COMIT'ID study to agree the tinnitus-related domains comprising a Core Outcome Set for drug-based clinical trials of chronic subjective tinnitus in adults

Consensus meeting report, Friday 27th October

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EXECUTIVE SUMMARY

The Core Outcome Set for testing whether drug-based treatments are beneficial for tinnitus considers the domains tinnitus intrusiveness and tinnitus loudness.

Everyone taking part in the COMIT'ID study agreed that one tinnitus-related outcome domain was important to assess no matter which type of tinnitus treatment is being tested. This outcome domain is tinnitus intrusiveness. Tinnitus intrusiveness describes the state of noticing the sound of tinnitus is there and it is invading your life or your personal space. The group recognised that intrusiveness can refer to a various different ways in which tinnitus can affect you or your activities or capabilities in a negative way. For testing drug-based therapies for tinnitus, tinnitus loudness (how loud your tinnitus sounds) should also be assessed. The final consensus group for drug-based clinical trials voted in favour of these two outcome domains with 100% agreement. The group also recognised that reporting adverse effects is a minimum requirement expected by the regulatory authorities.

Future efforts will pair these selected outcome domains with suitable outcome instruments.

PURPOSE

Different clinical trials measure and report patient benefit using different methods. As a consequence, the findings of different studies can't be compared and the data can't be pooled together. This hampers progress in finding the best treatments.

A Core Outcome Set refers to a small number of outcome domains and the corresponding instruments for measuring them that are recommended to be assessed and reported in all clinical trials. If we could agree a Core Outcome Set for tinnitus then that would go a long way to addressing current limitations.

The Core Outcome Set would *always* be measured in *every* clinical trial (at least before and after the intervention), but investigators would be free to add other outcomes as they wish.

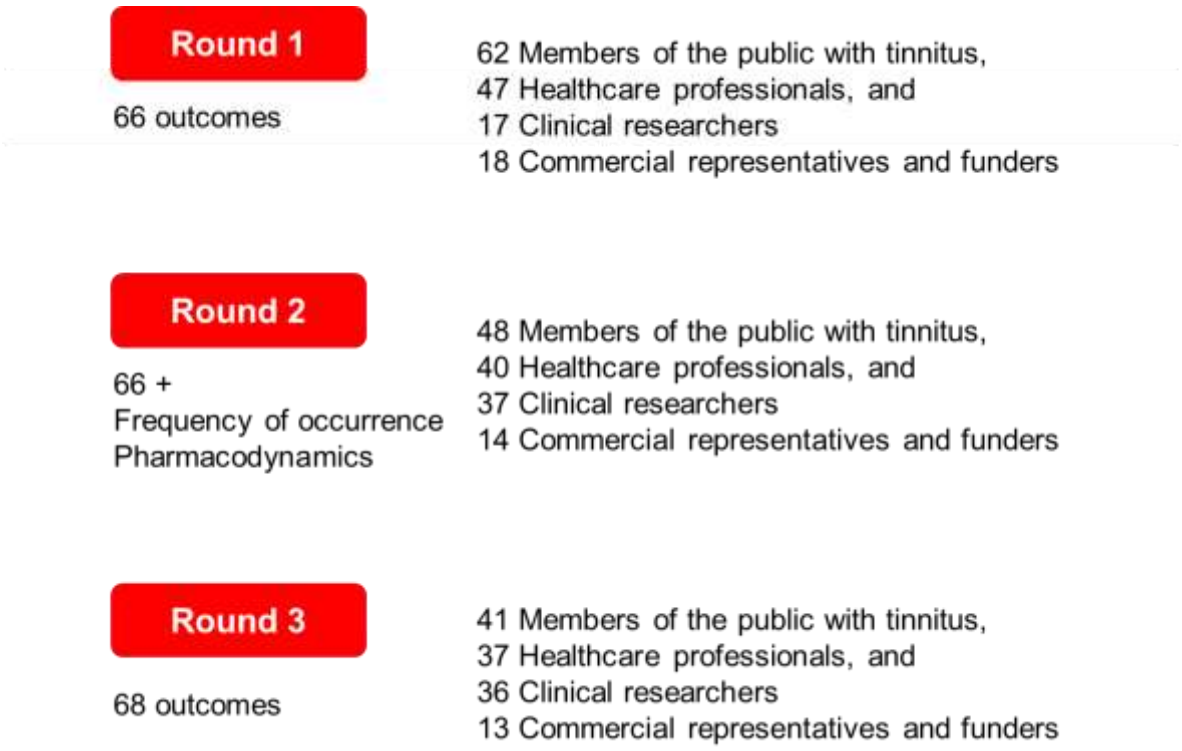
The purpose of this study is to define the tinnitus-related domains comprising a Core Outcome Set for drug-based interventions of chronic subjective tinnitus in adults.

Stage 1. The online Delphi survey

An online Delphi survey was completed first. Delphi surveys are a tried and tested method for developing consensus in decision making among a panel of experts. Across three survey rounds, we asked tinnitus experts to think about each one of 68 different possible outcomes related to tinnitus: "Is it critically important for deciding if a treatment has worked?"

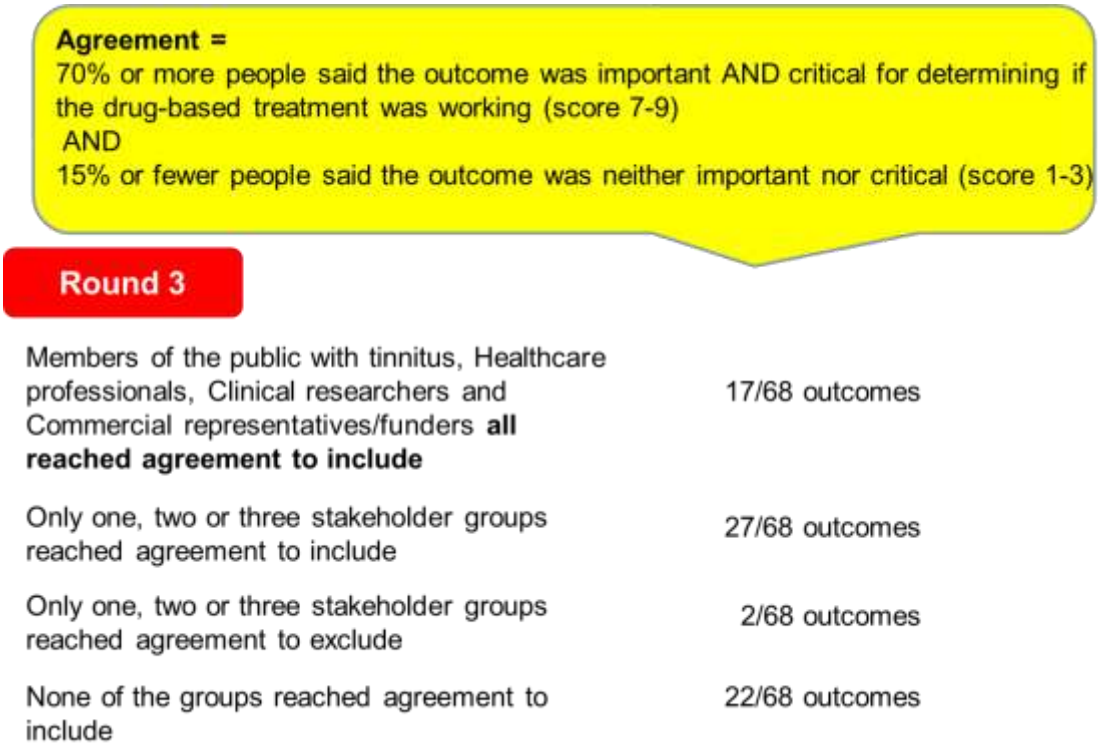
The following figure illustrates the number of outcomes considered at each round and the number of experts in each of the four different stakeholder groups. Participants were representing 29 countries across the world (UK, USA, France, Germany, Portugal, Brazil, Spain, Canada, Switzerland, Belgium, Italy, Poland, Argentina, Bulgaria, China, Finland, Lithuania, Malaysia, Malta, Mexico, Morocco, Norway, Romania, Russia, Serbia, Singapore, Slovenia, Sweden, and Turkey).

In round 1, we also invited participants to suggest any additional outcomes which they felt were missing from our original list of 66. From these suggestions, we identified 2 new outcomes that were not already covered by one of the outcomes already on the list. These were 'Frequency of occurrence of tinnitus episodes: How often you experience tinnitus symptoms (e.g. how many times and for how long)' and 'Pharmacodynamics: What a drug does to the body, with particular emphasis on the relationships between drug concentration and its effect on the body'. These were both added for consideration by all participants in round 2.



Delphi survey findings

The scores were evaluated for all those participants completing round 3. The study team had pre-defined agreement as when 70% or more participants in each stakeholder group said the outcome was important AND critical for determining if the drug-based treatment was working (score 7-9) AND 15% or fewer said the outcome was neither important nor critical (score 1-3). The following figure shows the results from this analysis about those outcomes reaching consensus.



All stakeholder groups agreed that these 17 outcome domains are important and critical:

Ability to ignore, Adverse reaction, Annoyance, Anxiety, Concentration, Confusion, Coping, Depressive symptoms, Difficulties getting to sleep, Impact on individual activities, Impact on social life, Impact on work, Quality of sleep, Tinnitus intrusiveness, Tinnitus loudness, Tinnitus unpleasantness, Treatment satisfaction.

Although we explicitly asked all participants to focus on considering outcome domains, we acknowledge that some may have found it difficult to evaluate those domains where there is a lack of current measurement instruments because it can be difficult for people to relate to an abstract future entity that is somewhat intangible. Pharmacodynamics is one possible example.

Stage 2. The face-to-face consensus workshop

16 participants attended this meeting (6 members of the public with tinnitus, 5 healthcare professionals, 2 researchers and 3 commercial representatives and funders).

In all voting, agreement was defined as at least 70% or more participants voting for either 'agree' or for 'disagree/unsure'.

The scope of this workshop was constrained by the result of the Delphi survey in which 17 outcomes were considered to be important and critical by all

stakeholder groups. If all 17 outcomes were voted into the Core Domain Set then this could potentially mean that all clinical trials would have to include at least 17 different measurement instruments. The Study Team were concerned that this was just not feasible for clinical trial sites, nor ethical in terms of burden placed on those patients who would have to complete them all. The consensus meeting therefore started with a discussion and vote on the scope of the agenda (Q1, Table 1). It was agreed that the discussion be constrained to the 17 outcomes, and that the goal should be to reduce these down to a Core Domain Set of no more than 5 outcomes. Remember that this Core Domain Set would *always* be measured in *every* clinical trial (at least before and after the intervention), but investigators would be free to add other outcomes as they wish.

First round: Top and bottom selections proposed by each subgroup

Participants were divided into two subgroups (n=8, n=8). Individuals in each subgroup had been asked in advance of the workshop to choose their top three outcomes from the list of 17. The combined total of these votes was then used to lay out cards (each containing one outcome name and description) on a table, ordered from the greatest number of votes at the top downwards.

Green table The combined votes for the subgroup facilitated by Harriet gave the following order:

Tinnitus intrusiveness (n=5), Tinnitus loudness (n=4), Concentration (n=3), Impact on social life (n=3), Quality of sleep (n=4), Annoyance (n=1), Anxiety (n=1), Coping (n=1), Tinnitus unpleasantness (n=1), Treatment satisfaction (n=1)

Orange table The combined votes for the subgroup facilitated by Deborah gave the following order:

Difficulties getting to sleep (n=4), Tinnitus loudness (n=3), Tinnitus intrusiveness (n=3), Concentration (n=3), Ability to ignore (n=2), Annoyance (n=2), Depressive symptoms (n=2), Adverse reaction (n=1), Anxiety (n=1), Confusion (n=1), , Coping (n=1), Treatment satisfaction (n=1), Treatment satisfaction (n=1)

The goal for each subgroup was to initially discuss and jointly agree which domains are sufficiently critical and important to make it into the Core Outcome Set (maximum = 5) and which are **not** sufficiently critical to include in every clinical trial. To facilitate discussion, the cards could be moved around the table and reordered according to the majority views of the subgroup. Two pieces of string marked the cut-offs for the top and bottom selections proposed by each subgroup.

Results from the two subgroups were first pooled to create three categories according to those selections:

Outcomes that were included in the top ‘set’ by both subgroups were: Concentration, Quality of sleep, Tinnitus loudness, and Tinnitus intrusiveness.

Outcomes included in the top set by one subgroup but not the other, or where there were mixed opinions within a subgroup were: Ability to ignore, Annoyance, Anxiety, Depressive symptoms, Coping, Impact on individual activities, Impact on social life, Impact on work, and Treatment satisfaction.

Outcomes that both subgroups selected as **not** critical and important for every clinical trial of a drug intervention were: Adverse reactions, Confusion, Difficulties getting to sleep, and Tinnitus unpleasantness.

This selection led to full group discussion and then voting on Q2 (Table 1). 100% of the group agreed to set aside Adverse reactions, Confusion, Difficulties getting to sleep, and Tinnitus unpleasantness from the Core Domain Set. Reasons given can be found in Table 2.

The subgroup on the Orange table came up with the suggestion that another concept might better capture feelings associated with both anxiety and depressive symptoms. Derek presented data from the Delphi survey for another outcome domain called 'Mood' which is described as a general sense of well-being, ranging from feeling very low or negative to very positive. This had not made it to the top 17, but had reached consensus for two of the stakeholder groups (Scoring 7-9: Members of the public = 76%, Healthcare professionals = 60%, Clinical researchers = 92%, and Commercial representatives and funders = 33%). In a previous consensus meeting, participants had recommended that the concept of mood could be defined to capture the concepts of 'anxiety' and 'depressive symptoms' since it refers to a broader sense of psychological well-being. A full group discussion ensured with the result that 'mood' was included for further consideration (see Q3, Table 1). This gave 14 outcomes for further discussion and voting.

Second round: Top and bottom selections proposed by each subgroup

Before the full group separated into subgroups, the facilitator clarified the scope of the Core Outcome Set for drug trials in tinnitus. It was reiterated that issues about distinguishing primary, secondary and exploratory outcomes fall outside the scope of this workshop. Nevertheless, it was recognised that the main purpose of the drug development process is to develop a treatment for tinnitus, typically with a lesser purpose to treat the consequences of tinnitus. There were a number of strong opinions that the Core Outcome Set should reflect the search for a cure. Related to this, it was acknowledged that there are different forms of tinnitus, and so it is likely that different kinds of drugs are needed (although at this point the group conceded that there are no biomarkers for tinnitus).

The next goal for each subgroup was to discuss and jointly agree no more than 5 outcomes for further consideration. To facilitate discussion, the cards could be moved around the table. This time only one piece of string marked the cut-off for the top and bottom selections proposed by each subgroup. The results from both subgroups were pooled to cluster the outcomes into three categories.

Outcomes that were included in the top 'set' by both subgroups were: Tinnitus loudness, Tinnitus intrusiveness, and Quality of sleep. However, there remained some dissenting opinions for Quality of sleep.

Outcomes included in the top set by one subgroup but not the other were: Mood, and Impact on individual activities

Outcomes that both subgroups judged were **not** to be critical in every clinical trial were: Annoyance, Ability to ignore, Anxiety, Concentration, Coping, Depressive symptoms, Impact on social life, Impact on work, and Treatment satisfaction.

This selection led to full group discussion and then voting on Q4 (Table 1). The decision was to set aside these outcomes from the Core Domain Set. Reasons given can be found in Table 2. This left 5 outcomes for individual voting.

Voting on the remaining individual domains

Table 1 Q5-9 shows the voting scores for Impact on individual activities, Mood, Quality of sleep, Tinnitus loudness, and Tinnitus intrusiveness.

Loudness and intrusiveness both received unanimous support (100%). None of the other three reached consensus criterion of 70% agree. Instead, the group recognised that key aspects of the negative impact of tinnitus on individual activities (and possible other aspects of daily life) should be captured at least by tinnitus intrusiveness which they felt refers to a various different ways in which tinnitus can negatively affect activities or capabilities. There were also recommendations for further discussion about whether Mood is important to consider with respect to the trial design instead of the outcome. For example, Mood could be considered at the point of patient selection into a trial either as an eligibility criterion, or to stratify allocation into treatment arms since it was broadly recognised that aspects of psychological well-being can substantially influence responsiveness to a drug treatment for tinnitus. Another major comment that was made with respect to trial design was whether hyperacusis should be considered. While it is different from tinnitus intrusiveness, the presence of hyperacusis as well as tinnitus could substantially influence responsiveness to a drug treatment for tinnitus.

Table 1. Questions posed and votes cast during the consensus meeting

	Agree	Disagree	Unsure
Q1) Today's discussion will focus on the 17 outcome domains that all 4 groups (Members of the public with tinnitus, Healthcare professionals, Clinical researchers, and Commercial representatives and funders) agreed to include in the COS. The remaining 51 domains will not be discussed. Do you agree?	94	6	0
Q2) These outcome domains are not critical to be measured in every clinical trial for drug-based tinnitus treatment. Do you agree? 'Adverse reactions' 'Confusion' 'Tinnitus unpleasantness' 'Difficulties getting to sleep'	100	0	0

Q3) Do you agree that 'Mood' should be a construct that replaces aspects of Anxiety and Depressive symptoms?	81	0	19
The group agreed that it was acceptable to set aside 'anxiety' and 'depressive symptoms' if these feelings were captured by 'mood' which describes a broader sense of psychological well-being.			
Q4) These outcome domains are not critical to be measured in every clinical trial for drug-based tinnitus treatment. Do you agree? 'Annoyance 'Ability to ignore 'Anxiety' 'Concentration' 'Coping' 'Depression' 'Impact on social life' 'Impact on work' 'Treatment satisfaction'	88	6	6
The person who disagreed felt that quality of life (e.g. impacts on social life/work) should be considered.			
Q5) Do you agree that 'Impact on individual activities' is critical to be measured in every clinical trial for a drug-based tinnitus treatment? ***Decision: No consensus, exclude***	69	31	0
Q6) Do you agree that 'Quality of sleep' is critical to be measured in every clinical trial for a drug-based tinnitus treatment? ***Decision: No consensus, exclude***	38	38	25
Q7) Do you agree that 'Tinnitus intrusiveness' is critical to be measured in every clinical trial for a drug-based tinnitus treatment? ***Decision: Consensus 'in' reached - include***	100	0	0
Q8) Do you agree that 'Tinnitus loudness' is critical to be measured in every clinical trial for a drug-based tinnitus treatment? ***Decision: Consensus 'in' reached - include***	100	0	0
Q9) Do you agree that 'Mood' is critical to be measured in every clinical trial for a drug-based tinnitus treatment? ***Decision: No consensus, exclude***	25	69	6

Table 2. Major comments raised during the workshop

Outcome domain reaching consensus in the Delphi	**Comments in favour**	**Comments against**
Ability to ignore	• N/A	• 'Ability to ignore' is much less ambitious than 'Intrusiveness'. The first one just suggests helping people to manage, the second suggests seeking a cure.

		• Can be interpreted differently by different people.
Adverse reaction	• Agreed important to measure for drug trials.	• It is already a necessity by the regulatory authorities for any properly conducted double-blinded randomised pharmacological trial and so on that basis it seems pointless to include here as a COS.
Annoyance	• Concept of annoyance can be easily explained and interpreted. • Can have an impact on a variety of activities (e.g. social interaction)	• Felt to be covered by other domains (e.g. intrusiveness). • Believed subjective and personality-dependent. • Some considered this too 'mild' or 'trivial'.
Anxiety	• Both anxiety and depressive symptoms could be captured together as feelings related to mood, which is more about having a sense of well-being than having a psychiatric classification.	• Patients are often in a state of anxiety, which is separate from depressive symptoms, but may be related. • Anxiety may be a secondary consequence of tinnitus. • Can be treated with other drugs.
Concentration	• N/A	• Concentration problems are not specific to tinnitus. • Some felt this was covered adequately by 'tinnitus intrusiveness'.
Confusion	• N/A	• Too general, may not necessarily be specific to tinnitus.
Coping	• N/A	• Coping techniques felt to be less relevant to pharmaceutical interventions.
Depressive symptoms	• Both depressive symptoms and anxiety could be captured together as feelings related to mood, which is more about having a sense of well-being than having a psychiatric classification.	• Patients often experience depressive symptoms, which is separate from anxiety, but may be related. • Both could be captured together as feelings related to mood, which is more about having a sense of well-being than a psychiatric classification. • Depressive symptoms may be a secondary consequence of tinnitus. • Can be treated with other drugs.
Difficulties getting to sleep	• N/A	• Difficulties getting to sleep can be part of a hierarchy of sleep problems that is better captured by 'quality

		of sleep'. Quality of sleep is more encompassing. • Not all people with tinnitus have problems with sleep and a good core outcome will be relevant to everyone.
Impact on individual activities	• Recognises the framework of the World Health Organisation (i.e. activity limitations) • Can be sensitive to change in the short term (i.e. during a clinical trial) • Indicator of well-being. • More relevant vs. 'impact on social life' as it covers both introvert and extrovert personality types.	•
Impact on social life	• Recognises the framework of the World Health Organisation (i.e. societal participation).	• Tinnitus can only partly influence this and it may be more to do with the number of social interactions the individual has. • Some doubt that patients could show a change on this parameter over a short time period (i.e. during a clinical trial). • More relevant to 'extrovert' vs 'introvert' personality type.
Impact on work	• N/A	• Not applicable to those who are in education, retired, or otherwise not working
Mood (replaced Anxiety and Depressive symptoms)	• Indicator of patient quality of life (QoL) (it was discussed that regulatory bodies typically seek evidence of QoL benefit in trials).	• Mood too unspecific. Implies emotional issues that may not be specific to the tinnitus. Can be influenced by external factors. • Can be treated with other drugs. • Could be more useful as a stratification tool when interpreting data from clinical trials.Impact on QoL can be captured by 'intrusiveness'
Quality of sleep	• Quality of sleep captures all different aspects of tinnitus-related sleep complaints. • Disruption of sleep quality described as a "cornerstone" complaint associated with tinnitus. • Can also be a root factor of tinnitus intrusiveness and loudness so therefore	• Not all people with tinnitus have problems with sleep and a good core outcome will be relevant to everyone. • May weaken the power of the trial because it is not common to all sufferers.

	important to capture to understand changes in these aspects.	
Tinnitus intrusiveness	• Tinnitus intrusiveness is related to loudness, but distinct from it. It's a target for developing a tinnitus cure based on pharmacology. • Intrusiveness captures aspects of tinnitus that are more relevant than loudness alone. • Relatively broad domain that is sensitive to the impact of tinnitus on a variety of areas of life/ quality of life.	• A few believe this is a sub-domain of loudness (i.e. you cannot have intrusiveness without loudness). • It may be problematic to explain the concept of intrusiveness consistently across different languages and cultures.
Tinnitus loudness	• Tinnitus loudness is all about the sensation of the sound. It's the direct target for drug treatments. Fix this and you fix everything else. • Considered a 'semi-objective' measure so therefore reliable and critical to include alongside wholly 'subjective' domains. • It needs to be measured with intrusiveness since they interrelate but they need to be kept separate.	• Some acknowledged that a change in loudness may not always reflect a tangible benefit on the patient's life.
Tinnitus unpleasantness	• N/A	• Some controversy about 'unpleasantness' since what is deemed to be unpleasant is quite individual and may be more driven by personality. • Individual aspect of the construct makes it hard to come up with a reliable measure. • Some doubts that a drug therapy can change degree of 'pleasantness' (i.e. believed unlikely to change tinnitus quality or pitch).
Treatment satisfaction	• N/A	• Not tinnitus specific.