremental analysis that could be implemented on the data collected by Argstatter et al.⁴,

so that greater knowledge about clinical significance can assist the tinnitus community in designing and reporting good quality trials. Argstatter et al. used the TQ, and this is in common use in clinical trials¹, especially in Germany where a German version is available¹⁰. Across the 228 trials in our systematic review¹, 17 trials identified treatment responders using criteria defined by a pre-post change score on the TQ and/or mini-TQ (an abbreviated version of the German TQ¹¹).

The first uncomfortable truth is that investigators don't agree on what change score a patient needs to show in order for their tinnitus condition to be considered 'improved' on the TQ and/or mini-TQ. All criteria are reported in (Table 1). In summary, investigators defined improvement as an absolute reduction of a predetermined number of points, a percentage reduction or a change that crossed a category boundary.

The second uncomfortable truth is that investigators typically don't involve patient viewpoints when deciding what the clinically important difference score should be. For example, Argstatter et al.⁴ chose their criterion based on the statistical formula ($1.96 \times \sqrt{2} \times \text{standard error}$) using data from the mini-TQ. While this calculation accounts for the measurement properties of the questionnaire, it does not tell us how the change score relates to the patient experience of tinnitus.

There isn't any single method for determining what the minimal clinically important difference should be. But one simple approach is an anchor-based method. This assesses what change on the TQ corresponds with a minimal important change defined on the anchor (an external criterion is used to operationalise a relevant or important difference). Typically the anchor is a single question that asks patients to rate the change in the severity of their condition on a point scale. The degree of change between the response categories 'minimally improved' and 'no change' is a good indicator of the smallest change in TQ scores that is important from the patients' perspective. Serendipitously, Argstatter et al.⁴ did ask patients about their global impression on discharge from the neuro-music therapy groups. The question was "Was your tinnitus percept changed by the music therapy?", with response options being "worsened", "unaffected" and "improved". Hence, a first approximation of the anchor-based method to determine the clinically important difference on the TQ could be

Table 1. Summary of numerical criteria for what constitutes a clinically meaningful change on versions of the TQ, using investigator-reported data extracted from 228 trials¹.

Questionnaire	Criterion of improvement	Investigator-reported data	Reference
Tinnitus Questionnaire (German version)	reduction > 5 points	Quote: "treatment responders (TQ reduction > 5)"	Langguth B. NCT01907022 Combined rTMS and relaxation in chronic tinnitus. 2013.
Tinnitus Questionnaire (German version)	reduction > 5 points	Quote: "treatment responders (TQ reduction > 5)"	Langguth B. NCT01663311 Repetitive magnetic stimulation with double cone coil in chronic tinnitus (Ti-CDC). 2012.
Tinnitus Questionnaire (English version, Translation status unknown)	reduction > 5 points	Quote: "'therapeutic success' (TQ reduction > 5)"	Chung HK, Tsai CH, Lin YC, Chen JM, Tsou YA, Wang CY, et al. Effectiveness of theta-burst repetitive transcranial magnetic stimulation for treating chronic tinnitus. <i>Audiol Neurootol</i> 2012;17(2):112-20.
Tinnitus Questionnaire (German version)	Reduction ≥ 5 points	Quote: "benefit from treatment, which was reflected by a reduction of the TQ score of five points or more"	Kleinjung T, Steffens T, Sand P, Murthum T, Hajak G, Strutz J, et al. Which tinnitus patients benefit from transcranial magnetic stimulation? <i>Otolaryngol Head Neck Surg</i> 2007;137(4):589-95.
Tinnitus Questionnaire (German version)	Reduction ≥ 5 points	Quote: "treatment response which was defined as amelioration of at least 5 points in the TQ"	Kreuzer PM, Landgrebe M, Schecklmann M, Poepl TB, Vielsmeier V, Hajak G, et al. Can Temporal Repetitive Transcranial Magnetic Stimulation be Enhanced by Targeting Affective Components of Tinnitus with Frontal rTMS? A Randomized Controlled Pilot Trial. <i>Front Syst Neurosci</i> . 2011;5:88.
Tinnitus Questionnaire (German version)	Reduction ≥ 5 points	Quote: "treatment response, which was defined as amelioration of at least 5 points in the TQ"	Kreuzer PM, Goetz M, Holl M, Schecklmann M, Landgrebe M, Staudinger S, et al. Mindfulness-and body-psychotherapy-based group treatment of chronic tinnitus:a randomized controlled pilot study. <i>BMC Complement Altern Med</i> . 2012;12:235.
Tinnitus Questionnaire (German version)	Reduction ≥ 5 points	Quote: "a clinical relevant change of tinnitus severity (i.e. 5 points on the [TQ] questionnaire of Goebel and Hiller"	Landgrebe M, Binder H, Koller M, Eberl Y, Kleinjung T, Eichhammer P, et al. Design of a placebo-controlled, randomized study of the efficacy of repetitive transcranial magnetic stimulation for the treatment of chronic tinnitus. <i>BMC Psychiatry</i> 2008;8:23.
Tinnitus Questionnaire (German version)	Reduction ≥ 5 points	Quote: "treatment responders (TQ reduction ≥ 5)"	Langguth B. NCT01663324 rTMS for the treatment of chronic tinnitus: optimisation by stimulation of the cortical tinnitus network (multisite rTMS). 2012.
Tinnitus Questionnaire (German version)	Reduction ≥ 5 points	Quote: "treatment responders, defined as a minimum difference of five points"	Langguth B, Landgrebe M, Frank E, Schecklmann M, Sand PG, Vielsmeier V, et al. Efficacy of different protocols of transcranial magnetic stimulation for the treatment of tinnitus: Pooled analysis of two randomized controlled studies. <i>World J Biol Psychiatry</i> 2014;15(4):276-85.
Tinnitus Questionnaire (German version)	Reduction ≥ 5 points	Quote:"treatment responders. Total score reduction ≥ 5"	Langguth B. NCT01965028 Daily bi-temporal transcranial random noise stimulation in tinnitus (tRNS-tin). 2013.
Tinnitus Questionnaire (German version)	Reduction ≥ 5 points	Quote: "treatment responders as defined by a reduction in the Tinnitus Questionnaire score of ≥ 5 points"	Lehner A, Schecklmann M, Kreuzer PM, Poepl TB, Rupprecht R, Langguth B. Comparing single-site with multisite rTMS for the treatment of chronic tinnitus-clinical effects and neuroscientific insights: study protocol for a randomized controlled trial. <i>Trials</i> 2013;14:269.
Tinnitus Questionnaire (German version)	reduction > 6.1 points	Quote: "a critical difference of 6.1 points"	Argstatter H, Grapp M, Hutter E, Plinkert PK, Bolay HV. The effectiveness of neuro-music therapy according to the Heidelberg model compared to a single session of educational counseling as treatment for tinnitus: a controlled trial. <i>J Psychosom Res</i> 2015;78(3):285-92.

Tinnitus Questionnaire (German version)	reduction > 10 points	Quote: "clinically relevant tinnitus Improvement... patients who demonstrated reduction of > 10 points"	Kleinjung T, Eichhammer P, Landgrebe M, et al. Combined temporal and prefrontal transcranial magnetic stimulation for tinnitus treatment: a pilot study. <i>Otolaryngol Head Neck Surg</i> 2008;138(4):497-501.
Tinnitus questionnaire (version unknown, translation status unknown)	reduction of 25%	Quote: "a 25% improvement to be clinically relevant"	Hoekstra CE, Versnel H, Neggers SF, Niesten ME, van Zanten GA. Bilateral low-frequency repetitive transcranial magnetic stimulation of the auditory cortex in tinnitus patients is not effective: a randomized controlled trial. <i>Audiol Neurootol</i> 2013;18(6):362-73.
Tinnitus Questionnaire (German version)	boundary crossing from 47 to 46	Quote: "Tinnitus is considered to be 'compensated' at a TQ level of = 46 (no secondary symptoms) and 'decompensated' at a TQ level of = 47 (permanent annoyance and psychological strain)"	Mazurek B, Haupt H, Szczepek AJ, Sandmann J, Gross J, Klapp BF, et al. Evaluation of vardenafil for the treatment of subjective tinnitus : a controlled pilot study. <i>J Negat Results Biomed.</i> 2009;8:3.
mini-Tinnitus Questionnaire	reduction ≥ 4 points	Quote: "an improvement of at least 4 points... to be classified as a therapy responder".	Jasper K, Weise C, Conrad I, Andersson G, Hiller W, Kleinstaubler M. Internet-based guided self-help versus group cognitive behavioral therapy for chronic tinnitus: a randomized controlled trial. <i>Psychother Psychosom</i> 2014;83(4):234-46.
mini-Tinnitus Questionnaire	Reduction > 5.8 points	Quote: "Any patient who has scores differing for more than 5.8 points... has achieved a clinically relevant change".	Argstatter H, Grapp M, Plinkert PK, Bolay HV. Heidelberg Neuro-Music Therapy for chronic-tonal tinnitus-treatment outline and psychometric evaluation. <i>Int Tinnitus J</i> 2012; 17(1):31-41.

calculated from these data reported in the International Tinnitus Journal.

Methodologists generally recommend triangulating the results of multiple methods for determining clinically important difference. Other methods include distribution-based methods such as the Standard Error of Measurement (SEM) and Smallest Detectable Change (SDC). With 151 patients allocated to intervention, Argstatter et al.⁴ have sufficient data to make these computations and to make a recommendation to the tinnitus community about the criterion for clinical significance of the TQ change score. This could greatly assist investigators at the design stage of the trial, and enhance consistency across studies.

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Deborah Hall

NIHR Nottingham Hearing Biomedical Research Unit,
113 The Ropewalk, Nottingham NG1 5DU