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**Clinical Protocol HDEC revised for 21.2 PMCF Tinnitus Study at University of Auckland**

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###### The following table should be updated every time the document is modified. The table includes the date, the initials of the subject(s) who modified the document, and a short description of the modification.

Change log:

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| **Revision** | **Date** | **Initials** | **Modification/action** |
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| 1.1 | 2021-05-17 | MOBM | Reviewed with comments. |
| 1.2 | 2021-05-18 | SCAL | Reviewed with comments. |
| 1.3 | 2021-05-20 | JOSJ | Addressed reviewers’ comments and comments from PI (sentexternally to JOSJ, because PI is without access to documentum) |
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# Definition and abbreviations

|  |  |
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| **Term** | **Definition** |
| Auckland | Shortened name for University of Auckland/research site |
| DNN | Deep Neural Network |
| DSLv5 | Desired Sensation Level, version 5. Amplification rationale developed by theUniversity of Western Ontario |
| FDA | Food and Drug Administration |
| GCP | Good clinical practice |
| HIG | Demant Hearing Instruments Group |
| HIPAA | Health Insurance Portability and Accountability act of 1996 (HIPAA) |
| IOI-HA | International Outcome Inventory for Hearing Aids |
| MPO | Maximum Power Output |
| MSI | MoreSound Intelligence (Oticon More noise reduction and directionalityfeature) |
| NAL-NL2 | National Acoustics Laboratory-Non-Linear version 2. Amplification rationaledeveloped by the National Acoustics Laboratory, Australia |
| Oticon More | Oticon More 1 miniRITE R |
| PTA4 | Pure tone average of the hearing loss in dB HL for the frequencies 0.5, 1, 2and 4 kHz |
| PMCF | Post Market Clinical Follow-Up |
| REAR | Real Ear Aided Response |
| REM | Real Ear Measurement |
| RITE | Receiver-in-the-Ear |
| SSQ | Speech-Spatial-Quality questionnaire |
| SSQ-12C | Speech-Spatial-Quality questionnaire Comparison version |
| UA | University of Auckland, New Zealand |
| UCL | Uncomfortable Loudness Level |

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**Roles and stakeholders**

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# Useful links

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# Introduction

This document describes the protocol for an external clinical research study to be carried out at the University of Auckland in New Zealand investigating the Tinnitus SoundSupportTM feature. In the 20.2 PMCF Plan, a gap was identified relating to this feature and planned to be followed up on in the product release 2021. This study aims to fulfil the identified gap by providing a targeted investigation on the Tinnitus SoundSupportTM feature, which is intended to provide temporary relief for patients suffering from tinnitus, to satisfy EU-MDR regulation requirements

This document is the Demant internal protocol version. The study consists of a field trial for the Oticon More 1 miniRITE R (Oticon More) with an activated Tinnitus SoundSupportTM feature on patients suffering from tinnitus symptoms.

The primary purpose of the study described in this protocol is related to fulfilling EU-MDR 2017 / 745 requirements to assess the mentioned identified gap in the clinical evidence that shall be covered in a post- market clinical follow-up (PMCF) investigation (for further details, refer to the 21.2 PMCF Plan).

The clinical research related to this purpose aims to assess the clinical performance of Oticon More and Tinnitus SoundSupportTM amongst experienced by new hearing aid (HA) users. The data will also be used to ensure the continued acceptability of the benefit-risk profile of the Tinnitus SoundSupportTM feature.

Therefore, the research background is related to clinical performance outcomes that support performance endpoints of the hearing-impaired user with HAs as listed in the Instructions for Use (IFU) for Oticon More and for the Tinnitus SoundSupportTM. These are described in section 1.1 as well as in the 21.2 PMCF plan.

The study has a secondary purpose of investigating potential added clinical benefits from safety and performance as described in the intended use for Tinnitus SoundSupportTM, which goes beyond the scope of PMCF. This part of the study aims to investigate the use of advanced features in hearing aid treatment for tinnitus patients, focusing on exploring possible benefits with the MoreSound Intelligence feature and Transient Noise Reduction, as well as exploring effects of individualizing the Tinnitus SoundSupportTM.

## Research background

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| Budget Agreement | Link to budget agreement and contract |
| UA Institutional Review Board Application | Link to IRB |
| External Protocol | N/A |

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The primary goal for this study is to assess the clinical performance (as described in the Instructions for Use) of the Tinnitus SoundSupportTM (TSS) feature to examine if it achieves the intended purpose of *generating sounds of sufficient intensity and bandwidth to provide temporary relief for patients suffering from tinnitus*. Because the TSS feature is part of hearing aid treatment, the study will also assess the clinical performance of the Oticon More to examine if the hearing aids achieve the intended purpose of a) *amplifying and transmitting sound to the ear,* to b) obtain the clinical benefit of *providing better speech understanding to help ease communication with the aim of improving quality of life*.

The clinical performance of TSS and Oticon More will be investigated by using both objective and subjective outcome measures in a partly randomized concurrent-controlled trial study design. The design will combine standard clinical practice and a field trial, in which subjects are their own control and randomization refers to the allocation of intervention order.

The intended purpose will be assessed by first investigating the hearing aid treatment, thus (a) *the audibility of speech achieved through amplification compared to non-amplified audibility with objective measurements*, and (b) *the ability to understand speech administered by self-reported listening benefit and quality of life.* When the hearing aid fitting has been established, the intended purpose of the TSS will be assessed via a) *the audibility of the TSS default and individualized output with objective measurements* and

b) *the effect of TSS on subjective tinnitus severity*.

This study will also explore possible effects on preference and satisfaction with the hearing aids for tinnitus patients when applying different settings in the features *MoreSound Intelligence* (MSI), *Transient Noise Reduction* (TNR), and audibility differentiation in the TSS output by using data logging and self-reporting.

#### Background for hearing aid investigation

The speech intelligibility index (SII) (ANSI S3.5 1997 R2007) is a measure ranging from 0.0 and 1.0 (also expressed in percentage from 0% to 100%) that quantifies the proportion of audible and usable speech information for a listener. Thus, SII = 0 means no speech information is available (i.e., audible, usable) to improve speech understanding, whereas SII = 1 implies all speech information is audible and usable. The SII can be related to the pure tone average of the hearing loss in decibels hearing loss (dB HL) for the frequencies 0.5, 1, 2 and 4 kHz (PTA4) for certain normative ranges for achieved aided SII, which have been established in publications (Folkeard et al, 2018; Dao et al, 2020). By using clinical best practice and verifying the audibility achieved by amplification by conducting real ear measurements (REM), the unaided SII and aided SII can be measured. Consequently, the SII benefit can be calculated, and it can be investigated if the achieved SII is within the normative range for aided SII (shown as regression lines with their 95% confidence intervals) (Dao et al, 2020), delivering an acceptable audibility of speech in relation to the hearing aids’ benefit-risk profile. The referenced publications have investigated fittings based on the DSLv5 amplification rationale. However, in this study, the fittings will be based on the NAL-NL2 rationale because NAL-NL2 is the rationale most often applied in the Auckland research clinic. The difference between NAL-NL2 and DSLv5 for adults for 65 dB level is within 5 dB (Bertozzo et al, 2019) and the SII based on NAL-NL2 is therefore expected to be at the lower end of the abovementioned published normative range.

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These two outcome measures (aided SII and SII benefit) objectively assess one aspect of the clinical performance of Oticon More (i.e., the amplification and transmission of sound to the ear). These objective measurements are complimented by the subjective, individual perception to get the full perspective of the intended purpose; for this part, hearing loss-related self-reported outcome questionnaires will be used. The validated *Speech, Spatial, and Quality of Listening Questionnaire* (SSQ49) (Gatehouse and Noble, 2004) measures a range of hearing disabilities across domains and can be used as an instrument to evaluate hearing aid intervention. Furthermore, to investigate the overall subjective outcome and impact on quality of life, the *International Outcome Inventory for Hearing Aids* (IOI-HA) (Arlinger et al, 2017; Heuermann et al. 2005; Cox et al. 2000; Cox et al. 2002; Cox et al. 2003) will be used, assessing the domains *daily use, benefit, residual activity limitations, satisfaction, residual participation restrictions, impact on others*, and *quality of life*.

#### Background for Tinnitus SoundSupportTM investigation

The TSS feature is in the category of ‘sound therapy’ approach for tinnitus treatment. Because the TSS is a special focus beyond the standard PMCF studies, a literature review was made on the existing evidence to create a starting point for the method decisions for this study.

*Literature review for tinnitus sound support*

Evidence exists that supports a clinical benefit of sound therapy by obtaining relief from tinnitus of the patient, and the evidence shows that the clinical benefit exceeds the risk of harm due to noise exposure from the sound therapy support (McFadden, 1982; Hazell et al., 1985; Tyler & Bentler, 1987).

In a literature review, several studies were found to have compelling or strong evidence and will be emphasized in this section. The evidence covers the focus areas of relief of tinnitus.

Dos Santos et al (2014) evaluated 49 patients using a blind randomized clinical trial. One patient group received a hearing aid combined with tinnitus relief sounds and a reference group received amplification alone. Both groups experienced a significant reduction in tinnitus annoyance as assessed using the Tinnitus Handicap Inventory (THI). The difference between groups, however, was not statistically significant. Henry et al (2017) found a clinically significant improvement in reaction to tinnitus for a majority of participants in their three intervention groups: receiver-in-the-ear hearing aids, the same hearing aids with a sound generator, and a custom-made deep fit hearing aid. The difference between groups, however, was not statistically significant using the Tinnitus Functional Index (TFI). In another study, participants were assigned to either an experimental group (combination instrument with tinnitus sound enabled) and a control group (combination instrument with tinnitus sound disabled). Both groups revealed significant improvement, as indicated by reductions in mean TFI index scores (Henry et al. 2015). Differences between groups at 3 months were not statistically significant. These results suggest that the use of hearing aids alone or hearing aids plus the use of sound generators both provide significant benefit with respect to alleviating effects of tinnitus. Whether one or the other type is preferred may be due to personal preferences.

Bauer et al (2017) found significant improvements in tinnitus impact after both Tinnitus Retraining Therapy (TRT) and a control group with standard care therapy, with a larger treatment effect obtained in the TRT group. Lasting therapeutic benefit was evident at 18 months in both groups. Both treatment groups received acoustic enrichment through the use of binaural combination hearing aids, and both received counselling, albeit not identical counselling (either TRT or standard care). A strength of the Bauer et al (2017) lies in the enrolment in the treatment arms of the randomized controlled trial (RCT) that was balanced for variables that might be expected to impact treatment (e.g., severity of tinnitus, gender).

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Two studies showed a fair evidence in this area as well. Henry et al. (2016) made a multisite RCT evaluating TRT and tinnitus masking (i.e., sound therapy) with mostly combination instruments found that TRT (and tinnitus masking) reduced tinnitus severity over a period of 18 months. The attention-control group only received amplification and was significantly better than a waiting-list control group, but not significantly different from the treatment groups TRT and TM. This study was ambitious in design (multisite and RCT), but the treatments was not completely balanced and homogeneous with regards to both treatment (combination instrument) and control group (amplification).

Barozzi et al. (2017) evaluated the effect of the sound generators power spectrum of a combination instrument in order to increase the effectiveness and acceptability of the tinnitus. The sound generator of a combination instrument usually offers more flexibility than a conventional white noise generator. They found a significant reduction in self-reported tinnitus handicap in both groups following 3 and 6 months after fitting, assessed by the THI. However, no significant difference was found between the two groups using one or the other type of sound.

Sweetow and Sabes (2010) tested a group of hearing impaired where ten out of 14 were non-hearing aid users. They observed their tinnitus annoyance over a period of 6 months when using a combination instrument with different fractal sounds. They found significant reduction in both THI and Tinnitus Reaction Questionnaire (TRQ) score after 6 months of therapy. Since most of the group did not wear hearing aid prior to the fitting, it cannot be determined if the tinnitus annoyance reduction was due to amplification alone, or the use of sound therapy.

Korres et al (2010) used a tinnitus group where 88% were hearing impaired who received a combination instrument. They concluded that at a follow-up one year post-initial treatment, the reduced tinnitus annoyance level was still valid. However, the authors assign the effect of the reduction to the TRT protocol and not to the amplification per se.

In a pilot study, Sereda et al (2017) evaluated physical aspects and noise options rather than evaluating the sound therapy itself. They found a wide variety in individual preferences, both across participants and across listening situations. They found that the ocean sound options did not mask tinnitus to the same extent as other therapeutic sounds, but rather provided a distraction and/or aided relaxation. In conclusive remarks, they point to adequate counselling behind sound therapy and the role of different sound types in providing tinnitus relief.

The results of Henry et al (2015, 2016, 2017), dos Santos (2014), Barozzi et al (2017), Bauer et al. (2017), Sweetow and Sables (2010), and Korres et al. (2010) are consistent with the body of studies that have investigated the use of combination hearing aids for tinnitus management (Tutaj et al. 2017).

These studies used combination instruments from different manufacturers, but the body of evidence show the general trend that using combination instruments result in significant improvement in the primary tinnitus outcome measure. This collective result is encouraging, given that the studies combine multiple approaches to manage tinnitus. Two important components in the different approaches are the management program and the sound type. The dominant therapy protocol used in the clinical setting is TRT. One of the main differences between management programs is related to the level of the noise used in the tinnitus therapy. Tinnitus masking (TM) aims to provide immediate relief from tinnitus, achieved by complete masking (if possible), without setting the masking sound to an uncomfortable level (Henry et al. 2006). Other approaches, such as TRT and Zen Therapy, recommend setting the noise at mixing point or below the level of tinnitus, arguing that habituation to the tinnitus symptom is not possible when tinnitus is completely masked, or the perception is markedly changed (Jastreboff & Jastreboff 2000). However, based on the literature review, it is not clear whether one management approach produced better outcomes than

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another. Of all eight retrieved tinnitus relief studies, there was a mix of different protocols: three were TRT, two were Progressive Tinnitus Management (PTM), one was Zen, one was both TRT and TM and one was a mix of TM and TRT protocols. This indicates that all three approaches provide some degree of relief. This was also concluded in a study by Tyler et al. (2012), where they showed that TRT and TM were equally effective for the habituation of tinnitus.

When it comes to the preference to sound type, there is a lack of studies investigating the more individualized sound therapy approach with combination instruments. Sereda et al. (2017) concluded that the availability of different sounds in the same combination instrument could play a role in the everyday life of the user, from a more masking paradigm towards distraction and/or aided relaxation, based on the individual’s situation.

In 2019, a multidisciplinary European guideline was published (Cima et al, 2019). The guideline found sound therapy to be useful for acute relief purposes (as is stated in the IFU for the TSS) but concluded no recommendation for sound therapy based on lack of high-level evidence on effectiveness. The guideline did, however, find evidence for safety for sound therapy.

Conclusively, the implications suggest TSS to be a safe feature for temporarily relieving tinnitus symptoms, but there are no guidelines for which sound types to fit and how the output level should be adjusted.

In addition to investigating the benefit of the TSS, this study will also examine whether advanced, personalized hearing aid features in the Oticon More hearing aids can be used both on their own, and in combination with the TSS, for tinnitus patients. The MSI and TNR features both offer noise reduction and possibilities for more comfort, which may benefit tinnitus patients (for example, if a patient is more prone to noise sensitivity, these features may help in those situations). This study will therefore also investigate if any trends can be found in preferences for feature settings in tinnitus patients.

*Brief descriptions for tinnitus methods and tools*

In this section, a brief description of the clinical tools relating to tinnitus that will be applied in this study are described.

* + - * **Tinnitus Handicap Inventory** (Newman et al, 1996) is a self-report questionnaire with 25 questions to which patients answer either “*yes”* (4 points), “*sometimes*” (2 points), or “*no*” (0 points). These questions help identify where their tinnitus cause problems in their daily life and activities; the total sum of scores categorize the tinnitus into severity ranging from very mild to catastrophic.
			* **Tinnitus Functional Index** (Meikle et al, 2012) consists of 25 items and eight subscales, where a 0– 10-point Likert scale measures the response to each item. The subscales address the domains where the tinnitus impacts the patient.
			* **Client Oriented Scale of Improvement in Tinnitus** (COSIT) (Searchfield, 2019) is a modified version of the Client Oriented Scale of Improvement (COSI) (Dillon et al, 1987) that is used in setting goals for hearing aid treatment. The COSIT is an open-ended questionnaire in which the patient lists five improvement goals they hope to realize with the therapy, and which assists the clinician in measuring the success of tinnitus therapy.
			* **Depression, Anxiety, and Depression Scales** (DASS) (Lovibond & Lovibond, 1995) is a self-report instrument that measures the dimensions of depression, anxiety, and stress separately. The patient rates each item (total 21 items) on a 4-point scale of how much each statement applies to them.

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Based on the scores, the level of psychological stress is categorized on severity ranging from normal to extremely severe.

* + - * **Tinnitus Sample Case History Questionnaire** (TSCHQ) (Langguth et al, 2007) is a 35-item, standardized questionnaire that clinicians can use to obtain tinnitus patients’ case history.

The method for conducting the research outcomes in the above sections are described in detail in section 2.

## Research questions

*Hearing aid investigation (excluding TSS)*

For experienced users

* + - Q1. Is the clinical performance of Oticon More same or better in comparison to own hearing aid for experienced users?
		- Q2. Does the clinical performance of Oticon More based on REM-controlled verification using NAL- NL2 prescription deliver comparable results to published data?
		- Q3. Is the self-reported listening performance measured by SSQ-12C same or better with Oticon More than with own hearing aids in at least one of the four listening programs implemented?
		- Q4. Is the self-reported benefit of hearing aid treatment including a question related to quality of life measured by the IOI-HA same or better with Oticon More than with own hearing aid in at least one of the two listening programs implemented?

For new users

* + - Q5. Is the clinical performance of Oticon More provided to new users better than unaided?
		- Q6. Does the clinical performance of Oticon More based on REM-controlled verification using NAL- NL2 prescription deliver comparable results to published data?
		- Q7. Is the self-reported listening performance measured by SSQ-12C better with Oticon More than unaided in at least one of the four listening programs implemented?
		- Q8. Is the self-reported benefit of hearing aid treatment including a question related to quality of life measured by the IOI-HA better with Oticon More than unaided in at least one of the four listening programs implemented?

*TSS Investigation*

* + - Is the clinical performance of TSS same or better in comparison to current tinnitus solution (if any)?
		- Are there any trends in the individually preferred output level for TSS compared to the default output (expressed by default output in dB – preferred level in dB)?

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* + - Are there any trends in the individually preferred sound type for TSS?
		- Is the self-reported tinnitus severity as measured by the THI and TFI same or better after 3 months’

use of TSS?

* + - How do tinnitus patients use the four different programs as measured by data-logging and interviewing?
		- Are there any trends in preferred settings of MSI and TNR for tinnitus patients?

## Expected outcomes and hypotheses

*Hearing aid investigation (excluding TSS) – PMCF focus*

1. The amplification with Oticon More will provide an SII benefit higher than 0 based on the calculation (minimum requirement for amplification outcome):

###### SII (aided) – SII (unaided) = SII (benefit) > 0

1. Oticon More will provide an aided SII for conversational speech level (65 dB) for PTA4 within the normative range for aided SII (95% confidence intervals, Dao et al, 2020) based on a REM-controlled verification and match to NAL-NL2 prescription rationale.
2. Self-reported listening performance for Oticon More as measured by the SSQ-12C will be **similar or significantly better** than own hearing aids as measured by the SSQ-12 (baseline, own devices) and SSQ-12C, or **significantly better** than unaided for new users (SSQ-12B).
3. Subjective overall outcomes and impact on quality of life for Oticon More will be **similar or significantly better** for experienced users, and **significantly better** for new users, different as assessed by the IOI-HA.

*TSS Investigation – PMCF focus*

1. The output level of the TSS will by default be above hearing threshold (i.e., audible) as measured by REM
2. The THI and TFI scores will be **similar or significantly better** after three months’ use of the Oticon

More with an activated TSS program

*TSS Investigation – experimental focus*

1. The tinnitus severity (measured by THI and TFI) will influence the preferred output level of the TSS (more severe tinnitus leads to higher output level)
2. Higher tinnitus severity (measured by THI and TFI) will lead to more frequent use of the program with enhanced MSI and TNR settings compared to a default amplification program
3. Tinnitus patients will prefer the TSS program with enhanced MSI and TNR settings compared to the TSS program with default MSI and TNR settings.

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# Procedures and methods

## Human subjects

This study will aim to recruit between 30-40 participants that meet the below criteria.

### Inclusion and exclusion criteria

Inclusion criteria:

* + - * Adults from 18 years of age and above
			* New and experienced hearing aid users with a symmetric slight (16 dB HL\*1) to moderately severe (70 dB HL\*) binaural symmetric (PTA4 difference between ears ≤ 15 dB) sensorineural or mixed flat or sloping hearing loss (see hearing loss ranges below in table 1).

***Table 1 Hearing loss ranges as defined by ASHA\****



* + - * Able and willing to use hearing aids
			* Fitting level for the 60- or 85-dB speaker and domes (OpenBass Dome, Bass Dome Double, Power Dome or GripTip), or custom molds including all types and configurations of hearing loss.
			* Self-reported tinnitus symptoms within the mild to severe category for at least 6 months Exclusion criteria:
			* Objective, pulsatile tinnitus

1 \* The hearing loss degrees from ASHA are related to PTA3

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### Terms of participation

Test persons will provide informed consent and be compensated according to the Institutional Review Board approval obtained by Auckland. The hearing aid devices used in this specific study will be provided for free.

## Test articles - hearing aids, software, and devices

* Commercially Oticon More 1 miniRITE R

The HAs will be coupled to the prescribed settings provided by the Genie 21.2 or more newly updated fitting software and individually adjusted to match NAL-NL2 targets using a REM based procedure. This protocol is based on following international state-of-the-art principles for best practice for hearing aid fittings (i.e., verifying target match) as well as standards for good clinical practice (i.e., by using SMART- TRIAL software for data reporting). Noah Link Wireless is the required programming device.

## Test setup and procedure

* + 1. ***Task and outcome measures***

All the clinical data reporting will be collected and managed via the clinical data collection cloud service, SMART-TRIAL Suite. SMART-TRIAL ([www.smart-trial.com](http://www.smart-trial.com/)) is a documented software cloud service providing electronic Case Report Forms (eCRF) for clinical investigations and PMCF that has been validated and verified, having been developed in accordance with safe design and software maintenance standards for medical software (IEC 62304) and is controlled via SMART-TRIAL’s quality management system (ISO 13485). By using SMART-TRIAL cloud service, the clinical data reporting is compliant with relevant standards and laws for electronic data reporting and data privacy (FDA CFR-21 Part 11; HIPAA), as well as good clinical practice (GCP) (ISO 14155).

The main steps of the study planned are the described below. Figure 2 shows a schematic study design.

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Off-line pre-

visit

Study webpage with

study explanation, screening, and sign- up available where participants give consent

Visit 1

* SSQ12
* COSIT

- THI

-TFI

-DASS

- Counseling on hearing aid use and/or tinnitus (if applicable)

- TSCHQ

* Fitting of Oticon More (REM

verification, SII calculation): P1

* Copying settings to P2, P3, P4
* Adjusting P2, P3, P4 with TSS, MSI, TNR features
	+ Fine-tuning (if applicable)
	+ Counselling on how to use the programs

Field 1 (3 months)

Use Oticon More in daily life,

switching programs at will

* Clinical or Remote follow-

up after 3 weeks

* Adjusting program order to suit preference
* Optional additional clinical

or Remote visit

Visit 2

- SSQ-12C (for experienced

users) or SSQ-12B (for new

users)

-IOI-HA

Interview on program use

and data-logging

-THI

-TFI

-DASS

***Figure 1 Schematic overview of study design***

* + - 1. *Clinical practice and field trial*

New and experienced HA users with chronic tinnitus will be recruited at the Hearing and Tinnitus Clinic in Auckland2 via local advertisement for the study and through the clinic’s own database of research participants and clinical pool of patients. The study consists of three clinical visits, where visit 1 comprises of a tinnitus and hearing assessment and a hearing aid fitting. Following this, subjects wear the devices for a three-month trial, in which a clinical follow-up visit is scheduled after three weeks, plus the option of an additional follow-up if needed. These one-or-two follow-ups are to adhere with normal clinical practice and to adjust the program order to suit the participant’s preference. Visit 3 is a follow-up and conclusive visit after the field trial of the Oticon More with TSS. The order of programs P2, P3, and P4 in the hearing aids will be randomized among test subjects to avoid an order effect of the experimental programs but will be adjusted at the three-week follow-up. This decision is based on clinical experience with patients not utilizing all programs when more than two programs are available.

2 For contact identification, refer to table **Roles and stakeholders**, Principal Investigators for Auckland

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* + - * 1. Visit 1

Hearing loss assessment is either available or will be assessed at the first clinic visit.

For the experienced users, the SSQ-12 will be administered to obtain a baseline of hearing aid satisfaction for subjects’ own hearing aids. The SSQ-12 will be handed out to the test subject in paper form and the clinician enters the answers from the paper-based results filled out by the test subject in the respective SMART-TRIAL form.

The clinician obtains the subject’s tinnitus history using the TSCHQ and enters the answers in the SMART-TRIAL form.

The subject fills out the THI and TFI questionnaires for self-reported tinnitus severity, and the clinician enters the scores in the SMART-TRIAL forms.

The subject fills out the COSIT questionnaire for identifying tinnitus treatment goals, and the clinician enters the answers in the SMART-TRIAL form.

Hearing aid fitting of Oticon More with an amplification program, a TSS program, and two additional tinnitus programs. The hearing aids will be fitted to the individual test subject under control of the receiver length and dome size/custom mold according to the patient’s ears, accordingly with New Zealand Audiological Society’s best practice guidelines, i.e., including performing real ear measurements for verification and target match. A fitting guide with specific step-by-step guidelines for the entire procedure is provided in English by the PMCF team to Auckland (see Fitting Guide for 21.2 PMCF Study Tinnitus SoundSupport).

REM AutoFit (Oticon) to NAL-NL2 to 65 dB

The Audioscan Verifit2 and Genie 2 REM Autofit allows for automatic REM verification and target match for Oticon devices with the possibility of manually adjusting subsequently. Using the automatic procedure, the hearing aids will first be analyzed for feedback risk (and then adjusted for minimizing feedback-risk if necessary). In the second step, REM Autofit measures the Real-Ear Aided Response (REAR) for soft, moderate, and loud speech levels, and automatically adjusts the frequency-specific overall gain settings to match the NAL-NL2 target for moderate (65 dB SPL) speech level. Finally, the maximum power output (MPO) will be measured using sweep tones and fine-adjusted manually (if necessary) with the goal of being below the Uncomfortable Loudness Level (UCL).

The unaided SII and the aided SII for soft, moderate, and loud levels will be reported via SMART-TRIAL Suite. Additionally, the Root mean square error (RMSE) calculated by Verifit2 to document achieved target match for the frequencies 0.5 (excluded for those with open fittings), 1, 2, and 4 kHz for soft, moderate, and loud levels will be reported via SMART-TRIAL Suite. The verified program settings (P1) will be copied to three more programs that create the amplification baseline for the TSS program (P2) and the two further experimental programs (P3 and P4).

The clinician activates the Tinnitus SoundSupport in P2 and selects the patient’s preferred sound type. Before fine-tuning, the clinician conducts a real-ear measurement of the sound pressure level in the ear canal to verify the audibility achieved by the **default output** of the selected relief sound. The clinician then fine- tunes the level according with patient’s preferences for sound level and conducts

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the real-ear measurement again on the **individually adjusted output** of the relief sound. The Verifit2 file is saved, and the clinician enters the output values in a table from 250-6000 Hz in the SMART-TRIAL form. Alternatively, the clinician may upload the screenshot from Verifit2 as shown with an example in figure 2 (where the orange line shows the default TSS output and the blue shows the adjusted TSS output, measured using Speech-live in Audioscan Verifit2).



***Figure 2 Example of TSS Output Default (orange) and Adjusted (blue), measured in Verifit2***

Using the individually adjusted output from P2, the clinician copies the TSS output to P3. For P3, the MSI and TNR features are set to their maximum settings.

For P4, the MSI and TNR features are set to their maximum settings (deactivating the TSS in this program).

If there is a need for any final fine-tuning, the clinician performs these and logs the changes in the SMART-TRIAL form.

The subject is counseled on using the hearing aid and the charger. Each program is discussed and a plan for when to use them is given to the subject:

P1 is the default program for general amplification that the subject will most likely use the most for everyday situations

P2 is the TSS program the subject should use as needed for tinnitus relief (most likely in quiet situations, when winding down, or when the tinnitus symptoms feel bothersome)

P3 and P4 should be used when tinnitus symptoms feel bothersome, but when the subject is not in a quiet situation, e.g., if they are at an office with some noise, in social situations, and so on. These two programs have enhanced noise reduction settings, and therefore require some level of disturbing sound to be effective.

P2, P3, and P4 are randomized in order for the first trial period to avoid an initial order effect. The programs will be named so the participants can

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easily identify when to use the programs. A plan for when to use which program during the first three weeks is made between the clinician and test subject. During these three weeks, one aim is to find an initial preference amongst the four programs – when subjects have then landed on some preferences, this program order can be re-arranged so the two most used programs are placed as P1 and P2.

Finally, the subject is handed out the respective IFUs, and a follow-up visit three weeks later is planned.

##### Field trial and clinical follow-up(s)

During the three-month trial period, the subject shall come in for a clinical (or remote) visit, where any necessary fine-tuning or adjustments are discussed and performed. Here, the clinician and subject discuss the program use and the clinician can look at data-logging. In agreement with the subject, the clinician re-arranges the program order if necessary (i.e., if the subject uses P4 the most, this program can be put as P1, and so on). If any changes are made from the first fitting, these changes are logged by the clinician in the SMART-TRIAL form.

##### Visit 2

The test subject fills out the SSQ-12C (if experienced user) or the SSQ-12B (if new user) and the IOI- HA questionnaires.

The clinician interviews the test subject on subjective experiences with the tinnitus management programs and any preferences are discussed, noted down, and logged in the SMART-TRIAL form. The clinician also retrieves the data-logging, from which program use can be derived and entered in the SMART-TRIAL form.

The test subject fills out the THI, TFI, and DASS, and the clinician enters the answers in the SMART- TRIAL form.

If the test subject wishes to purchase the devices, this option is given at a reduced cost. If the test subject does not wish to keep (i.e., purchase) the devices, the devices and all belonging accessories are returned to the Hearing and Tinnitus Clinic.

## 2.4 Data reporting and analysis

### 2.4.1 Statistical considerations

The statistical considerations for this study are based on sample size calculations for the variables that are tested in this study (i.e., the SSQ-12, SSQ-12C, and SSQ-12B for the hearing aid investigation, and the THI, and the TFI for the TSS investigation).

*Sample size estimation, statistical power analysis*

To estimate the minimum required sample size necessary for detecting a statistically significant result, the sample size for the abovementioned outcome parameters will be estimated. The parameter that gives the greatest sample size will be utilized to estimate the minimum required sample size with sufficient statistical power.

Cohen’s d (Cohen 1988) is a standardized method to estimate effect size and will be utilized in this study. An effect size (d) of 0.2 to 0.3 is considered a "small" effect, around 0.5 a "medium" effect, and 0.8 to infinity, a "large" effect.

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SSQ variants:

There are several SSQ variants: the original SSQ49 (Gatehouse and Noble 2004), the reduced SSQ12 (Noble et al. 2013), the comparative SSQ-B (**49** items aided benefit) and the shortened version with 12 items, SSQ- 12B, SSQ-C (comparing two conditions), and the SSQ12-C (comparative, shorter version with **12** items).

Several studies have been compared across SSQ variants by pooling the responses into the three dimensions of the test (Speech, Spatial, and Quality) by furthermore combining these into an overall rating. By combining all items this way, the statistical power of the overall rating is increased.

For SSQ-12C, no published studies exist to the author’s knowledge. Cañete et al., 2020, used the related SSQ12 (absolute version) on 83 hearing-impaired listeners (average age 53.9, SD 20.3; range 20–88 years, better ear PTA4 = 45.7 dB HL) and had an overall SSQ mean rating = 5.5 (SD = 2.5). Additionally, unpublished data exists on SSQ12 with aided hearing-impaired listeners that found an overall SSQ mean =

6.2 (SD = 2.4) (STM project, by Zaar et al, IRU, 2020). This unpublished data supports the published value from Cañete et al, 2020.

SSQ-12C uses a scale from -5 (much worse than compared HA) to +5 (much better than compared HA), where a mean rating of 0.1 (SD = 1.4) is observed. This suggests that the comparative SSQ-12C is more sensitive than the absolute SSQ12. However, taking into consideration the ‘worst-case scenario’ based on the above data, an SD of 2.5 from the SSQ12 is assumed for this study.

For an effect size of 0.7, the estimated difference on the SSQ-C scale will be SSQ-C = 0.7\*2.5 = 1.75. Even though the sample size calculation performed in this study is for the mean to be above zero (new HA better than own HA, or hearing aid better than unaided), participants would be able to report below zero (own hearing aid or unaided better than new hearing aid), hence a two-tailed t-test will be applied for this analysis. The significance level was set to alfa = 0.05 and the statistical power (1 – beta) = 0.8.

Using G\*Power version 3.1.9.4 ([https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-](https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.html) [und-arbeitspsychologie/gpower.html](https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.html)) the calculation is done as follows:

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***Figure 3 Sample size calculation for SSQ-12C and B***

THI and TFI

In the literature review in section 1.1.3, several studies are mentioned that have found significant effects of sound therapy (both in isolation and in combination with a hearing aid). Not all studies report effect size, but those that do found variations in effect sizes, ranging from none to very large-to-infinity. Based on that, a medium-to-large effect size of 0.6 was selected for sample size calculation.

Even though the sample size calculation performed for THI and TFI is for the mean to be above zero (TSS better than no TSS/current tinnitus solution), participants would be able to report below zero (TSS worse than no TSS/current solution), hence a two-tailed t-test will be applied for this analysis. The significance level was set to alfa = 0.05 and the statistical power (1 – beta) = 0.8.

Using G\*Power version 3.1.9.4 ([https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-](https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.html) [und-arbeitspsychologie/gpower.html](https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.html)) the calculation is done as follows (**Figure 4**).

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***Figure 4 Sample size calculation for THI and TFI outcomes***

Thus, it was found that the minimum required sample size to achieve statistical power for the outcomes from THI and TFI is **N = 24.** This also corresponds well with the sample size required for a 13-point change in the TFI with a population mean of 35 points and a standard deviation of 20, with an alpha of 0.05 and a power of 0.09. The latter calculation gives an N = 25.

In summary, a total sample size of **N = 25** participants is decided for the study. This is based on the above assumptions and calculations. The **N** (i.e., 25 participants) is taken from the largest required sample size (N = 25 from the TFI). However, recruitment will aim for enrolling between 30 and 40 participants, because a) a certain amount of participants may drop out, b) the field test is rather long, so the risk of drop out is increased, and c) tinnitus studies notoriously have large variations in parameters around the test subject (severity of symptoms, psychological stress amongst participants, hearing aid use and experience, hearing loss configurations, etc.), so even though the sample size shows N = 24, a larger sample size would be preferable.

### 2.4.2 Analysis

The Demant PMCF team will perform statistical analysis on the hearing aid investigation, and the PI at UA will perform statistical analysis on the tinnitus outcomes.

## Technical measurements

N/A

## Project structure

### Research team and collaborators

See section *Roles and Stakeholders* on page 3.

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Adjusted due to contract delays.

### Timeline

It should be noted that recruitment for special focus studies on a specific population such as this one can be hard to predict, the timeline below is an estimate. The study has been given start and end date June 2021- June 2022 in the ethics application, but the test period and data analysis may be finished before May-June 2022.

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| ***Activity/month*** | *Mar**‘21* | *April**‘21* | *May**‘21* | *Jun e**‘21* | *Jul y**‘21* | *Aug**‘21* | *Sept**‘21* | *Oct**‘21* | *Nov**‘21* | *Dec**‘21* | *Jan**‘22* | *Feb**‘22* | *Mar**‘22* | *April**‘21* | *May**‘22* | *June**‘22* |
| *Protocol**writing and test planning* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Closing budget**(black) and protocol (grey)* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Ethical approval and**trial registry* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Test preparation* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Test period* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Data analysis, updates to regulatory**documents* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

# Administrative documentations

## Regulatory compliance

All instruments used in the study are commercially released and will, together with fitting software, follow international standards in terms of safety and effectiveness and fulfill regulatory standards.

Test persons who wish to discontinue the study before termination of the full study period can do so without retribution from University of Auckland or Demant A/S.

## Ethics

The study falls under the ethics approval provided by University of Auckland.

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## Minimal risks

All instruments and accompanying fitting software and accessories used in this study are released for sale and CE-marked for safe use.

Participation in all tests is voluntary and on the test subjects’ own responsibility. There are no known risks of participating in this test other than a small potential risk of increased tinnitus symptoms. However, some people may experience discomfort in the ear canal due to wearing a HA. Furthermore, as for own HAs, there may be a small risk of feedback occurrence.

The Auckland site is responsible for making sure the study is in adherence to local Covid-19 restrictions, which may be subject to change several times during the study period. An informal safety committee is established for trials in the Audiology section, consisting of Clinic audiology staff.

## Budget

Please refer to the Budget Agreement.

## Contract

Please refer to the contract agreed upon by both parties.

## Funding/ownership

The study is funded by Demant A/S. Demant A/S retains ownership of data, but the data will be accessible by both parties. Demant A/S will provide investigational products, equipment, and related software. The principal investigator at Auckland will conduct the experiment and thus provide individual results and statistical analysis.

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# Appendix