TINNET recommendations for designing and reporting trials of clinical efficacy

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Prepared by COMiT, EU COST Action (BM1306) TINNET Working Group 5 "Outcome measurement"

Chair: Deborah Hall
Co-chair: Alain Londero

WG5 participants, 16th March 2016: David Baguley, Rilana Cima, Luca Del Bo, Thomas Fuller, Haula Haider, Magdalena Jozefowcz-Korczynska, Veronica Kennedy, Birgit Mazurek, Marzena Mileczarek, Anna Pajor, Sarah Rabau, Agnieszka Szczepek, Jonas Dyhrfjeld-Johnsen, Kathryn Fackrell, Jacqui Sheldrake.

The main goals of this working group are to establish standards for clinical trials in tinnitus, in particular for outcome measurement. A RoadMap published in 2015 describes the research process by which we will seek to achieve an evidence-based consensus (Hall et al., 2015a). Seventeen members of COMiT TINNET WG5 met on 16th March 2016, during the 1st EU COST TINNET conference held in Nottingham, to discuss the implications of the evidence base gathered as part of a recent systematic review of clinical trials of tinnitus interventions (Hall et al., 2015b; 2016). From this evidence, COMiT TINNET WG5 makes the following recommendations to the tinnitus community concerning the specification and reporting of outcomes in trials of clinical efficacy. These recommendations are intended not only for **investigators** designing and reporting clinical efficacy trials, but also for **journal editors** and **journal reviewers** who play an important role in the publication process.
These core recommendations are consistent with international reporting guidelines aiming at positively influencing the quality of published research reports. For parallel group randomised trials, the CONSORT statement should be considered (www.consort-statement.org, see also Moher et al., 2010). The CONSORT statement is also preferable for reporting other trial designs, including parallel group non-randomised trials and cross-over designs. The equator network (**E**nhancing the **QUA**lity and **T**ransparency **O**f health **R**esearch) maintains a library of this and other reporting guidelines and toolkits for authors (www.equator-network.org).

Recommendations:

1. For trials of clinical efficacy, COMiT TINNET WG5 recommends that investigators clearly specify **what** they expect their intervention to change. Examples include "how loud the tinnitus is perceived" or "how distressed the person feels by their tinnitus". These specific dimension(s) or domain(s) of tinnitus define the clinical trial outcome. See footnote 1.

2. For each outcome, COMiT TINNET WG5 recommends that investigators clearly specify **which** specific instrument will be used to measure change in that outcome, and preferably this should have been validated for responsiveness to treatment-related change in the

appropriate patient population. It is also preferable to provide some explanation about why that particular instrument was selected.

3. For each outcome of interest, COMiT TINNET WG5 recommends that investigators clearly specify **when** the outcome will be measured. It is preferable to describe the endpoint relative to the start (not the end) of the intervention to avoid any misinterpretation about the timescale between pre- and post-intervention assessments.

Use of the following format of wording would help to realise these recommendations:

''what is measured using which instrument and when"
e.g. fear of tinnitus, measured using the Fear of Tinnitus Questionnaire (Cima et al., Ear Hear. 2011;32(5):634-41) at 3 months after the start of the intervention.

4. If the intervention is intended to influence more than one tinnitus-related complaint (such as fear of tinnitus *and* sleep disturbance), then COMiT TINNET WG5 recommends investigators specify which one of these is the primary determinant of treatment efficacy. Thus, we recommend investigators to specify *a priori* **one** outcome measure and **one** time point as the **primary** outcome in trials of clinical efficacy. This may not always be the case in all efficacy trials. But we caution investigators that if they should decide to specify multiple primary outcomes, then **all** of those outcomes should demonstrate a significant change to drive any conclusions about therapeutic benefit. Additional outcomes can also be defined either as secondary outcomes and/or exploratory outcomes, but these would not be expected to drive any conclusions about therapeutic benefit.

5. COMiT TINNET WG5 recommends that investigators address patient safety issues as importantly as efficacy ones. Safety may be considered as a secondary outcome, but the recommended term is **harms**. Harms can be thought of as the direct opposite of benefits. The importance of harms-related issues is not adequately captured by a single item about reporting adverse events and so an extension of the CONSORT statement is available for guidance on reporting harms outcomes (Ioannidis et al., 2004). See footnote 2.

References

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Footnote 1.

To help patients, doctors and other health professionals make decisions about interventions, it is important to have evidence about what works best. Investigators test out interventions to make sure they work and are safe. To do this, investigators need to look at the effects those treatments have on patients. Researchers do this by measuring an 'outcome'. Outcomes should be specific. For example, "how loud the tinnitus is perceived" or "how distressed the person feels by their tinnitus". General descriptions such as "tinnitus severity" or "tinnitus handicap" are not suitable outcomes because it is not clear what these terms mean precisely and because they could be differently interpreted by different investigators or stakeholders.

Footnote 2.

The purpose of a trial is to collect and appropriately report good and bad events and outcomes so that they may be compared across treatment groups (Ioannidis et al., 2004). Adverse events describe harmful events that occur during a trial and these terms are preferred over and above 'safety' or 'side effects'. Safety refers to substantive evidence for the absence of harm. It is often misused when there is simply an absence of evidence of harm. Side effects suggest that the harms are caused by the intervention. Adverse events do not suggest causality. It is often difficult to know whether an observed harmful event is partially or entirely due to the intervention, or not related at all.