Methodological aspects of clinical trials in tinnitus: A proposal for an international standard

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Abstract

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Chronic tinnitus is a common condition with a high burden of disease. While many different treatments are used in clinical practice, the evidence for the efficacy of these treatments is low and the variance of treatment response between individuals is high. This is most likely due to the great heterogeneity of tinnitus with respect to clinical features as well as underlying pathophysiological mechanisms. There is a clear need to find effective treatment options in tinnitus, however, clinical trials differ substantially with respect to methodological quality and design. Consequently, the conclusions that can be derived from these studies are limited and jeopardize comparison between studies. Here, we discuss our view of the most important aspects of trial design in clinical studies in tinnitus and make suggestions for an international methodological standard in tinnitus trials. We hope that the proposed methodological standard will stimulate scientific discussion and will help to improve the quality of trials in tinnitus.

Keywords

tinnitus; clinical trials; trial methodology; guideline

Tinnitus is a world-wide problem of high prevalence and socio-economic relevance

Tinnitus, the phantom sensation of sound in the absence of overt acoustic stimulation, is a significant problem that negatively impacts the quality of life of patients throughout the world. Tinnitus is classified according to whether the perceived noise has an identifiable source (for example, myoclonic contractions of the tensor tympani muscle or blood vessels, *objective tinnitus* or *somatosounds*) versus the lack of a specific sound source (*subjective tinnitus*). Subjective tinnitus is by far the most common form of tinnitus and henceforth in this article will be referred to as tinnitus. Notably in subjective tinnitus there is no identifiable sound source but well characterized alterations of neuronal activity in auditory and nonauditory pathways [1, 2].

Almost everyone has experienced phantom sounds at least once in their life for a short time. While in the majority of cases, these sounds vanish after seconds, minutes or hours, in a significant portion of the general population the tinnitus perception is unremitting [3, 4] and leads to significant restrictions in quality of life. Based on recent data, tinnitus occurs in 25.3% of American adults (50 million people) with 7.9% experiencing it frequently (16 million people) [5]. Epidemiological studies reveal comparable prevalence rates throughout Europe [6-9] and similarly high prevalence in Asia [10, 11] and Africa [12, 13] indicating that tinnitus is a significant health problem throughout the world.

Tinnitus and its associated comorbidities have great financial costs. As the most common medical complaint among US war veterans returning from Iraq and Afghanistan, the annual disability compensation by the Department of Veteran's Affairs for tinnitus and defective hearing exceeded USD $2 billion in 2009 and are expected to further increase [14]. The socioeconomic relevance is also illustrated by a large prospective Swedish cohort study demonstrating that sickness absence because of tinnitus was related to a more than threefold increased risk of disability pension as compared to sick leave due to other diagnoses [15]. Furthermore, tinnitus is frequently accompanied by symptoms such as anxiety, depression, insomnia and/or concentration difficulties [16-19].

Evidence-based treatment options for tinnitus are limited

Available treatments for the management of tinnitus are diverse. Highest evidence for clinical efficacy is available for cognitive-behavioral therapies [20, 21]. Further established

treatments include counseling [22] and various forms of sound therapies [23]; methods that attempt to increase input to the auditory system, such as hearing aids [24, 25] and cochlear implants [26] (for use in patients whose tinnitus is caused by deprivation of signals to the auditory nervous system); pharmacological treatments [27]; neurobiofeedback [28]; and various forms of electrical stimulation of brain structures, either through implanted electrodes [29] or by inducing electrical current in the brain with transcranial direct current stimulation [30] or transcranial magnetic stimulation [31, 32]. However, evidence for the effectiveness of these different treatment strategies is scarce [33].

The methodologic quality of clinical trials is variable

Many of the clinical trials in tinnitus have critical methodological limitations including: inappropriate outcome measures and statistical methods, insufficient sample sizes, poorly defined interventions, problems with study blinding and randomization and insufficient reporting of study details [33-35]. The heterogeneous quality of tinnitus treatment studies is echoed by all Cochrane Reviews regarding tinnitus treatment studies [20, 23, 36-39] and has led to efforts to describe basic methodological recommendations for the designs of clinical tinnitus trials [40].

Specific methodological challenges for clinical trials in tinnitus

Since tinnitus is a purely subjective condition, its assessment is not trivial. Tinnitus loudness can be assessed by matching procedures or by visual analogue- or numeric rating scales. For the assessment of tinnitus related handicap several questionnaires have been developed and validated. Since no drug has yet been approved for the treatment of tinnitus [41], there is also no standard defined by regulatory authorities with respect to treatment outcome measures. However, variable outcome measures across trials make comparisons difficult.

The heterogeneity of tinnitus is a further challenge in clinical tinnitus research. Tinnitus can differ in many aspects such as tinnitus localization, sound characteristics, temporal course, underlying cause, co-morbid conditions, etc. Thus, there are different forms of tinnitus that presumably differ in their pathophysiology and in their response to specific treatments [42]. This may be one reason that results from clinical studies also show great variability, with some promising results from pilot studies (e.g., nortriptyline [43], gabapentin [44]) which have never been replicated [45, 46]. Therefore an exact description of the patients under study in a specific trial is mandatory.

Based on the accumulated evidence of results from numerous clinical studies in tinnitus underlining its heterogeneity, it seems more and more likely, that specific sub-forms of tinnitus will benefit from specific treatment interventions.

In summary the low methodological quality of many trials together with the heterogeneity of tinnitus (i) limits the conclusions, which may be drawn from the available treatment trials, (ii) jeopardizes comparability of trial results, and (iii) impedes the scientific progress in the treatment and prevention of this common and debilitating condition.

There is an urgent need for better evidence of tinnitus treatments

The lack of good evidence hampers both decision making in the therapeutic management of tinnitus patients and the development of clinical guidelines [47-49]. In light of the urgent need to find effective treatments for the different forms of tinnitus, initiatives have been started to establish an expert consensus of how to clinically characterize tinnitus patients and how to measure outcomes in treatment trials [50]. Based on this consensus, an international database project has been initiated with the aim to improve clinical characterization of

tinnitus patients and enhance investigation of new promising treatment approaches [51]. Nevertheless, a prerequisite for such international collaborative research approaches is an international minimal standard for designing and conducting clinical trials in tinnitus [34, 52], which accounts for the special requirements due to the nature of tinnitus. Here, we would like to discuss different methodological aspects of clinical trials and make methodological suggestions for future clinical trials in tinnitus. Although we focus specifically on clinical trials in tinnitus, some aspects may also apply to clinical trials in other disorders, which share some of the clinical characteristics of tinnitus (e.g. psychosomatic disorders such as chronic fatigue, fibromyalgia, irritable bowel syndrome, etc.).

Clinical Trials for investigating the Treatment of Tinnitus

Randomized clinical trial methodology has been established over many years, especially in the context of the process of drug development, and has resulted in a widely accepted standard. Clinical trials are differentiated according to different phases in the development of therapeutic interventions.

Preclinical trials are performed in vitro (e.g. in cell cultures) or in vivo in animal experiments to obtain preliminary efficacy and toxicity information. Several animal models of tinnitus [53, 54], and behavioral testing procedures [55, 56] are established and recently an in vitro testing approach appropriate to these models was proposed [57]. Animal models of tinnitus have been used to decide which interventions merit further development as an investigational new drug [58, 59] and to refine intervention parameters [60].

Preclinical trials can either be performed as screening of many potential interventions or based on a clear hypothesis derived from the pathophysiological understanding of the disease. With the lack of availability of valid high through-put screening methods for tinnitus, the second approach is more important in tinnitus research. Another relevant path for the discovery of new treatment options is serendipity [61]: an unexpected beneficial effect of a compound for a disease other than the originally indicated, e.g., sildenafil, which was developed for pulmonary hypertension before demonstrating efficacy for erectile dysfunction [62].

Clinical trials proceed in four phases. Phase I trials are the first stage of testing performed in healthy human subjects independent of the intended indication of the intervention. Phase I trials serve to assess the safety and tolerance of an intervention and, in the case of drug treatment, the pharmacokinetic and pharmacodynamic profiles. Phase II trials are used to assess dosing requirements (Phase IIA), the efficacy of an intervention, (Phase IIB) and to continue Phase I safety assessments in a larger groups of study participants. Phase II trials are typically designed as randomized controlled trials with several active treatment arms (e.g., a drug at different dosages) and a placebo arm [63]. Phase III studies are randomized controlled trials of large patient groups intended to assess the efficacy of an intervention. In tinnitus for example, Phase III trials are currently underway to assess the efficacy of tinnitus retraining therapy (clinical trials: NCT01177137), transcranial magnetic stimulation (controlled trials: ISRCTN89848288; [64]) and of neramexane (clinical trials: NCT00955799; NCT00772980; NCT00739635). Phase IV studies are larger, open-label investigations aimed at collecting safety information for drugs that have gained approval for a specific indication.

Despite the large variety of potential treatments for tinnitus, no drugs have been approved and no treatment has reached the level of a Phase IV study. Therefore, the TRI database project [51] is collecting data from various clinical trials in tinnitus patients in a systematic

and transparent way similar to a Phase 4 study to monitor the safety and potential clinical effects of treatments for tinnitus

Key Aspects of Trial Designs for the study of Tinnitus Treatments

Key aspects of trial designs in tinnitus patients will be considered as follows:

1. Trial type (randomized controlled trials vs. open trials; sample sizes, power calculations)

2. Control condition and blinding

3. Trial duration

4. Study population

5. Outcome measures

6. Statistical significance vs. clinical relevance

7. Trial reporting

8. Ethical aspects of clinical trials

1. Trial type

When planning a clinical trial, the first and general question is, which trial design should be chosen. Randomized controlled trials (RCT) are the gold standard for evaluating the efficacy of a treatment intervention [65]. The major advantage of randomized controlled trials is that they control for potential non-specific and placebo effects. With large enough samples, randomization balances out all known and unknown factors related to the patient (e.g., patient history, tinnitus duration, comorbidity, age, gender, etc.) across treatment and control groups. Thus, randomization is performed to eliminate potential biases (i.e. systematic errors that jeopardize the interpretation of the study results) that may be generated by confounding factors. However, randomization does not always balance known prognostic factors and this imbalance may ultimately impact on assessment of treatment [66].

RCTs should be performed in a double-blinded manner to guarantee that neither the therapist nor the patient is aware of the treatment condition (intervention or control group). Blinding is essential to control for non-specific and placebo effects, which have been shown to play a relevant role in different medical conditions [67], including tinnitus [34]. Methodological advantages of a RCT must be weighed against the disadvantages: RCTs are expensive and time consuming. Therefore, only "promising" interventions justify the performance of a RCT. The choice of a promising intervention is difficult and can be based on clinical pilot data, medical expertise and experience, computational models (e.g. coordinated reset auditory stimulation [68]) and/or from animal studies (e.g., combination of paired acoustic stimuli with vagal nerve stimulation; [60]). Moreover a RCT can only test a limited number of treatment interventions (in most cases one active intervention) against a control condition. Thus detailed information about the intervention and its effects are required when a RCT is planned. These include aspects such as dosage, temporal dynamics of the effect, effect spectrum and effect sizes. Such information can be derived for example from case reports, preclinical studies, phase I or II studies, or cohort studies. This information is necessary for planning the design of RCTs (e.g., parameters of the intervention, choice of outcome parameters, duration of the trial, etc.) and particularly for estimating the sample size, in order to minimize the risk of false negative studies. False negative results mean that the trial suggests that a treatment is not more effective than placebo although the intervention is superior to placebo. Reasons for false negative results include inappropriate choice of the primary outcome parameter, insufficient trial duration or

a sample size, which is too small to detect the difference between both study arms (i.e. an underpowered study). This pitfall can be avoided by defining clinically meaningful changes (e.g., reduction of a given number of points in a tinnitus questionnaire; see below), performing power calculations as well as sample size calculations while planning a RCT. However, a precondition for power calculations is an effect size estimation of the intervention under study, indicating the necessity of pilot studies or pilot data for the planning of a RCT. The power estimation and the definition of a sufficient sample size have among other factors to consider the balance between type I and type II error.

RCTs often include primary outcome measures that are defined as continuous variables and the main analytical approach is to calculate mean values for the primary outcome measure within each arm and then compare these mean values across the different study arms. While the analysis of mean values within the different study arms continues to be the gold standard approach to prove efficacy of a given treatment, it should be noted that this approach may not adequately represent treatment effectiveness [69]. The reason this is so is that the effect of a given treatment in the whole study population may be weak and thus differences between groups may not reach statistical significance. Yet individual participants may experience big treatment effects, which would be missed with group statistics. This may be especially the case in tinnitus, where it is known that some patients respond well to treatment while others fail the same treatment. Hence, besides comparing overall mean changes, treatment responders should be analyzed. An alternative approach to address the heterogeneity of tinnitus is to start with an open-label phase and to enter only responders in the blinded, randomized phase of the trial [34]. However, the subject selection phase does not necessarily have to be open label, because of possible confounding effects on the next phase of the trial. Instead, the first phase can also be performed in a blinded, randomized-controlled way in which persons who meet predefined criteria for treatment response at the end of the first phase continue on to the next phase of the RCT, whereas those who fail are triaged to an alternative condition. Double-blind RCTs are difficult to perform for non-pharmacologic treatments. For example, it is a matter of debate what is an adequate control condition for psychotherapeutic interventions and how effective blinding can be performed. Finally, RCTs may imply some ethical aspects, especially when a placebo arm is included. In particular this is the case when treatments have been established in routine clinical care without having ever been proven effective in well-controlled RCTs (e.g. steroid treatment in acute hearing loss; [70]).

Other forms of controlled trials include matched-pair group designs, partially and non-randomized controlled trials. The alternative to controlled trials are open trials, which do not include a placebo control condition and both, the patient and the therapist know about the treatment. Open trials may include an observational control group. Open trials are much easier to design and conduct. Patient recruitment for the study is easier and there is no need to design a placebo condition, to perform randomization or to ensure blinding. However, the main disadvantage of open trials is that they cannot rule out major threats to the validity of the trial, and so, even if a treatment appears to work well this interpretation is in question. Nevertheless, open trials are an important instrument to screen potential new treatments for their efficacy. They can serve to estimate effect sizes, to identify optimal parameters of treatment interventions (e.g. dose finding studies), tolerability and to identify response predictors. However, it should be kept in mind that interventions, which have shown positive results in open trials have to be tested in subsequent placebo-controlled double-blind RCTs, before firm conclusions about their efficacy can be drawn.

In the conduct of a RCT, there are two general alternatives: (i.) a cross-over design, in which each patient serves as his or her own control or (ii.) a parallel group design. The cross-over design minimizes the influence of confounding factors, since all confounding factors

introduced by the patients will be the same in both groups. As a result, a smaller sample size is sufficient to reach the same statistical power. However, a cross-over design does not allow longer follow-up periods and potential carry-over effects have to be considered. Carry-over effects are especially problematic when tested interventions are expected to cause long-lasting changes, like psychotherapeutic interventions, or to induce neuroplastic changes like transcranial magnetic stimulation [71]). A further problem of crossover designs is that participants can directly compare the different treatment interventions under study. Since the control condition never matches the treatment under study in all aspects (e.g. side effects of medication or superficial sensory stimulation in brain stimulation techniques) both the patient and the investigator may be able to guess what was the real treatment and what was the control condition [72]. Also, cross-over designs are problematic when the timing of the intervention is critical. In contrast, parallel-group designs allow longer follow up periods and there are no carry-over effects. However, parallel group designs have the risk of an unequal distribution of confounding variables despite a randomized allocation of participants to study arms, especially in the case of relatively small sample sizes. Furthermore, the problem of blinding the experimenter to treatment, as with some sham techniques for rTMS, are not eliminated by a parallel group design.

2. Control Conditions and Blinding

Using a placebo treatment as control condition serves to differentiate specific effects of an intervention from non-specific effects. Non-specific effects include expectation, anticipation, patient care, the investigator's attention or spontaneous improvement.

In order to ensure that study results are not confounded by anticipation or expectation, both the participants and the investigators should be blinded with respect to the individual treatment allocation. Whenever possible, clinical trials should therefore use double blinding. One possibility to assess successful blinding is to ask both study participants and investigators at the end of the study to guess which treatment the individual patient received.

Whereas placebo treatment and blinding can be performed relatively easy in pharmacologic trials, the choice of an adequate control condition becomes more challenging for non-pharmacological interventions. For brain-stimulation techniques it has been shown that the development of a truly indistinguishable sham condition is possible [72-74]. For psychotherapeutic or physiotherapeutic interventions, control conditions should be chosen, which resemble the active treatment in the number and duration of sessions in order to control for non-specific effects of patient care and therapeutic attention. Thus unstructured group meetings could represent a control condition for a specific psychotherapy. Or specific new interventions can be compared to treatment as usual [75]. Pure waiting list control groups are vulnerable to expectations and non-specific effects of the interaction between patient and therapist, they tend to overestimate the effects of the active intervention [76] and have recently been shown to vary largely in their outcome [77]. Complete blinding is impossible for these interventions, since the therapist cannot be blinded. A possible attempt to achieve some form of blinding is when the patients, investigators/raters, and those who perform the study analysis are blinded.

When the goal of a RCT is to demonstrate non-inferiority (or even superiority) to an established intervention, an active control condition can be chosen [78]. However it is preferable to perform such trials as three-arm trials including both an active control condition (established treatment) and a placebo control condition [79].

3. Trial duration

An important aspect in the design of clinical trials is treatment duration and the duration of the follow-up period after treatment. This requires knowledge about the dynamics of the effects of the intervention under study. When treatments, which exert their effect with delay (e.g., cognitive-behavioral therapy), are tested, a sufficiently long follow-up period is essential to detect treatment effects. If follow-up times are too short, the risk of a negative study outcome is increased since the onset of the therapeutic effect of the tested intervention may be missed. On the other hand, trials with longer treatment and observation periods are more difficult to perform and bear the risk of higher participant drop-out. Treatments that are believed to result in permanent or long-lasting benefit following intervention should also include a washout period of sufficient time to ascertain that the effect seen is maintained following treatment, or if the effects are only present during active treatment.

The fluctuation of severity and spontaneous resolution of tinnitus has also to be considered in the planning of study duration. Multiple assessments during both the pre-intervention and the follow-up period may make results more valid. When long trials are planned, spontaneous tinnitus improvement over time should be expected [80].

4. Study populations

There is increasing consensus in the scientific community that tinnitus is a heterogeneous condition [50]. Different forms of tinnitus might differ in their response to specific interventions. Thus, a likely explanation for the high variance in treatment outcome encountered in most tinnitus treatment trials is that the included patients suffer from different forms of tinnitus [81]. One strategy to address this problem is the creation of homogenous study samples based on strict inclusion criteria. At best, these inclusion criteria should select patients, who are expected to be most likely to respond to the tested intervention. Characteristics which have shown to influence treatment outcome, for some interventions, include: tinnitus quality (pure tone versus noise-like [29]), baseline severity [82, 83], somatosensory modulation [84], and tinnitus duration [83, 85]. However, other factors such as tinnitus laterality, accompanying hyperacusis, or other comorbid conditions, like anxiety, depression or sleep problems may play a role as well. In this context, reporting exact information about different clinical and demographic characteristics of the sample under study and the way how this was assessed is mandatory [50].

The importance of different tinnitus characteristics for planning of a clinical trial may be illustrated using the example of tinnitus duration. The assumed neuronal correlates of tinnitus have been shown to change with increasing tinnitus duration [86-88]. The mechanisms involved in the generation of tinnitus are assumed to differ from those involved in the maintenance. Thus, there may be a specific time window after tinnitus onset for specific interventions, such as antiglutamatergic agents [89]. This time window has to be exactly defined by inclusion and exclusion criteria; otherwise, the non-responding subgroup may be artificially increased. However, when only patients with acute tinnitus are included, it has to be considered that these patients may have a higher spontaneous recovery rate. This, however, makes it more difficult to detect a significant difference between the intervention tested and placebo, requiring a larger sample size. A higher rate of spontaneous recovery may further increase the drop-out rate, which, in turn, may lead to problems with data analysis and interpretation.

While a well-characterized study sample increases the chances to find an effective intervention, the generalizability of the results is reduced since the study population is no longer representative of the majority of tinnitus patients. This problem is well described in pharmaceuticals trials, for example in depression, where typical patient subgroups (e.g.,

accompanying personality disorders, drug addiction or psychotic features of depression) are excluded from study participation. However, a prerequisite for this approach is, that predictor variables for treatment response are known, which is often not the case at the beginning of a clinical trial. Alternatively, *post hoc* responder analyses may help to identify responder groups, which can be best performed, if all relevant clinical characteristics have been collected in a standardized manner. Results of these post hoc analyses must be interpreted carefully and confirmed in future prospective RCTs, before firm conclusions regarding the effectiveness of the intervention can be drawn.

Another aspect for the selection of the study population is additional tinnitus-specific treatments that are given at the same time. Whenever possible, patients who are currently using tinnitus treatments should be excluded from the study, but this may be difficult for long-time treatments, such as the use of sound therapy (e.g., hearing aids or noise generators). If exclusion of patients who are currently using tinnitus treatments is not possible, then notation of such treatments should be made and separate analyses performed.

5. Outcome measures

Assessment of outcome is probably the single most important factor in conducting a clinical trial in tinnitus. The effectiveness of a potential treatment tested in a clinical trial is judged according to its effect on the primary outcome measure. As tinnitus is a purely subjective condition, the definition of outcome measurements is challenging [90]. Furthermore, clinical experience shows that in many patients tinnitus severity fluctuates over time and is influenced by many known (e.g., anticipation and expectation, comorbid conditions, etc.) and unknown factors. This fluctuation in severity has important consequences for designing a clinical trial. In general, efficacy of a tested intervention is evaluated by the change of the defined primary outcome measure from baseline to one (or more) defined follow-up time-point(s). This indicates the relevance of a reliable and stable baseline value, which is not influenced by nonspecific effects, like anticipation or expectation. One possible approach to enhance stability of the baseline is to collect more than one baseline value (e.g., three measurements of tinnitus severity with a tinnitus questionnaire in the week before start of the treatment, [64] and efficacy calculations are then based on the mean value of these measurements. A RCT in tinnitus, where fluctuation in baseline measurement is expected, might compare a week's worth of baseline measurement to a week's worth of post-treatment or follow up measurement.

Currently, all established tinnitus outcome measures are based on subjective evaluation. Even neuroimaging data, or oscillatory activity in the auditory cortex, derived from electro/magneto-encephalography are only validated in light of how well they correlate with subjective estimates of tinnitus loudness [91-95]. Hence, neuroimaging is far from being an established objective method to measure and quantify tinnitus.

Comprehensive assessments of tinnitus would ideally address three, subjective principal components (1) auditory features of the tinnitus percept including intensity, location, masking, and pitch, (2) emotional features like distress, and (3) attentional features like awareness of tinnitus in daily life and cognitive interference impacting executive decision-making and short-term memory. Separate assessment of these different components is especially relevant, since they correlate only relatively weak with each other [80]. According to current neurobiological research, these components are reflected by activation changes in independent and overlapping neural networks devoted to acoustic, emotional and attentional processing [1]. The impact of tinnitus on quality of life, for example on concentration, sleep and activities, should be separately assessed and depends on all three mentioned components (acoustic, emotional, attentional). In light of these different aspects of tinnitus, the goal of a careful selection of outcome measures is a comprehensive

assessment of tinnitus, which includes psychoacoustic measures or ratings of loudness and annoyance as well as questionnaires measuring tinnitus impact.

5.1.Assessment of tinnitus loudness—Subjective tinnitus intensity can be estimated by use of a visual analogue scale (VAS) or a numeric rating scale (NRS). Even widely used, these scales have not been systematically validated for assessment of the different aspects of tinnitus. Tinnitus loudness can be quantified by matching methods. Matching is achieved by presenting different tones to the patient and asking what frequency and intensity best fit their tinnitus. When matching the tinnitus to an external sound presented to the ear without tinnitus, the vast majority of the patients rate their tinnitus as less than 5—10 dB above hearing threshold expressed as dB sensation level (dB SL) [96]. An alternative method for quantifying tinnitus loudness is masking, the estimation of the minimum noise level required to mask the tinnitus [76]. However, it has to be taken into consideration that the tinnitus of some patients cannot be masked at all. Moreover clinical experience suggests that tinnitus loudness estimation by matching or masking procedures does not always correlate with the subjectively perceived tinnitus loudness as assessed by visual analogue scales and by numeric rating scale. It is obvious that better paradigms to quantify loudness or loudness levels are needed to advance this area.

5.2. Assessment of tinnitus-induced handicap and distress—The disability and the amount of distress that tinnitus evokes can be assessed by validated self-report tinnitus questionnaires (see Table 1). Of these, the most established instruments are the Tinnitus Handicap Inventory (THI; [97]), the Tinnitus Handicap Questionnaire (THQ; [98]), the Tinnitus Questionnaire (TQ; [99]) including its short versions (e.g. the Mini TQ; [100]) and the Tinnitus Reaction Questionnaire (TRQ; [101]). The scores of these questionnaires correlate highly with each other (for a review see [102]) and are generally used to infer the impact on the patient's quality of life [20]).

In addition to scores on individual items, the majority of tinnitus questionnaires (for example, THI) apply an index score, which captures the impact of tinnitus on a patient's daily life. Most of these questionnaires were developed for diagnostic purposes or classification of severity of tinnitus at one point in time. Few instruments were developed specifically to measure change over time. Nevertheless, most of these instruments have been used as outcome measures in clinical trials and have been shown to be sensitive to treatment-related changes (e.g. in studies investigating cognitive behavioural therapy [20, 103]). However, the available questionnaires may vary in their responsiveness to treatment related changes. This variability of the questionnaires with respect to sensitivity to treatment-related changes is firstly related to the relation between items, which reflect state and trait variables. A large amount of change-insensitive trait-variables make it difficult to detect treatment effects and may even obscure them. Another factor related to the responsiveness of a questionnaire is the number of items and the number of answer options for each item, which vary among the most widely used tinnitus questionnaires between 3-point ordinal scales (THI) and 0-100 interval scales (THQ) (Table 1).

In the choice of the questionnaire it should further be considered that not all questionnaires cover all aspects of the condition and that some questionnaires may be weighed to detect certain symptoms [104]. Having recognized the limitations of existing questionnaires, a new questionnaire, the Tinnitus Functional Index, was developed [105], which has been constructed following an analysis of important aspects of health-related questionnaire construction (e.g., item selection, test–retest reliability and construct validity) and important symptoms of tinnitus to be represented [106].

5.3 Assessment of tinnitus attention and awareness—It is increasingly clear, that neural networks serving attention, conscious awareness and self perception are altered in association with tinnitus [107] although awareness of tinnitus is typically assessed indirectly. A patient's awareness of tinnitus in daily life can be measured using an analogue scale like those used for ratings of loudness. Several tinnitus questionnaires have individual items and subscales that assess annoyance and intrusiveness of tinnitus [108], which are relevant to the concepts of attention and awareness but probably also assess loudness and emotional components. Separating out these components is important as treatments might affect one dimension more than another and because our ability to validate the concept that tinnitus alters the function of multiple neural networks depends on the ability to disassociate these components of tinnitus.

5.4. Practical recommendations for the choice of outcome measures—A comprehensive assessment of tinnitus should include both perceptual aspects of tinnitus (especially loudness and awareness) and tinnitus-related impairment in quality of life (e.g., by assessment of tinnitus related distress or tinnitus-related handicap). These aspects are complementary and correlate only weakly with each other in cross-sectional studies [80]. In light of these considerations, it is essential to assess the effect of a therapeutic intervention on tinnitus-related suffering and not only on perceptual aspects [34], when conducting clinical trials in tinnitus. Also, therapeutic interventions may differ in their aims. Some interventions may focus on abolishing tinnitus or changing its sensory aspects (e.g., loudness levels), others may aim at reducing tinnitus-related distress or handicap. This is of relevance for the trial design, especially the choice of the outcome measures. Thus, treatment interventions that aim to reduce tinnitus loudness, should not only be assessed by questionnaires of tinnitus annoyance but also by measurements of tinnitus loudness [76]. Vice versa, the therapy for which best evidence is available is cognitive behavioral therapy (CBT) [20, 33], but CBT only improves quality of life and does not reduce tinnitus loudness. Thus even if a comprehensive assessment of the different aspects of tinnitus is desirable for the evaluation of all treatment methods, the primary outcome measure should be chosen according to the expected changes induced by the treatment under study.

In general, there is consensus among tinnitus experts [50] that clinical trials in tinnitus should use at least one of these validated questionnaires as an outcome measure. In addition, there was consensus that comparability of results from different trials and centers can be facilitated by including one specific questionnaire in each trial. Being aware of the pros and cons of the different validated tinnitus questionnaires, the Tinnitus Handicap Inventory (THI) [97] has been suggested to be included in every study as a primary or secondary outcome measure [50]. One of the major advantages of the THI is its wide use and validation in many languages. A disadvantage of the THI is, as already discussed, the limited number (3) of response categories. However it should be noted that direct comparisons of outcomes measured using different translations of questionnaires, or even the same questionnaire in different settings, should be interpreted with caution, as even subtle cultural differences can modify question meaning and consequently outcomes [109].

6. Statistical significance vs. clinical relevance

If clinical trials show statistically significant results, this does not necessarily mean that these results are clinically meaningful. Statistical significance only means that the error rate (i.e. the difference between two treatment arms is due to chance) is below a pre-defined level (e.g. less than 5 %). Whether a result reaches statistical significance depends on several factors: the mean difference between the groups, the variability of the results (e.g., expressed as standard deviation) and the sample size. For example, a clinical trial with a large sample size that describes small and clinically meaningless differences between groups may

nevertheless achieve statistical significance due to the sample size [110]. On the other hand, a clinical trial with a small sample size that describes clinically meaningful differences between groups may not achieve statistical significance. Because of the impact of sample size, confidence intervals should be used for the correct interpretation of clinical trial results [111].

In quality-of-life research, a difference of more than half a standard deviation is assumed to be clinically relevant [112]. With respect to clinically relevant changes in tinnitus trials, evidence is sparse. It has been suggested that a reduction of at least six [113] or five points [114] in the German version of the TQ defines responders, but this assumption has only been based on clinical experience and is not supported by data. Recently, a first data driven analysis of clinical relevance in tinnitus trials based on 210 patients has shown that a reduction of the THI score by 7 points or more is clinically relevant [115]. While these data give a first landmark, it has to be kept in mind that among the available tinnitus questionnaires only the Tinnitus Functional Index has been developed with the purpose to detect treatment-induced changes. Thus, more research is needed to determine for most of the tinnitus questionnaires what magnitude of change is clinically meaningful.

7. Trial reporting

The last and very important step in planning and conducting a clinical trial is to report the results (even if negative). Publishing results from clinical trials is essential in order to inform the scientific community of what was done and what are the results. Therefore, negative results should also be published. Trial publication should start even before the first patient has been enrolled by registration of the trial in a clinical trial registry (e.g., www.ClinicalTrials.gov or www.controlled-trials.com). Primarily, these registries have been introduced to improve public access to clinical trials, but they also ensure methodological quality standards, since the key aspects of the trial design (i.e. sample sizes, primary outcome measure, statistical analysis methods) are described. Furthermore, registration of the clinical trial before the conduct of the trial is a mandatory requirement for publication of the trial results in almost all high-ranked clinical journals.

In addition to registration of the trial, the protocol of the trial may be published, which also enhances transparency of details of trial design. There are several journals, which support the publication of trial protocols, for example the platform of open access journals "BioMed Central" (http://www.biomedcentral.com/info/authors/protocols). Finally, the results of the clinical trial should be published following a common scientific standard set by the CONSORT Group ("consolidated standards of reporting clinical trials" http://www.consort-statement.org); [116, 117]). The main objective of CONSORT is to facilitate critical appraisal and interpretation of RCTs by providing guidelines on how to report methods and results of a RCT. The methodological details, which are required to be reported, are summarized in the CONSORT statement and checklist (http://www.consort-statement.org/consort-statement/). This checklist describes the relevant methodological information that must be included in the reporting of the results of a clinical trial. In this way, the reader is able to critically assess the quality of the data and whether the data support the author's conclusions.

8. Ethical aspects of clinical trials

Clinical trials in humans, especially in the case of RCTs including a placebo condition, will often raise ethical issues, which have to be considered. In a placebo-controlled RCT testing a new intervention against placebo, patients are on the one side exposed to a new intervention of unknown safety and efficacy and on the other side, patients in the placebo-arm are possibly withheld from a potential beneficial new treatment option. This dilemma

cannot be solved but it is widely agreed that RCTs have to follow the highest ethical standards and especially evidence regarding the safety of the tested new intervention has to be sufficient. Furthermore, this dilemma should not be that problematic in tinnitus patients, since there are no clearly established tinnitus treatments in clinical routine with high evidence for efficacy. Therefore, the patients will not be withheld from a clearly effective treatment option. Finally, tinnitus represents, in most cases, a chronic condition, in which a short delay of treatment initiation does not seem to play a critical role. Therefore, placebo treatment before "treatment as usual" should not have severe consequences. In contrast, it appears unethical to submit patients to established treatments in clinical routine, which have never been shown to be effective in RCTs.

In general, ethical aspects of a clinical trial have to be reviewed by an independent Institutional Review Board (IRB) and ethical approval from the IRB has to be obtained before the trial can be started. In addition, according to Good Clinical Practice-(GCP)-Guidelines, the participants have to be informed about the nature, benefits and potential dangers of the trial as well as alternative treatment options and have to sign an informed consent form before they can be enrolled into the study.

A suggestion for a methodological standard of clinical trials in tinnitus

Clinical research in tinnitus is still a relatively young field. Performing clinical trials for evaluating treatment interventions in tinnitus is methodologically challenging for various reasons, which have been discussed above and are essentially related to the subjective nature of tinnitus, the heterogeneity of tinnitus, and the lack of established standards. At the same time, there is a clear need to improve the methodology of clinical trials in order to obtain reliable information about the safety and the efficacy of the various treatment approaches that have been proposed for tinnitus. Moreover, there is no good reason why generally accepted quality criteria for clinical trials, such as those outlined in the CONSORT statement, should not be applicable for clinical trials in tinnitus.

In this methodological overview we provided information on the points, which we believe should be kept in mind when planning a clinical trial in tinnitus. We aimed to address the most important and critical aspects of trial design and we discussed potential strategies how to deal with the particular challenges of tinnitus treatment studies. While many other points may remain a matter-of-debate, there are some essential aspects, which are from our point of view most critical and which may help to improve the quality of trials and the inter-study comparability. These aspects are summarized in Table 2 and are proposed as an international standard for clinical trials in tinnitus. We hope that this overview and the proposed standards will stimulate the scientific discussion about basic requirements and methodological approaches in tinnitus research and contribute to improve methodological standards in tinnitus research. Enhancing the quality of clinical research in tinnitus may finally pave the way to the ultimate goal of finding a cure for tinnitus!

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Table 1

Ten widely used tinnitus questionnaires for outcome measurement

Questionnaire name	Authors and year	Number of items	Response options for each item	Psychometric Properties	Available (validated) Languages[1]
Tinnitus Questionnaire	Hallam et al., 1988 [99]	52	3 levels: true, partly true, not true	Internal Consistency Reliability: Cronbach's alpha=.91-.95 Test-Retest Reliability: r=.91-.94	English, German, Dutch, French, Chinese
Mini TQ	Hiller&Goebel, 2004 [100]	12	3 levels: true, partly true, not true	Internal Consistency Reliability:Not available Test-Retest Reliability: r=.89	German, Portugese
Tinnitus Handicap Questionnaire	Kuk et al., 1990 [98]	27	100 levels: 100 = strongly agree, 0 = strongly disagree	Internal Consistency Reliability: Cronbach's alpha=.95 (total score) Test-Retest Reliability: r=.89 (total score)	English, French
Tinnitus Severity Scale	Sweetow and Levy, 1990 [118]	15	4 levels: wording of response options varies between items	Internal Consistency Reliability: Cronbach's alpha= not available Test-Retest Reliability: r=.86	English
Subjective Tinnitus Severity Scale	Halford and Anderson, 1991 [119]	16	2 levels: yes/no	Internal Consistency Reliability: Cronbach's alpha=.84 Test-Retest Reliability: not available	English, Dutch, French
Tinnitus Reaction Questionnaire	Wilson et al., 1991 [101]	26	5 levels: not at all, a little of the time, some of the time, a good deal of the time, almost all the time	Internal Consistency Reliability: Cronbach's alpha=.96 Test-Retest Reliability: r=.88	English, French
Tinnitus Severity Index	Meikle, 1995 [120]	12	5 levels[2]: never, rarely, sometimes, usually, always	Internal Consistency Reliability: Cronbach's alpha>.87 Test-Retest Reliability: not available	English
Tinnitus Handicap Inventory	Newman et al., 1996 [97]	25	3 levels: yes, sometimes, no	Internal Consistency Reliability: Cronbach's alpha=.93 Test-Retest Reliability: r=.92 (total score)	English, French, Danish, Spanish, Korean, Portugese, German, Italian, Chinese
Tinnitus-Beeinträchtigungs-Fragebogen[3]	Greimel et al., 1999; Bankstahl et al. 2012 [121,122]	12	3 levels: never, sometimes, often	Internal Consistency Reliability: Cronbach's alpha=.90 Test-Retest Reliability: r=.92 (total score)	German, English, French, Spanish, Polish, Dutch
Tinnitus Functional Index	Meikle, 2012 [105]	25	10 levels	Internal Consistency Reliability: Cronbach's alpha=.97 Test-Retest Reliability: r=.78 (total score)	English

[1] Language, in which the questionnaire has been developed, is given first.

[2] Original version of Tinnitus Severity Index used more complex response options: six items had three levels, six items had four levels, with wording of response system options varying between items.

[3] A short version of the THI that was first published in a German version.

Table 2

Basic requirements for clinical trials in tinnitus

- Trial planning
  - Clear formulation of the research question
  - Choice of adequate trial design
  - Definition of one or more main outcome measure(s) (i.e. a validated tinnitus questionnaire)
  - Tinnitus Handicap Inventory (THI) should be included in every trial at least as secondary outcome to improve inter-study comparability
  - Sample size estimation based on power calculations (e.g. based on data from pilot studies)
  - Ethical approval
  - Informed consent
  - Establishment of a statistical analysis plan
  - Registration in a clinical trials registry

- Study performance
  - The clinical trial should be performed according to good clinical practice (GCP) and CONSORT guidelines

- Reporting of results
  - All clinical trails should be published
  - Results should be reported according to CONSORT guidelines