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A clinical investigation of the benefit of directionality as a function of microphone location: BTE hearing aids versus ITE hearing aids.
Statistical Analysis Plan

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Statistical Plan BF003-1808

version 2.0

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Contents

1. Introduction

This test will compared two devices with the following label:

- **Reference Medical Device (RMD):** marketed Bernafon behind-the-ear (BTE) device fitted with standard clinical procedure,
- **Investigational Medical Device (IMD):** a custom made device placed in-the-ear (ITE).

While the IMD might present some advantages for handling, it must be ensured that it does not degrade speech reception or reduce perceived sound quality.

The **primary objective** is to assess the effect that microphone location has on the speech scores of the end users. The speech scores of the IMD will be compared to the RMD.

A **secondary objective** is to determine if the performance of the IMD is as good as the RMD. The performance of the IMD will be validated using the RMD as the control. The performance of the IMD should not be inferior to the RMD. The performance will be measured for both the RMD and IMD using a standardized questionnaire

The **primary outcome** is the objective speech testing results of the IMD compared with the RMD. It will be measured two times during the trial. Speech will be tested with the RMD and the IMD at the second and third appointments. Two speech tests, the OLSA and the GÖSA, will be used under three listening conditions: unaided, aided with the RMD, and aided with the IMD.

There are little evidences from literature research (Jensen et al. 2013 and Kuk et al. 2014) that the IMD will be superior to the RMD for speech reception thresholds with equivalent technology. Benefit from a more closed fit might be partially compensated by the larger distance between microphone on the BTE placement. Therefore, we can expect that the performance should be at least as good with the IMD. A non-inferiority trial aims to demonstrate that the investigational device is at least as good as the current marketed device by more than a pre-specified, small amount. This amount, known as the non-inferiority margin δ, has to be determined before the trial start on the main outcome based on clinical and statistical reasoning.

Speech Reception Threshold (SRT) from a previous experiment (BF001-1611) with the RMD and the OLSA test material will be used to determine δ and the required sample size.

The **secondary outcomes** will evaluate self-reported outcomes. The standardized questionnaire provides a standard scoring method for comparing the overall performance of the two devices, and the in-house questionnaires will specifically address localization, comfort, and occlusion factors between the devices, as well as preference for the two styles.

2. Test Design

The treatment will be approximately 2 weeks of use with the IMD during which they will not use the RMD. During the study they will stop using the RMD and switch to the IMD for the assigned period. There will be lab tests during which the participants will use the RMD and the IMD, for up to 2 hours at a time during testing in the clinic. There is no measurable period effect in the given test design. The subjects are experienced hearing aid wearers and no acclimatization period is expected.

2.1 Hypothesis

SRT benefit expressed in terms of benefit with amplification (SRT unaided - SRT aided), will be used as primary outcome in the following hypothesis and sample size calculation. As there is no technical motivation to find a benefit with the IMD, the tested hypothesis should therefore focus on the non-inferiority of the IMD compared to the RMD:

H0: average benefit with the IMD (μ_{IMD}) is not non-inferior to the average benefit with the RMD (μ_{RMD})

$$\mu_{IMD} \leqslant \mu_{RMD} - \delta$$

H1: average benefit with the IMD (μ_{IMD}) is non-inferior to the average benefit with the RMD (μ_{RMD})

$$\mu_{IMD} > \mu_{RMD} - \delta$$

where δ is the non-inferiority margin.

2.2 Timeline

The participants will be tested sequentially with the IMD and RMD. For each speech test session three listening condition (unaided, aided BTE, and aided ITE) have to be performed targeting 50% (SRT50) and 80% (SRT80) understanding. The test order (condition x target) has to be randomized for each tested subject.

3. Outcomes

3.1 Primary outcomes

The speech test are chosen to cover different aspect of communication. Using an open set version, the subjects' task is to repeat all the words which have been understood. The experimenters' task is to compare subjects' verbal responses with the sentence displayed on the control screen and indicate the correctly repeated words.

- **OLSA:** a matrix speech test which incorporates 5-words semantically unpredictable sentences of a fixed grammar structure (name, verb, number, adjective, and noun). The utterances are composed of words from a 50-word base matrix.
- **GÖSA:** the most complex speech material is represented by the GÖSA test. This test comprises meaningful sentences of everyday speech, of a different semantical and syntactical difficulty. Collecting data from two different speech materials should help to generalize our findings. However, due to different test properties (Kollmeier et al., 2011), a separate analysis must be conducted with each test material. As we don't have reference data for the GÖSA test, we cannot compute a non-inferiority margin. Therefore, the benefit of amplification will be evaluated with both tested devices and with exploratory analysis. The hypothesis is that there is a significant improvement of SRTs in the aided over the unaided condition with the GÖSA test.

3.2 Secondary outcomes

3.2.1 APHAB

The APHAB (Cox & Alexander, 1995) is a 24-item self-assessment inventory in which patients report the amount of trouble they are having with communication or noises in various everyday situations. Benefit is calculated by comparing the patient's reported difficulty in the unaided condition with their amount of difficulty when using amplification. The APHAB produces scores for 4 subscales: Ease of Communication (EC), Reverberation (RV), Background Noise (BN), and Aversiveness (AV). A global scale will capture the overall benefit of amplification with both tested devices.

Johnson et al. (2010) established APHAB norms with WDRC hearing aids. Their results will be used as a reference before comparing both devices used in the test.

3.2.2 BF003 Specific Questionnaire

Product questionnaire: will investigate specific aspect of experience with hearing aids.

- Sound quality: five-level Likert item
- Artefact: Yes/No and optional comments
- Wearing comfort: Yes/No and optional comments
- Acoustic feedback: five-level Likert item
- Occlusion: 10cm visual analogue scale
- Localisation of sound sources: Yes/No

Preference questionnaire: will conclude the test period with the IMD. An overall feedback is asked to summarize the experience.

- Overall preference: five-level Likert item (IMD much, IMD somehow, No, IMD somehow, IMD much)
- Certainty of the preference: 10 points discrete scale
- Motivations for preference: multiple choice (sound quality, intelligibility, listening effort, audibility, comfort, own voice)

4. Non-inferiority margin and sample size calculation

4.1 Non-inferiority margin

The non-inferiority margin determination follows the guidelines of Flight & Julious (2016). The non-inferiority margin is defined to be the clinical acceptable difference allowing us to conclude that there is no difference between the treatments. We will base our reflection on SRT benefit from the validation of the RMD to satisfy the following requirements:

- **Assay sensitivity**, the RMD should provide a benefit over the unaided condition. This can be verified by the achieved mean benefit of +4 dB SNR (SD = 0.8 dB SNR).
- **Constancy assumptions**, the IMD will be tested in the same conditions and the eligibility criteria are similar between both studies.
- **Minimized bias**, to reduce the influence of results variability from natural fluctuation the difference between conditions is used rather than absolute SRT results.

From the reference study, a significant and audible difference could be found between the tested devices. This was also reflected by a difference of 1.3 dB SNR (SD = 1.6 dB SNR) in the SRT scores. The OLSA test manufacturer states that the precision to determine the SRT lies around 1 dB for within subject measures. We can therefore set the non-inferiority margin to 1 dB SNR which correspond to a little bit less than 80 % of an audible effect measured with the test. With a non-inferiority margin of 1 dB, we are still ensuring that the IMD has a positive effect over the unaided condition.

4.2 Sample size proposal

The results with the IMD and the RMD are collected on the same subject. SRTs are continuous and normally distributed data. We can therefore apply the sample size determination for mean difference on one sample. The formula to compute the sample size is:

$$n = (\frac{\sigma(z_{1-\alpha} + z_{1-\beta})}{\delta})^2$$

With n the sample size, σ the standard deviation from the population, δ the non-inferiority margin, α the type I error, and 1-β the power of the test. With the following input: σ = 1.6 dB SNR, δ = 1 dB SNR, α = 0.05, and 1-β = 0.8:

```
sigma=1.6
delta=1
alpha=0.05
beta=0.2

n = (sigma*(qnorm(1-alpha)+qnorm(1-beta))/delta)^2

ceiling(n)
```

```
## [1] 16
```

A sample size of 16 will be use to test the non-inferiority hypothesis with a non-inferiority margin of 1 dB.

5. Analysis

5.1 Non-inferiority Analysis

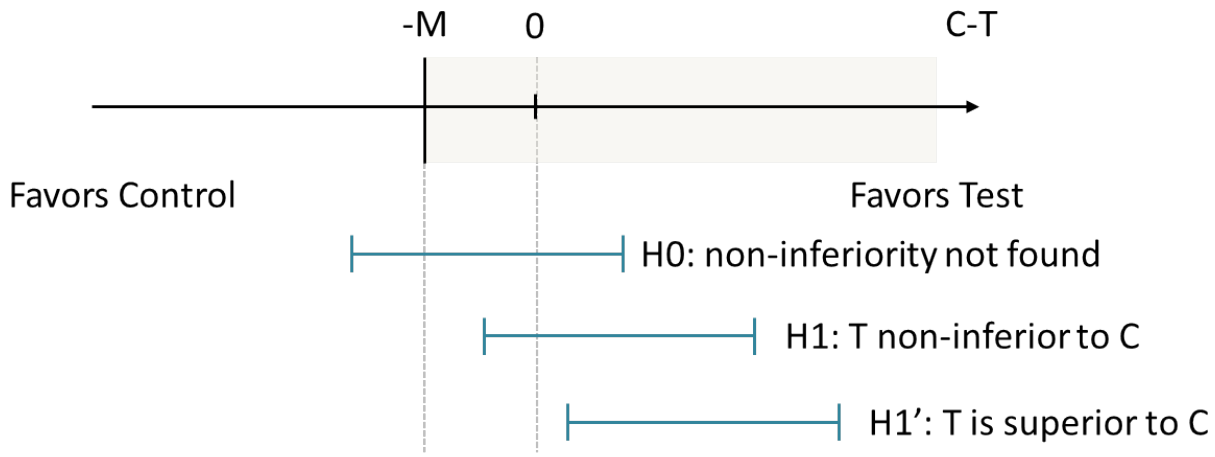
The paired t-test usually tests that the mean differences are zero. The non-inferiority test compares the difference to a non-zero quantity δ (or -M).

The assumptions of the paired t-test are:

1. The data are continuous (not discrete).
2. The data, i.e., the differences for the matched-pairs, follow a normal probability distribution.
3. The sample of pairs is a simple random sample from its population. Each individual in the population has an equal probability of being selected in the sample.

5.2 Switching to superiority hypothesis

If the confidence interval for the difference between both devices lies entirely above 0, then *"it is acceptable to calculate the P value associated with a test of superiority and to evaluate whether this is sufficiently small to reject convincingly the hypothesis of no difference. There is no multiplicity argument that affects this interpretation because, in statistical terms, it corresponds to a simple closed test procedure. Usually this demonstration of a benefit is sufficient on its own, provided the safety profiles of the new agent and the comparator are similar."*



Reference: Committee for Proprietary Medicinal Products (CPMP). (2001). Points to consider on switching between superiority and non-inferiority. British Journal of Clinical Pharmacology, 52(3), 223–228.

5.3 Model Speech Inteligibility Data

The SRT is compute folllowing an adaptive procedure described by Brandt & Kollmeier (2002). The SRT50 and SRT80 are estimated points that should capture the result of an experiment with 20 sentences. However, recent litterature (Hu et al. 2015, Naylor 2016, Rhebergen et al. 2016) recommend to extend the data analysis over a broader SNR range by taking into account each test item. The model can follow a parametric or non-parametric distribution and the difference between both test device can be described as a function of the test SNR (dSNR).

We will therefore use the SRT50 as main indicator for the analysis as described in point 5.1. However, a section of the report will describe speech intelligibility model with the dSNR to better understand variation of intelligibility.

5.4 Analysis tools

R (latest available and validated version) downloaded from official Comprehensive R Archive Network (https://cran.r-project.org/). R-Studio IDE will be used to integrate analysis to the report. R provides adequate packages for descriptive statistics (base, stats, and Rmisc), data vizualisation (ggplot2), and inference statistics with mixed effect models (lmer, lmerTest, and nlme).

6. Randomisation

The order of test condition and target has to be defined for each subject for the speech test. The listening condition will be randomly assigned first. The target will be then assigned as it requires "only" a change in the test set parameter. It should reduce the amount of changes in listening conditions.

```
#set experimental data up to 20 subjects
size <- 20
conditions <- c("Unaided", "IMD", "RMD")
target <- c("50%", "80%")
```

- **OLSA** with 40 test lists

```
set.seed(456)
set_order_OLSA <- data.frame(
  subject = paste("TC", rep(1:size, each=length(conditions)), sep="_"),
  condition_seq = rep(1:3, size),
  condition = as.vector(replicate(size, sample(conditions))),
  target = t(replicate(size*length(conditions), sample(target))),
  list =  t(replicate(60, sample(1:40,2)))
)
knitr::kable(head(set_order_OLSA))
```

subject	condition_seq	condition	target.1	target.2	list.1	list.2
TC_1	1	Unaided	50%	80%	13	34
TC_1	2	RMD	50%	80%	11	4
TC_1	3	IMD	50%	80%	37	32
TC_2	1	RMD	80%	50%	37	27
TC_2	2	IMD	80%	50%	10	7
TC_2	3	Unaided	80%	50%	19	12

- **GOESA** with 10 test lists

```
set.seed(123)
set_order_GOESA <- data.frame(
  subject = paste("TC", rep(1:size, each=length(conditions)), sep="_"),
  condition_seq = rep(1:3, size),
  condition = as.vector(replicate(size, sample(conditions))),
  target = t(replicate(size*length(conditions), sample(target))),
  list =  t(replicate(60, sample(1:10,2)))
)
knitr::kable(head(set_order_GOESA))
```

subject	condition_seq	condition	target.1	target.2	list.1	list.2
TC_1	1	Unaided	80%	50%	9	3
TC_1	2	IMD	50%	80%	8	3
TC_1	3	RMD	80%	50%	6	5
TC_2	1	RMD	80%	50%	3	6
TC_2	2	IMD	80%	50%	10	9
TC_2	3	Unaided	80%	50%	3	10

7. References

7.1 Litterature

Brand, T., & Kollmeier, B. (2002). Efficient adaptive procedures for threshold and concurrent slope estimates for psychophysics and speech intelligibility tests. The Journal of the Acoustical Society of America, 111(6), 2801–2810.

Cohen, Jacob (1988). Statistical Power Analysis for the Behavioral Sciences. Routledge.

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Naylor, G. (2016). Theoretical Issues of Validity in the Measurement of Aided Speech Reception Threshold in Noise for Comparing Nonlinear Hearing Aid Systems. Journal of the American Academy of Audiology, 27(7), 504–514.

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Wagener, K.C.,Brand, T., and Kollmeier, B. (1999c). Entwicklung und evaluation eines satztests für die deutsche sprache-teil III: evaluation des oldenburger staztests (in english: development and evaluation of a german sentence test. Part III: evaluation of the oldenburg sentence test). Z. für Audiologie, 38, 86-95

7.2 Randomisation list

7.2.1 OLSA speech test

```
set_order_OLSA
```

```
##    subject condition_seq condition target.1 target.2 list.1 list.2
## 1     TC_1             1   Unaided      50%      80%     13     34
## 2     TC_1             2       RMD      50%      80%     11      4
## 3     TC_1             3       IMD      50%      80%     37     32
## 4     TC_2             1       RMD      80%      50%     37     27
## 5     TC_2             2       IMD      80%      50%     10      7
## 6     TC_2             3   Unaided      80%      50%     19     12
## 7     TC_3             1   Unaided      50%      80%     32     16
## 8     TC_3             2       RMD      50%      80%     28      3
## 9     TC_3             3       IMD      50%      80%     35     40
## 10    TC_4             1       IMD      50%      80%     18     23
## 11    TC_4             2   Unaided      50%      80%     22     27
## 12    TC_4             3       RMD      80%      50%     33      3
## 13    TC_5             1       RMD      50%      80%     19      8
## 14    TC_5             2       IMD      80%      50%     22     24
## 15    TC_5             3   Unaided      80%      50%      2     11
## 16    TC_6             1       IMD      80%      50%     35      7
## 17    TC_6             2       RMD      80%      50%      4     31
## 18    TC_6             3   Unaided      80%      50%     12      9
## 19    TC_7             1       RMD      50%      80%     15      5
## 20    TC_7             2   Unaided      80%      50%     26      3
## 21    TC_7             3       IMD      50%      80%      9     26
## 22    TC_8             1       RMD      50%      80%     18     13
## 23    TC_8             2       IMD      80%      50%      6      8
## 24    TC_8             3   Unaided      80%      50%     22      5
## 25    TC_9             1       RMD      80%      50%     32     11
## 26    TC_9             2       IMD      80%      50%     34      8
## 27    TC_9             3   Unaided      50%      80%     33     39
## 28   TC_10             1       IMD      80%      50%     36     40
## 29   TC_10             2   Unaided      80%      50%      4     34
## 30   TC_10             3       RMD      80%      50%      6     20
## 31   TC_11             1       RMD      50%      80%     16     14
## 32   TC_11             2   Unaided      50%      80%     11     25
## 33   TC_11             3       IMD      50%      80%     33     39
## 34   TC_12             1       IMD      80%      50%     25     33
## 35   TC_12             2       RMD      50%      80%     36     14
## 36   TC_12             3   Unaided      80%      50%      6     16
## 37   TC_13             1       RMD      80%      50%     24     40
## 38   TC_13             2       IMD      50%      80%      5     16
## 39   TC_13             3   Unaided      50%      80%     25      2
## 40   TC_14             1       IMD      50%      80%     26     10
## 41   TC_14             2   Unaided      50%      80%     21     26
## 42   TC_14             3       RMD      50%      80%     35      1
## 43   TC_15             1   Unaided      50%      80%     13     34
## 44   TC_15             2       RMD      80%      50%     10     38
## 45   TC_15             3       IMD      50%      80%      4      1
## 46   TC_16             1   Unaided      80%      50%      7     25
```

```
## 47   TC_16              2       IMD      50%      80%      1     40
## 48   TC_16              3       RMD      50%      80%     14      5
## 49   TC_17              1       IMD      50%      80%      9     11
## 50   TC_17              2       RMD      80%      50%     18     27
## 51   TC_17              3   Unaided      50%      80%      8     23
## 52   TC_18              1       RMD      50%      80%     18     21
## 53   TC_18              2   Unaided      80%      50%     37     12
## 54   TC_18              3       IMD      80%      50%     37      9
## 55   TC_19              1       IMD      80%      50%      5     20
## 56   TC_19              2       RMD      80%      50%     31     21
## 57   TC_19              3   Unaided      50%      80%     38     26
## 58   TC_20              1       IMD      80%      50%      3     28
## 59   TC_20              2   Unaided      80%      50%     36     11
## 60   TC_20              3       RMD      50%      80%      8     33
```

7.2.2 GOESA speech test

```
set_order_GOESA
```

```
##    subject condition_seq condition target.1 target.2 list.1 list.2
## 1     TC_1             1   Unaided      80%      50%      9      3
## 2     TC_1             2       IMD      50%      80%      8      3
## 3     TC_1             3       RMD      80%      50%      6      5
## 4     TC_2             1       RMD      80%      50%      3      6
## 5     TC_2             2       IMD      80%      50%     10      9
## 6     TC_2             3   Unaided      80%      50%      3     10
## 7     TC_3             1       IMD      80%      50%     10      6
## 8     TC_3             2       RMD      50%      80%     10      5
## 9     TC_3             3   Unaided      50%      80%      5      6
## 10    TC_4             1       IMD      50%      80%      2      6
## 11    TC_4             2       RMD      50%      80%      3      9
## 12    TC_4             3   Unaided      50%      80%      7      5
## 13    TC_5             1       RMD      50%      80%      5      8
## 14    TC_5             2       IMD      80%      50%      4      3
## 15    TC_5             3   Unaided      80%      50%      2     10
## 16    TC_6             1       RMD      50%      80%      5      3
## 17    TC_6             2   Unaided      50%      80%      3      7
## 18    TC_6             3       IMD      50%      80%      1      7
## 19    TC_7             1   Unaided      80%      50%      4     10
## 20    TC_7             2       IMD      50%      80%      9     10
## 21    TC_7             3       RMD      80%      50%      3      9
## 22    TC_8             1       RMD      50%      80%      8      7
## 23    TC_8             2       IMD      50%      80%      1      4
## 24    TC_8             3   Unaided      80%      50%      5      6
## 25    TC_9             1       IMD      50%      80%      7      9
## 26    TC_9             2       RMD      80%      50%      7      4
## 27    TC_9             3   Unaided      50%      80%      6      1
## 28   TC_10             1       IMD      80%      50%      3      4
## 29   TC_10             2   Unaided      80%      50%      2      8
## 30   TC_10             3       RMD      80%      50%      2      8
## 31   TC_11             1       RMD      80%      50%      6     10
## 32   TC_11             2       IMD      50%      80%      2      6
## 33   TC_11             3   Unaided      50%      80%      4      7
## 34   TC_12             1       RMD      50%      80%      4      9
## 35   TC_12             2   Unaided      50%      80%     10      7
## 36   TC_12             3       IMD      80%      50%      3      2
## 37   TC_13             1       RMD      80%      50%      6      3
## 38   TC_13             2   Unaided      80%      50%      6      8
## 39   TC_13             3       IMD      80%      50%      2      4
## 40   TC_14             1   Unaided      80%      50%      5      8
## 41   TC_14             2       RMD      50%      80%     10      8
## 42   TC_14             3       IMD      50%      80%      7      9
## 43   TC_15             1       IMD      80%      50%      6     10
## 44   TC_15             2   Unaided      50%      80%      4     10
## 45   TC_15             3       RMD      50%      80%      1      5
## 46   TC_16             1   Unaided      80%      50%      9      1
## 47   TC_16             2       RMD      50%      80%      1      2
## 48   TC_16             3       IMD      50%      80%      8      7
```

```
## 49   TC_17             1   Unaided      80%      50%     10      5
## 50   TC_17             2       IMD      50%      80%      1      6
## 51   TC_17             3       RMD      80%      50%      8      2
## 52   TC_18             1       IMD      80%      50%      4      3
## 53   TC_18             2       RMD      50%      80%      1      4
## 54   TC_18             3   Unaided      80%      50%      1      3
## 55   TC_19             1       IMD      50%      80%      1      7
## 56   TC_19             2   Unaided      80%      50%      3      1
## 57   TC_19             3       RMD      80%      50%      1      8
## 58   TC_20             1       RMD      80%      50%      8     10
## 59   TC_20             2       IMD      50%      80%     10      1
## 60   TC_20             3   Unaided      80%      50%      1      8
```