Study Protocol & Statistical Analysis Plan

Assessment of Novel Sound Changing Principles in Hearing Instruments to Determine Their Application – Sonova2020_09

NCT04578457

Clinical Study Protocol: Assessment of novel sound changing principles in hearing instruments to determine their application

Study Identifier: S&T-P4AC

Assessment of novel sound changing principles in hearing instruments to determine their application

Clinical Study Protocol

ASSESSMENT OF NOVEL SOUND CHANGING PRINCIPLES IN HEARING INSTRUMENTS TO DETERMINE THEIR APPLICATION.

[A methodical evaluation of novel sound changing principles in CE-labelled Sonova brand hearing instruments (e.g. Phonak hearing instruments) is intended to be conducted on hearing impaired and normal hearing participants. These sound changing principles are enabled by respective hearing instrument technologies and hearing instrument algorithms. The aim of the study is to investigate and asses strength and weaknesses of these novel sound changing principles in terms of hearing performance to determine their application in hearing instruments (Phase of development). Both, objective laboratory measurements as well as subjective evaluations in real life environment will be carried out. This will be a controlled, single blinded and randomised active comparator clinical evaluation which will be conducted mono centric at Sonova AG Headquarter based in Stäfa]

Study Type:	Clinical trial with Medical Device (MD)
Study Categorisation:	Risk category according to LHR is A
Study Registration:	This study will be registered at clinicaltrials.gov as a primary register and additionally it will be registered in the Swiss Federal Complementary Database as soon as the ethics application is approved by CEC
Study Identifier:	S&T-P4AC
Sponsor:	Sonova AG Contact Person: Juliane Raether Laubisrütistrasse 28 CH-8712 Stäfa Email: Juliane.Raether@sonova.com Phone: 058 928 86 37
Investigational Product:	MD: Sonova brand hearing systems (primarily Phonak hearing systems). The hearing systems comprise hearing instruments containing respective hearing instrument software and acoustic couplings, fitting software and wireless accessories.
Protocol Version and Date:	Version 1.4, 28.06.2018

Signature Page(s)

Study number	Study-ID: 2016-00624
Study Title	Assessment of novel sound changing principles in hearing instruments to determine their application

The Sponsor-Investigator and trial statistician have approved the protocol version 1.3 (dated 07.06.2018, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor: **Sonova AG (contact person: Juliane Raether)**

Stäfa / 28.06.2018 _____

Place/Date Signature

Principle Investigator: **Juliane Raether**

Stäfa / 28.06.2018 _____

Place/Date Signature

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	Sonova AG Laubisrütistrasse 28 CH-8712 Stäfa
Principal investigator	Juliane Raether

Stäfa / 28.06.2018 _____ _____

Place/Date Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Table of Contents

STUDY SYNOPSIS

(ClinO, Appendix 3, 1.1, 2.1, 3.1, 4.1; Appendix 5, 2b; AGEK Summary)

Sponsor / Sponsor-Investigator	Sonova AG
Study Title:	Assessment of novel sound changing principles in hearing instruments to determine their application
Short Title / Study ID:	S&T-P4AC / 2016-00624
Protocol Version and Date:	Version 1.3, 07.06.2018
Trial registration:	After approval by CEC in: • clinicaltrials.gov • Swiss Federal Complementary Database
Study category and Rationale	Risk category A. The study is a trial with medical devices (comprising hearing instruments, hearing instrument software, acoustic couplings, fitting software and wireless accessories). All investigational devices are CE-labelled and their application is done according to the specialised information.
Clinical Phase:	Phase of development
Background and Rationale:	This study is the description of a series of several studies concerning the evaluation of novel sound changing principles in hearing instruments which are continuously developed and improved. For each sound changing principle a separate (sub-) study will be conducted. These sound changing principles are enabled by respective hearing instrument technology and hearing instrument algorithms. The mentioned technology and algorithms are applied in hearing instruments as features and functions and intend to improve the hearing performance for an hearing impaired end-user. The purpose of this evaluation is to investigate these novel applications regarding their supposed benefit and possible secondary effects with respect to hearing performance. The results should promote the hearing instrument development to create meaningful applications, improve the hearing instrument products and hence provide a maximum benefit in terms of hearing performance for an end user.
Objective(s):	All studies pursue the same goal: to investigate the audiological performance for each of these novel sound changing principles on hearing impaired subjects using respective hearing performance outcome measures. The results are assessed in referenced to those from sound changing principles used in recent hearing instruments and/or with the sound changing principle disabled. Primary Objective: Assess the performance of the respective novel applications for their intended use and examine different parameter settings of the sound changing principles for the associated hearing dimensions. These hearing dimensions are either: - speech intelligibility, - signal clarity or - sound quality / hearing comfort Secondary Objective: Investigate the effect of the respective applications to hearing impaired subjects in real world environment.

Outcome(s):	The primary outcomes are the laboratory test results. These tests intend to evaluate the hearing performance for a corresponding hearing dimension (speech intelligibility, signal clarity, sound quality / hearing comfort). For each sound changing principle the suited test method is chosen. The secondary outcomes are the subjective test results and comments gathered in real world environment (e.g. during guided walks) and with questionnaires during the home trials.
Study design:	Active comparator study, controlled, single blinded, randomised, cross-over design.
Inclusion / Exclusion criteria:	Participants fulfilling all of the following inclusion criteria are eligible for the study: • Adult hearing impaired persons (minimum age: 18 years) with and without (experience with) hearing aids • Adult normal hearing persons (minimum age: 18 years) • Healthy outer ear (without previous surgical procedures) • Ability to fill in a questionnaire conscientiously • Informed Consent as documented by signature The presence of any one of the following exclusion criteria will lead to exclusion of the participant: • Contraindications to the MD in this study, e.g. known hypersensitivity or allergy to the investigational product • Limited mobility and not in the position to attend weekly appointments • Limited ability to describe listening impressions/experiences and the use of the hearing aid • Inability to produce a reliable hearing test result • Massively limited dexterity • Known psychological problems • Known central hearing disorders
Measurements and procedures:	The study intervention comprises hearing performance assessment measures concerning speech intelligibility, signal clarity and sound quality / hearing comfort. Each study concerns the evaluation of a specific sound changing principle. With respect to the particular sound changing principle and the focused aim regarding hearing performance the corresponding outcome measures will be chosen.
Study Product / Intervention:	MD: Sonova brand hearing systems (comprising hearing instruments with respective hearing instrument software and acoustic couplings, fitting software and wireless accessories). Primarily Phonak hearing systems will be chosen. The product will be applied for the duration of the study only.
Control Intervention (if applicable):	MD: Sonova brand hearing systems (comprising hearing instruments with respective hearing instrument software and acoustic couplings, fitting software and wireless accessories). Primarily Phonak hearing systems will be chosen. The product will be applied for the duration of the study only.
Number of Participants with Rationale:	For a single study one or more pre-studies are conducted with only a few participants to proof the study concept and/or find valuable settings. If the results of the pre-studies are promising, the respective main study will start. For each pre-study a maximum of 5 participants is considered. For the main study normally 20 - 25 participants are considered. If possible a power analysis is carried out for each study to determine the necessary number of subjects. A maximum of 60 subjects will participate per year. This is a maximum of 600 subjects in total over 10 years.
Study Duration:	10 years (01.07.2016 – 30.06.2026)
Study Schedule:	Month Year of First-Participant-In (planned): March 2018 Month Year of Last-Participant-Out (planned): June 2026

Investigator(s):	Juliane Raether (Principle Investigator, further investigators are specified in a staff list) Sonova AG, Laubisrütistrasse 28, 8712 Stäfa, Phone: 058 928 01 01
Study Centre(s):	Single-centre (Sonova AG, Stäfa).
Statistical Considerations:	Sample size according to experience and to established specialized literature. Descriptive statistics: Frequency distribution, mean and standard deviation, median and quartile, boxplot, histogram, scatterplot, correlation coefficient (Pearson, Spearman). Inferential statistics: t-Test, Mann-Whitney-U-Test, Wilcoxon-Test, ANOVA, MANOVA.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

STUDY SUMMARY IN LOCAL LANGUAGE

In dieser Studienreihe findet eine methodische Evaluation neuartige Schalländerungsprinzipien in Hörgeräten an Studienteilnehmern mit Hörminderung statt. Die Schalländerungsprinzipien werden durch entsprechende Hörgerätetechnologien und Hörgerätealgorithmen ermöglicht. Diese Technologien und Algorithmen sind als sogenannte „Features und Funktionen“ in Hörgeräten implementiert. Sie haben das Ziel die Hörleistung für den Nutzer in Bezug auf Sprachverständlichkeit, Signalklarheit und Klangqualität / Hörkomfort zu verbessern.

Das Ziel der Evaluierungsstudien ist es, diese neuartigen Schalländerungsprinzipien bezüglich ihres Nutzens sowie möglicher Sekundäreffekte für schwerhörige Personen zu untersuchen. Dazu werden den Probanden Hörgeräte angepasst und entsprechende audiologische Testverfahren im Labor und Befragungen mit Hilfe von Fragebögen nach Tests in realen Umgebung durchgeführt. So sollen Stärken und Schwächen der jeweiligen Applikation bestimmt und in Referenz zu Ergebnissen mit bisherigen Hörgeräten bewertet werden. Des Weiteren sollen unterschiedliche Parametereinstellungen der neuen Schalländerungsprinzipien untersucht werden um die für den Hörgerätenutzer sinnvollste Einstellung zu ermitteln. Die Studien erfolgen unter kontrollierten, randomisierten Bedingungen am Hauptsitz der Sonova AG in Stäfa.

Die Resultate dieser Untersuchungen unterstützen die Weiterentwicklung von Hörgeräten. Es sollen sinnvolle Anwendungen der neuen Technologien und Algorithmen bestimmt und die Hörgeräte hinsichtlich ihres Nutzens verbessert werden. Das Ziel dieser Entwicklung ist es, den grösstmöglichen Vorteil für den Hörgerätenutzer zu erzeugen.

ABBREVIATIONS

AE	Adverse Event
ANL	Acceptable Noise Level
ASR	Annual Safety Report
BMLD	Binaural Masking Level Difference
BTE	Behind-The-Ear device
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
CU	Categorial Unit
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin)*
CTCAE	Common terminology criteria for adverse events
dB	Decibel
DD	Device Deficiencies
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDA	Electro Dermal Activity (Galvanic Skin Response)
EDC	Electronic Data Capture
EEG	Electroencephalography
EMG	Electromyography
FM	Frequency Modulation

GCP	Good Clinical Practice
GöSa	Göttinger Satztest
HEG	Hemoencephalography
IB	Investigator's Brochure
IIC	Invisible-In-Canal device
ILD	Interaural Level Difference
IPD	Interaural Phase Difference
ISF	Investigator Site File
ITD	Interaural Time Difference
ITE	In-The-Ear device
Ho	Null hypothesis
H1	Alternative hypothesis
HI	Hearing instrument
HFG	Humanforschungsgesetz (Law on human research)
HMG	Heilmittelgesetz
HRA	Federal Act on Research involving Human Beings
IMP	Investigational Medicinal Product
ISO	International Organisation for Standardisation
ITT	Intention to treat
JND	Just Noticeable Difference
KlinV	Verordnung über klinische Versuche in der Humanforschung *(in English: ClinO, in French OClin)*
LPTh	Loi sur les produits thérapeutiques
LRH	Loi fédérale relative à la recherche sur l'être humain
MD	Medical Device
MUSHRA	Multi-Stimulus Test with Hidden Reference and Anchor
N/A	Not Applicable
OClin	Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain *(in German : KlinV, in English : ClinO)*
OLSA	Oldenburger Satztest
pCRF	Paper Case Report Form
PI	Principal Investigator
PPT	Phoneme Perception Test
REM	Real-Ear Measurement
RIC	Receiver-In-The-Canal device
SNR	Signal-to-Noise Ratio
SOP	Standard Operating Procedure
SPL	Sound Pressure Level
SRT	Speech Reception Threshold
SSQ	The Speech, Spatial and Qualities of Hearing Scale
SUSAR	Suspected Unexpected Serious Adverse Reaction

TEN test	Threshold-Equalizing-Noise test
TMF	Trial Master File
UAT	User Acceptance Test
UCL	UnComfortable Level
WaKo	Einsilber-Reimtest nach von Wallenberg und Kollmeier

STUDY SCHEDULE

(AGEK 4.2; SPIRIT #13; ICH E6 6.4.2)

For each study there are two parts (pre-study and main study). Each study part consists of a screening, several study appointments and one follow-up appointment.

The pre-study serves to determine and test sensitive outcome measures. Furthermore several parameter adjustments of the sound changing principle will be investigated with the aim to find the most promising setting for the main study for different kinds and degrees of hearing loss. Thereby the number of unnecessary appointments in the main study shall be reduced to cause less burden for the test subjects. Several pre-studies may be necessary and conducted. The Schedule for a pre-study is visualized in Table 1. The number of the pre-study appointments may vary, a maximum of 6 appointments is considered (Number of participants N = max 5).

Table 1: Pre-Study schedule

Study Period	Screening	Pre-study appointments				Follow-up (final appointment)
Visit Number	1	2	(3)	(4)	(5)	3…6
Time [hrs]	1.5	2	(2)	(2)	(2)	2
Subject Information and Informed Consent	x					
Audiological History	x					
Physical Examination of Ear and Ear Canal	x	x	(x)	(x)	(x)	x
Audiogram	x					x
Check In- /Exclusion Criteria	x					
Decision Subject Participation	x					
Encoded Subject ID	x					
Fitting HI		x	(x)	(x)	(x)	(x)
Objective Measurements		x	(x)	(x)	(x)	(x)
Subjective Measurements		x	(x)	(x)	(x)	(x)
Introduction to Handling (depending on randomisation list for home trials)		x	(x)	(x)	(x)	
Scheduling Next Visit	x	x	(x)	(x)	(x)	
Capture of Adverse Events and Device Deficiencies		x	(x)	(x)	(x)	x

To determine the most useful settings for the main study, a looped workflow is foreseen (Figure 1). A maximum of 3 loops is considered resulting in a maximum of 4 pre-study appointments, whereas fewer appointments are possible.

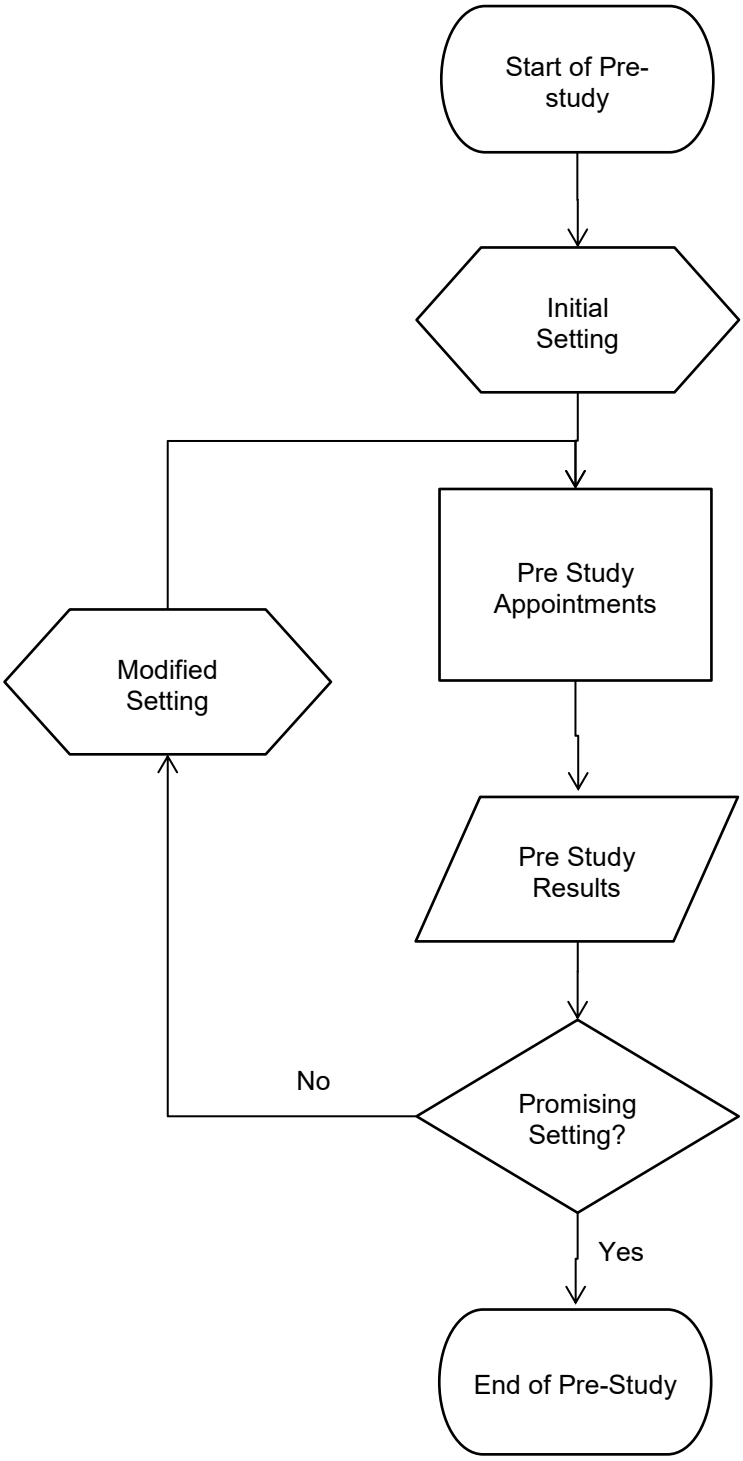

Figure 1: Looped pre-study workflow

The main study represents the actual study for the investigation of one sound changing principle. The results from the pre-studies are used to specify the main study. The Schedule for a main study is visualized in Table 2. The number of the study appointments may vary depending on the number of tests and test methods being executed for a respective sound changing principle. For a main study a maximum of 8 study appointments is considered.

Table 2: Main study schedule

Study Period	Screening	Main study appointments						Follow-up (final appointment)
Visit Number	1	2	3	(4)	(5)	(6)	(7)	4…8
Time [hrs]	1.5	2	2	(2)	(2)	(2)	(2)	2
Subject Information and Informed Consent	x							
Audiological History	x							
Physical Examination of Ear and Ear Canal	x	x	x	(x)	(x)	(x)	(x)	x
Audiogram	x							x
Check In- /Exclusion Criteria	x							
Decision Subject Participation	x							
Encoded Subject ID	x							
Fitting HI		x	x	(x)	(x)	(x)	(x)	(x)
Objective Measurements		x	x	(x)	(x)	(x)	(x)	(x)
Subjective Measurements		x	x	(x)	(x)	(x)	(x)	(x)
Introduction to Handling (depending on randomisation list for home trials)		x	x	(x)	(x)	(x)	(x)	
Scheduling Next Visit	x	x	x	(x)	(x)	(x)	(x)	
Capture of Adverse Events and Device Deficiencies		x	x	(x)	(x)	(x)	(x)	x

1. STUDY ADMINISTRATIVE STRUCTURE

(ICH/E6 6.1.2-6.1.7; AGEK 1.1; SPIRIT 5a-d)

This section contains complete contact details.

1.1 Sponsor, Sponsor -Investigator

(ICH/E6 6.1.2; AGEK 1.1; SPIRIT 5b)
ICH: Name and address of the sponsor .....

The Sponsor is the company Sonova AG. Sonova AG will provide the study budget, the staff, the spatial resources, the measurement equipment and the investigational products (hearing systems including the hearing instruments).

Company: Sonova AG, Stäfa
Contact: Juliane Raether, Dipl.-Ing. (FH)
Address: Laubisrütistrasse 28, CH-8712 Stäfa
Phone: 058 928 86 37
Email: Juliane.Raether@sonova.com
Role: Financier

1.2 Principal Investigator(s)

(ICH/E6 6.1.5, 6.1.6; AGEK 1.1; SPIRIT 5a-d)
ICH: Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

In Sonova AG, the Performance Profiling Team within the P4AC (Program Algorithmic-, Audiological-, Acoustical- and Assessment-Concepts) group undertakes clinical trials to investigate the audiological performance of novel sound changing principles in hearing instruments.

Each Performance Profiling Team member is qualified to take on the role as an Investigator. The function as the Principle Investigator is taken on by:

Site: Sonova AG, Stäfa
Contact: Juliane Raether, Dipl.-Ing. (phone: 058 928 01 01)
Address: Laubisrütistrasse 28, CH-8712 Stäfa
Email: juliane.raether@sonova.com
Role:

- Study design
- Data collection
- Data analysis
- Report

1.3 Statistician ("Biostatistician")

(ICH/E6 6.1.7; SPIRIT 5a-d)
ICH: Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

The role as the Statistician is adopted by the Principle Investigator.

1.4 Laboratory

(ICH/E6 6.1.7; SPIRIT 5a-d)
ICH: Name(s) and address(es) of the clinical laboratory(ies) ..... involved in the trial.

The study will take place in the research labs of the Headquarter of Sonova AG, Laubisrütistrasse 28, 8712 Stäfa (see 08_QualifikationPruefort_d_S&T-P4AC.docx).

1.5 Monitoring institution

(ICH/E6 6.1.2; SPIRIT 5a-d)
ICH: Name and address of the …. monitor (if other than the sponsor).

Monitoring is not conducted by an external institution but by the sponsor.

1.6 Data Safety Monitoring Committee

(ICH/E6 6.1.7; SPIRIT 5a-d)
ICH: Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

N/A

1.7 Any other relevant Committee, Person, Organisation, Institution

(ICH/E6 6.1.7; SPIRIT 5a-d)
ICH: Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

N/A

2. ETHICAL AND REGULATORY ASPECTS

(ICH/E6 6.12; AGEK 11; SPIRIT #24, 5)
ICH: Description of ethical considerations relating to the trial.

The decision of the CEC and Swissmedic/foreign competent authority concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

(ClinO, Art. 1d, 64; SPIRIT #2a-b)

This study will be registered at clincaltrials.gov as a primary register and, additionally, it will be registered in the Swiss Federal Complementary Database as soon as the ethics application is approved by the CEC.

2.2 Categorisation of study

(ClinO, Art. 19, 20, App 3, 1.1)

Risk category A.

The study is a trial with medical devices (comprising hearing instruments, hearing instrument software, acoustic couplings, fitting software and wireless accessories). All investigational devices in this trial are CE-labelled and their application is done according to the specialized information.

2.3 Competent Ethics Committee (CEC)

(ClinO, Art 24-29; SPIRIT #24)

The responsible investigator ensures that approval from an appropriately constituted CEC is sought for the clinical study.

Reporting duties and allowed time frame have to be abided concerning all changes in the research activity and all unanticipated problems involving risks to humans, including in case of planned or premature study end and the final report. No essential changes are made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report will be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

(ClinO, Art. 23, 27, 30-39, 42, 43, 46-48, 57; SPIRIT #24)

There is no need for a CA approval or other local requirements because this study is of risk category A according to LHR.

2.5 Ethical Conduct of the Study

(ClinO, Art. 5; AGEK 11; ICH E6 6.12, 6.2.5)
ICH: A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

(ClinO, Art. 3b; SPIRIT #28)

In accordance to ISO 14155 and KlinV, Art. 3b scientific integrity will be preserved. Therefore, any potential conflicts of interest, including financial, that interfere with the conduct of this clinical investigation or interpretation of the according results could be disclosed.

2.7 Patient Information and Informed Consent

(ClinO, Art. 7-9, Art. 15-17, Appendix 3, 1.4, 2.4, 3.4, 4.3, Appendix 4, 3.6; AGEK submission checklist item 5; SPIRIT #26, 32)

The investigators will explain to each subject the nature of the study, its purpose, the procedures. involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject will be informed that the participation in the study is voluntary and that he may withdraw from the study at any time and that withdrawal of consent will not lead to consequences for the subject. The subject must be informed that his medical records may be examined by authorized individuals.

All subjects for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for subjects to make an informed decision about their participation in the study. This participant information sheet contains also a list of independent fiduciary doctors which can be contacted by the participant, especially in cases of undesirable events, whereas these doctors have no relation to the described study (see 03_Studieninformation_ST_P4AC_Version_1.2) The subjects will be given enough time (minimum time frame for this study: 1 week) for their participation decision. The patient information sheet and the consent form will be submitted to the CEC to be reviewed and approved.

The formal consent of a subject, using the approved consent form, must be obtained before the subject is submitted to any study procedure. The subject should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

(ClinO, Art. 18; ICH/E6 6.10; AGEK 12.2, SPIRIT #27)
ICH: The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

The investigator affirms and upholds the principle of the subject‘s right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the subjects shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject audiological information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to measurement data in the computer files.

For data verification purposes, authorised representatives of the Sponsor, a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the measurement records relevant to the study, including participants’ audiological history.

2.9 Early termination of the study

(ClinO Art. 47; ICH/E6 6.4.6; SPIRIT #21b)
ICH: A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.

The Sponsor or the Principle Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,

- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.10 Protocol amendments

(ClinO, Art. 29, 34, 55; SPIRIT #25)

Every person who is involved in the study performance is able to draft an amendment. All amendments have to be reviewed and signed by the Principle Investigator of the main study site before they get forwarded to the responsible approval institution.

Substantial amendments are only implemented after approval of the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.

All non-substantial amendments are communicated if applicable to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

(ICH 6.2; AGEK 3; SPIRIT #6)

This section includes any statements that rely on existing knowledge or published information concerning the study.

3.1 Background and Rationale

(ICH/E6 6.2; AGEK 3.1; SPIRIT #6)

Research with hearing instruments on hearing impaired participants has been done frequently with the aim to investigate and assess the effect of the respective devices. Extensive surveys have shown, that recent development in hearing instrument technology provides benefit for the end users. Additionally it has been shown that further improvement is requested by the end users [10, 11]. Therefore novel sound changing principles, which aim to improve the hearing performance for the end user, are continuously developed and improved. This study is the description of a series of studies concerning the evaluation of novel sound changing principles in Sonova brand hearing instruments. For each sound changing principle a separate (sub-) study will be conducted. These sound changing principles are enabled by respective hearing instrument technology and hearing instrument algorithms. The mentioned technology and algorithms are applied in hearing instruments as features and functions and intend to improve the hearing performance provided by the device.

The purpose of this evaluation is to investigate these novel sound changing principles regarding their supposed benefit and possible secondary effects for hearing impaired users. The results should promote the hearing instrument development to create meaningful applications, improve the hearing instrument products and hence provide a maximum benefit in terms of hearing performance for an end user. The primary purpose is to investigate and assess the performance of the novel sound changing principles and compare them to those recently used in hearing instruments. Furthermore different parameter adjustments of the respective novel applications will be examined with the aim to determine the optimal setting. The secondary purpose is to investigate the effect of the applications in real world environment.

Study Overview:

A table of relevant and clinical significant studies with hearing instruments concerning audiological benefit can be found below (Table 3). The mentioned literature investigates for the most parts the following hearing instrument features and functionalities: Automatic Functionality, Binaural Directionality, Feedback Management, Frequency Lowering, Monaural Directionality and Noise Suppression.

Table 3: Overview of relevant studies

Reference #	Relevant and Significant Literature	Level of Evidence	Publication Class
1.	Appleton J, König G. Improvement in speech intelligibility and subjective benefit with binaural beamformer technology. Hearing Review. 2014;21(11)[Nov]:40-42.	IIb	b
2.	Aspell E, Picou E, Ricketts T. Directional benefit is present with audiovisual stimuli: limiting ceiling effects. J Am Acad Audiol. 2014 Jul-Aug;25(7):666-75.	Ib	a
3.	Bentler R., Palmer C.V., Mueller H.G.: Evaluation of a Second-Order Directional Microphone Hearing Aid: I. Speech Perception Outcomes, Journal of the American Academy of Audiology, Vol. 17, No. 3, 2006	Ib	a
4.	Bentler RA, Tubbs JL, Egge JL, Flamme GA, Dittberner AB. Evaluation of an adaptive directional system in a DSP hearing aid. 2004 Am J Audiol. 2004 Jun;13(1):73-9.	IIb	a

5.	Boymans M, Dreschler WA.Field trials using a digital hearing aid with active noise reduction and dual-microphone directionality.Audiology. 2000 Sep-Oct;39(5):260-8.	IIb	a
6.	Büchler MC, Algorithms for Sound Classification in Hearing Instruments, Diss. ETH no 14498 (2002), pp 33-37 / Internal library	IIb	d
7.	Büchler, M. (2001). Nützlichkeit und Akzeptanz einer automatischen Programmwahl in Hörgeräten., Hörakustik 10/2001, 64–71 / Internal library	IIb	b
8.	Chung K., Killion MC., Christensen LA.: Ranking hearing aid input-output functions for understanding low-, conversational-, and high-level speech in multitalker babble. J Speech Lang Hear Res., Vol. 50, 2007.	Ib	a
9.	Dillon H. et al.: Sound quality comparisons of advanced Hearing Aids, The Hearing Journal, Vol. 56, No. 4, 2003	IIa	b
10.	Dyrlund O, Henningsen LB, Bisgaard N, Jensen JH, “Digital feedback suppression (DFS). Characterization of feedback-margin improvements in a DFS hearing instrument,” Scand Audiol 1994; 23(2):135-8.	IIb	b
11.	Ellis, R. Benefit and predictors of outcome from frequency compression hearing aid use. University of Manchester 2012, doctoral thesis.	Ib	d
12.	Fortune T.W.: Real Ear Compression Ratios: The Effects of Venting and Adaptive Release Time, American Journal of Audiology, Vol. 6, No.2, 1997	IIa	a
13.	Glista D. Nonlinear Frequency Compression Hearing Aid Signal Processing for Listeners with High-Frequency Hearing Loss: Aided Speech Perception and Acclimatization Effects. University of Western Ontario 2010, Doctoral Thesis	Ib	a
14.	Hearing_Review_user_control_of_directional_focus_jan09.pdf Hearingreview.com, 2009_01	IIa	b
15.	Hoetink A, Körössy L, Dreschler W (2009) Classification of steady state gain reduction produced by amplitude modulation based noise reduction in digital hearing aids. Int J Audiol; 48:444 455	IIa	a
16.	Johnson EE, Ricketts TA, Hornsby BW. The effect of digital phase cancellation feedback reduction systems on amplified sound quality. J Am Acad Audiol. 2007 May;18(5):404-16.	IIb	b
17.	Keidser G, O'Brien A, Hain JU, McLelland M, Yeend I. The effect of frequency-dependent microphone directionality on horizontal localization performance in hearing-aid users. Int J Audiol. 2009 Nov;48(11):789-803.	IIb	a
18.	Kühnel V, Margolf-Hackl S, Kiessling J. Multi-microphone technology for severe-to-profound hearing loss 2001 scandinavian Audiology 2001, Vol. 30, No. 1 , Pages 65-68	IIb	a
19.	Lebart, K. Boucher, J.M. (2001) A New Method Based on Spectral Subtraction for Speech Dereverberation. Acta Acustica, Vol 87, pp 359-366	IIb	a
20.	Levitt H, (2001) Noise reduction in hearing aids: An overview. J Rehabil Res Dev 38	III	a
21.	Mackenzie E, Lutman ME. Speech recognition and comfort using hearing instruments with adaptive directional characteristics in asymmetric listening conditions. 2005 Ear Hear. 2005 Dec;26(6):669-79.	IIa	a
22.	McCreery RW, Venediktov RA, Coleman JJ, Leech HM. An evidence-based systematic review of frequency lowering in hearing aids for school-age children with hearing loss. Am J Audiol. 2012 Dec;21(2):313-28.	Ia	a
23.	Mueller H.G., Weber J., Bellanova M.: Clinical evaluation of a new hearing aid anti-cardioid directivity pattern. International Journal of Audiology, 2011, 50(4).	IIa	a
24.	Mueller, G.H., Weber, J., & Hornsby, B.W.Y. (2006). The effects of digital noise reduction on the acceptance of background noise. Trends in Amplification, 10(83), 83-93.	Ib	a
25.	Nordrum S, Erler S, Garstecki D, Dhar S. Comparison of performance on the hearing in noise test using directional microphones and digital noise reduction algorithms. 2006 Am J Audiol. 2006 Jun;15(1):81-91.	IIb	a
26.	Peeters H, Kuk F, Lau C, Keenan D. (2009) Subjective and Objective Evaluation of Noise Management Algorithms. J Am Acad Aud, 20 (2): 89-98	Ia	a
27.	Picou EM, Aspell E, Ricketts TA. Potential benefits and limitations of three types of directional processing in hearing aids. Ear Hear. 2014 May-Jun;35(3):339-52.	Ib	a
28.	Preves DA, Sammeth CA, Wynne MK. Field trial evaluations of a switch directional/omnidirectional in-the-ear hearing instrument.1999 J Am Acad Audiol. 1999 May;10(5):273-84.	IIb	a
29.	Ricketts T; Johnson E; Federman J: Individual Differences within and across Feedback Suppression Hearing Aids. Journal of the American Academy of Audiology, Volume 19, Number 10, November/December 2008 , pp. 748-757(10)	IIb	b
30.	Ricketts TA and Henry P. Evaluation of an adaptive, directional-microphone hearing aid. 2002 International Journal of Audiology 2002, Vol. 41, No. 2 , Pages 100-112	IIb	a
31.	Ricketts TA, Picou EM. Speech Recognition for Bilaterally Asymmetric and Symmetric Hearing Aid Microphone Modes in Simulated Classroom Environments. A2. Ear Hear. 2013 Mar 21. [Epub ahead of print] PubMed PMID: 23524508.	IIa	a

32.	Savage I, Dillon H, Byrne D, Bächler H.: Experimental evaluation of different methods of limiting the maximum output of hearing aids. Ear & Hearing, Vol. 27, No. 5, 2006.	Ia	a
33.	Simpson A, Hersbach AA, McDermott HJ. Improvements in speech perception with an experimental nonlinear frequency compression hearing device. Int J Audiol. 2005 May;44(5):281-292.	Ib	a
34.	Smith P., Davis A., Day J., Unwin S., Day G., Chalupper J.: Real-world preferences for linked bilateral processing. Hearing Journal, Vol. 61, No.7, 2008	Ia	b
35.	Sockalingam R., Holmberg M., Eneroth K., Schulte M.: Binaural Hearing Aid communication shown to improve sound quality and localization, Hearing Journal., Vol. 62, Issue. 10, 2009	IIa	b
36.	Souza PE, Arehart KH, Kates JM, Croghan NB, Gehani N. Exploring the limits of frequency lowering. J Speech Lang Hear Res. 2013 Jun 19.	Ib	a
37.	Surr RK, Walden BE, Cord MT, Olson L. Influence of environmental factors on hearing aid microphone preference. 2002 J Am Acad Audiol. 2002 Jun;13(6):308-22.	IIb	a
38.	Uys M, Pottas L, Vinck B, van Dijk C. The influence of non-linear frequency compression on the perception of music by adults with a moderate to severe hearing loss: subjective impressions. S Afr J Commun Disord. 2012 Dec;59:53-67.	Ib	a
39.	Wolfe J, John A, Schafer E, Nyffeler M, Boretzki M, Caraway T, Hudson M. Long-term effects of non-linear frequency compression for children with moderate hearing loss. Int J Audiol. 2011 Jun;50(6):396-404.	Ib	a
40.	Wolfe J, John A, Schafer E, Nyffeler M, Boretzki M, Caraway T. Evaluation of nonlinear frequency compression for school-age children with moderate to moderately severe hearing loss. J Am Acad Audiol. 2010 Nov-Dec;21(10):618-28.	Ib	a
41.	Wu YH, Stangl E, Bentler RA, Stanziola RW. The effect of hearing aid technologies on listening in an automobile, A1. J Am Acad Audiol. 2013 Jun;24(6):474-85. doi: 10.3766/jaaa.24.6.4. PubMed PMID: 23886425.	IIa	a
42.	Wu YH, Stangl EA, Bentler RA, Stanziola RW (2012): “The effect of hearing aid technologies on listening in cars.” JAAA (accepted)	IIb	a

Levels of Evidence

Ia - Well-designed meta-analysis of >1 randomized controlled trial

Ib - Well-designed randomized controlled study

IIa - Well-designed controlled study without randomization

IIb - Well-designed quasi-experimental study

III - Well-designed no experimental studies, i.e., correlational and case studies

IV - Expert committee report, consensus conference, clinical experience of respected authorities

Publication Class

a. Public peer reviewed
b. Published
c. Conference contribution
d. Phd thesis
e. Master / Bachelor thesis
f. Expert opinion / white paper / letter
g. Internal reports / Unpublished

3.2 Investigationa l Product (t reatment, de vice) and Indic ation

(ICH/E6 6.2.1; AGEK 2; SPIRIT #6)
ICH: Name and descripti on of the investigatio nal prod uct(s).

All investigational products are CE-labelled MDs. All MDs (hearing instruments with respective hearing instrument software and acoustic couplings, fitting software and wireless accessories) are bearing product names and unique serial numbers for an unambiguous assignment and retracing of the product to the subject. State of the art methods may be used to verify the fitting of the hearing systems (e.g. Real Ear Measurements [12]).

Hearing Instruments:

In general, the hearing instruments themselves can be separated in different form factors: In-The-Ear (ITE), Invisible-In-Canal (IIC), Receiver-In-Canal (RIC) and Behind-The-Ear (BTE) including different acoustic couplings depending on the hearing loss and on the anatomical conditions of the hearing instrument user.

Hearing Instrument Software:

The hearing instrument software comprises the operating system and the signal processing of a hearing instrument. It contains the algorithmic approaches and can be operated in a respective hearing instrument.

Acoustic coupling:

Together with a BTE or RIC, the acoustic coupling (e.g. earpiece) is a system which is also a medical device. Without the merge of the acoustic coupling and hearing instrument the earpiece has no medical harness.

Fitting Software:

The hearing instruments will be set and fine-tuned to the individual hearing loss and needs of the subject by using the corresponding fitting software in accordance to the specialised information whereof the latest version can always be printed out (e.g. of the Phonak Fitting Software).

Wireless Accessories:

The Sonova brand Wireless Accessories comprise various solutions to simplify the volume adjustment as well as the program switching in a hearing instrument but also to enhance speech intelligibility in noisy environments, in making phone calls or in bridging distances between a talker and the hearing instrument user like in class/conferences/lectures. The subsequent current Sonova brand Wireless Accessory solutions are also MDs. They also have a unique serial number for an unambiguous assignment and retracing of the product to the subject. The intended purpose is also according to the instruction manual.

3.3 Preclinic al Evidence

(ICH/E6 6.2.2; SPIRIT #6a)
ICH: A summary of findings from nonclinical studies that potentially have clinical significance …..

For MD this entry is only applicable if needed for pre-marketed/marketed devices needing Swissmedic notification (Guidance on the biological evaluation of medical devices is given in ISO 10993). Therefore, this entry is not applicable for this study.

3.4 Clini cal Evidence to Date

(ICH/E6 6.2.2; SPIRIT #6a)
ICH: A summary of findings from … and from clinical trials that are relevant to the trial.

There is no available clinical research data to date on the investigational product.

3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

(ICH/E6 6.2.4; SPIRIT #6a)
ICH: Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
The hearing instruments will be set and fine-tuned to the individual hearing threshold and needs of the subject in accordance to established audiological test methods and according to the best knowledge and conscience of trained staff to promote new developments.

3.6 Explanation for choice of comparator (or placebo)

(AGEK 11.3; SPIRIT #6b)

To investigate the effect of the sound changing principles in hearing instruments, different parameter settings of the respective application will be compared. This may include a setting in which the sound changing principle is disabled (switched off). If applicable the novel sound changing principle will be compared with those used in previous hearing instruments. Depending on which application will be compared the number of comparators may differ.

3.7 Risks / Benefits

(ClinO, Appendix 4, 3.5; Art 25d2; ICH/E6 6.2.3; AGEK 11.1; SPIRIT #6a; MD: ISO 14155 Annex A & ISO 14971)
ICH: Summary of the known and potential risks and benefits, if any, to human subjects.

Risks regarding the Investigational device (MD).

1. Infections can be caused by injuries of the ear canal which can occur by the placement of the acoustic coupling (e. g. receiver, earpiece) to the outer ear canal or by the placement of an ITE or IIC device. Therefore, the ear canal will be thoroughly checked and assessed during the study.

2. Pressure points can be caused by the hearing instrument or the acoustic coupling. In case of pressure points, the hearing instrument should not be worn until it healed up. The cause of the pressure point would then be investigated.

3. Tinnitus can be caused by wearing of the hearing instrument. An existing tinnitus can be temporarily amplified. If the tinnitus doesn't improve after several days of not wearing the hearing instrument, an assessment with an independent doctor (ENT) is necessary.

4. A headache can occur, especially for new hearing instrument users. If a headache appears, the subject is instructed to interrupt the hearing instrument use until the audiologist applies a new fitting (e.g. reduced gain level) to acclimatize the subject to the devices.

5. The hearing instrument can reach a high maximum power output (MPO). The MPO will be set accordingly to clinical expertise at a level that no injuries can occur.

Risks regarding the involved procedures.

1. Used Loudspeakers or Headphones can reach high maximum power outputs. Only standard Loudspeakers and Headphones having a limited maximum power output will be used.

2. Study appointments might be tiring for the subjects, therefore regular pauses will be done during the appointments.

Benefits of the study.

1. Participating subjects learn something new about their own hearing.

2. Participating subjects are fitted with the latest hearing system products and have the opportunity to try it out during the study period.

3. Participating subjects acquire knowledge about how she/he can be served audiologically.

4. Gained knowledge about novel and innovative sound changing principles will drive further development to provide audiologically meaningful and useful solutions for hearing impaired end-users.

3.8 Justification of choice of study population

(ClinO, Art 25d4, Art. 15-17; ICH/E6 6.2.6; AGEK 11.2)
ICH: Description of the population to be studied.

In this study, adult persons with different degrees of hearing abilities will participate. The sound processing in the inner ear significantly differs between normal hearing and hearing impaired persons and, furthermore, is dependent on the degree of the hearing loss. For this reason, the benefit and the performance of new sound changing principles in hearing instruments, which can be individually fitted to a hearing loss, can only be reliably evaluated by appropriate hearing impaired persons. To know the performance for normal hearing abilities also normally hearing subjects may be included. For the assessment of psychoacoustic, behavioural and psychophysiological performance data (Table 6) it is essential to have a comparison against the performance of normal hearing participants who serve as a control group and as an anchor for these kinds of tests. Normal hearing subjects are considered as vulnerable population.

Sonova Employees may be selected for the experiments as they have special education and experience in evaluation trials for sound changing principles and/or work in innovation projects. Additionally they are easily accessible and are highly interested into meaningful evaluation studies. They are considered as vulnerable population since they are in a dependence-relation to Sonova.

4. STUDY OBJECTIVES

(ICH/E6 6.3; AGEK 3; SPIRIT #7)
ICH: A detailed description of the objectives and the purpose of the trial.

This section includes a description of the overall, primary and secondary objective(s) of the study.

4.1 Overall Objective

This study is the overall summation of a series of several sub-studies concerning the evaluation of novel sound changing principles in hearing instruments over the next 10 years. These novel sound changing principles are continuously developed and improved in the mentioned time frame. For each sound changing principle a separate study (sub-study) will be conducted. All of these sub-studies pursue the goal to investigate strength and weaknesses of the respective novel sound changing principle.

The overall objective is to investigate the audiological performance for each of these sound changing principles on hearing impaired subjects using respective hearing performance outcome measures. The results are assessed in referenced to those from sound changing principles used in recent hearing instruments and/or with the sound changing principle disabled.

4.2 Primary Objective

The primary objective of each study is to determine and assess the benefit of these novel sound changing principles for their intended use in terms of the associated hearing dimension (speech intelligibility, signal clarity and sound quality / hearing comfort) respectively. Depending on the aim of the respective sound changing principle the associated hearing performance outcome measure will be

chosen. Furthermore different parameter adjustments of the novel sound changing principle will be examined to determine the most useful setting. The results are assessed in referenced to those from sound changing principles used in recent hearing instruments and/or with the sound changing principle disabled.

4.3 Secondary Objectives

The secondary objective is to investigate and assess the effect of the respective sound changing principle in real world environment. The results are assessed in referenced to those from sound changing principles used in recent hearing instruments and/or with the sound changing principle disabled.

4.4 Safety Objectives

N/A

5. STUDY OUTCOMES

(ICH/E6 6.4.1; AGEK 4.1; SPIRIT #12)
ICH: A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

This section includes a description of the outcomes of the study including the specific measurement variable and analysis metric.

5.1 Primary Outcome

The primary outcomes are the laboratory test results. These tests intend to evaluate the hearing performance in terms of speech intelligibility, signal clarity and sound quality / hearing comfort. With help of the received data from these outcome measurements it can be concluded whether the experimental condition is superior to the comparator with regard to hearing performance.

Each sub-study focuses specifically on one of these hearing dimensions. The corresponding other hearing dimensions may be additionally examined to investigate a trade-off (e.g. trade-off for speech intelligibility versus sound quality / hearing comfort). Depending on the investigational sound changing principle and the corresponding focused feature or function (aim) the appropriate audiological testing method will be chosen (Table 4).

Table 4: Audiological testing methods for outcome measures in the laboratory

Performance	Aim	Method	Result [unit]
Speech intelligibility	Assessment of speech intelligibility in quiet	Freiburger Sprachtest [13]	Discrimination [%]
	Assessment of speech intelligibility in noise	Oldenburger Satztest (OLSA) [14, 15]	Speech intelligibility threshold in noise [dB SNR]
	Assessment of speech intelligibility in quiet or in noise	Einsilber-Reimtest nach von Wallenberg und Kollmeier (WaKo) (quiet/noise) [16]	Discrimination [%]
	Assessment of speech intelligibility in quiet or in noise	Göttinger Satztest (GöSa) (quiet/noise) [17]	SRT in quiet [dB], in noise [dB SNR]
	Assessment of speech intelligibility with variable target location and talker identity	Coordinate Response Measure [18, 19, 20]	SRT [dB] or performance level (%-correct responses)
	Assessment of cognitive influences on speech perception	Cognitive Measures, e.g. for Working-Memory Capacity (e.g., Reading Span [21]), Executive Functioning and Attention (e.g., Stroop Task), Overall Cognitive Ability (e.g., MoCA [22])	Performance Level [%-correct responses or time-to-complete outcomes]
	Objective Assessment of Listening Effort and Spare Capacity	Response Delays during above listed Speech Intelligibility Tests; Dual-Task Paradigms with Speech Intelligibility as primary task and a Cognitive Outcome Measure as the Secondary Add-On Task (e.g., Assessment of Cognitive Capacity for tasks of Selective Attention or Working Memory during the Primary Task [23, 24, 25])	SRT [%] and Errors [%] or Response Times [ms]
Signal Clarity	Determination of hearing threshold of pure tones	Pure Tone Audiometry [26]	Yes/No replies
	Determination of threshold of fricatives	Phoneme Perception Test (PPT) [Error! Reference source not found. - 29]	Detection, Distinction and Recognition Threshold [dB SPL]
	Determination of localization capabilities with and/or without hearing systems	Localization Test in Quiet, Noise, Reverberation. [31]	Average RMS localization error [°], back-front confusions [%]
	Assessment of music perception	Adaptive Music Perception Test [32]	Detection Threshold
Sound Quality / Hearing Comfort	Qualitative description	Interviews: Qualitative and Quantitative (ad hoc list of questions, semi-standardized, standardized or normed), Focus Groups [43]	Narrative, open/closed replies, ranking, single/multiple choice, or point on a rating scale
	Assessment of sound quality	Subjective Rating Scale [33, 34]	Point on a scale

	Judgment which of the entities in pairs is preferred or has a greater amount of some quantitative property	Paired Comparison [35]	Preference or point on a scale
	Subjective evaluation of the audio quality of a defined sound	Multi-Stimulus Test with Hidden Reference and Anchor (MUSHRA) [36]	Point on a scale
	Quantitative assessment of a person's perception of facts or circumstances regarding hearing system	Semantic Differential Analysis/ Polarity Profile [37]	Point on a scale
	Assessment of a person's perception of a specific listening situation through selected hearing systems or hearing aid programs	Simulations of Various Listening Situations (in Car/Cafeteria/Reverberation) via Loudspeakers including Preference Rating or Subjective Rating Scale	Preference or point on a scale
	Determination of acceptable noise intensities while listening to speech	Acceptable Noise Level (ANL) Test [38, 39]	Tolerated SNR [dB]
	Assessment of the subjectively perceived loudness of a test signal	Categorial Loudness Scaling [40]	Loudness [CU]
	Assessment of a hearing aid user's affection by objective occlusion (closed ear canals)	Occlusion Measurement and Leakage Measurement using REM method [41]	Frequency Responses [magnitude and phase of the output as a function of frequency] => Level differences [dB] and Level Loss [dB]

5.2 Secondary Outcomes

The secondary outcomes are the subjective test results and comments gathered in real world environment (e.g. during guided walks) and with questionnaires during the home trials. Depending on the investigational sound changing principle and the corresponding focused feature or function (aim) the appropriate audiological testing method will be chosen. A collection of possible methods is listed below (Table 5).

Table 5: Audiological testing methods for outcome measures in real world environment

Performance	Aim	Method	Result [unit]
Subjective test in real world environment	Subjective Assessment of Listening Effort and Hearing Fatigue	Questionnaires about Listening Effort in Everyday Life (e.g., CTO [42]), Rating Scales of Effort perceived during above listed Audiological Tests	Score on a Continuous Rating Scale or on a Likert Rating Scale
	Assessment of system stability	Quantitative Questionnaires [43]	Yes/No replies and open-ended
	Assessment of real-time individual information regarding hearing system and/or listening situation via Phonak App on Smartphone in daily life	MobEval [44, 45, 46]	Logging of predefined HI parameters, time [h/min/s], open/closed replies or single/multiple choice
	Survey of audibility of distortions, artefacts, interruptions, feedback, system noise or other malfunctions	Quantitative Questionnaires [43]	Yes/No replies and open-ended
	Determination of individual information or circumstances regarding hearing system and/or listening situation	Interviews: Qualitative and Quantitative (ad hoc list of questions, semi-standardized, standardized or normed), Focus Groups [43]	Narrative, open/closed replies, ranking, single/multiple choice, or point on a rating scale
	Measurement of self-reported auditory disability across a wide variety of domains, reflecting the reality of hearing in the everyday world	The Speech, Spatial and Qualities of Hearing Scale (SSQ) [47]	Score on a Continuous Rating Scale

5.3 Other Outcomes of Interest

Other outcomes of interest are potential side effects and informal feedback from the subjects regarding subjective rating of the performance. Additionally further measures (e.g. regarding psychoacoustic function) may be used to determine the individual hearing abilities and/or compare and correlate these results with the ones from the primary outcomes (Table 6Table 6:).

Table 6: Additional furth er measures

Performance	Aim	Method	Result [unit]
Auditory function	Assess Psychoacoustic measures	Basic psychoacoustic measurements (e.g. ITD/IPD/ILD, JNDs, BMLDs, frequency discrimination thresholds, measures of frequency selectivity, frequency modulation detection), Tinnitus pitch and loudness matching, TEN (Threshold-Equalizing-Noise) Test [48 - 51]	Detection threshold
Behavioural observations	Observation of behaviour during the test session	Video analysis, recordings, motion- and position sensor, reaction time measurement	Analysis of respective observation method
Peripheral psychophysiological observations	Assess Peripheral psychophysiological measures	HEG (hemoencephalography), EEG (electroencephalography), ECG (electrocardiogram), EMG (electromyography), EDA (Electro Dermal Activity or Galvanic Skin Response), Respiratory rate, Pulse rate, Pupillometry [52 – 54]	Respective result of peripheral psychophysiological measure

5.4 Safety Outcomes

N/A

6. STUDY DESIGN

(ICH/E6 6.4; AGEK 4; SPIRIT #8)

This section describes the design of the study and its rationale, the type, allocation ratio and framework.

6.1 General study design and justification of design

(ICH/E6 6.4.2, 6.4.5; AGEK 4.2; SPIRIT #8)

ICH: The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design.

ICH: A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

ICH: The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

A methodical evaluation of novel sound changing principles in CE-Labelled Sonova brand hearing instruments (primarily Phonak hearing instruments) is intended to be conducted on hearing impaired and normal hearing subjects. This will be a controlled, single blinded (participants), randomised (sequence of test procedure and sequence of tested setting/device), cross-over (investigational product/setting) active comparator study which will be conducted mono centric at Sonova AG Headquarters based in Stäfa.

Treatments/Interventions:

Hearing systems (hearing instruments with hearing instrument software and respective acoustic coupling, fitting software and wireless accessories). All CE labelled MDs.

Population:

Adult participants with different degrees of hearing abilities. In the pre-studies it is planned to include up to 5 participants. The main studies will normally include 20 - 25 participants each. If possible a power analysis is carried out for each study to determine the necessary number of subjects.

Level and method of blinding/masking:

The tests will be at least single blinded.

When testing different parameter settings of the novel application and/or comparing novel with previous applications whereas these approaches are available as optional settings in one hearing instrument, the subjects will not know which setting is activated during the respective testing.

In cases where these settings are not accessible in one hearing instrument (e.g. previous sound changing principle is not supported by the latest hearing instrument technology any more), the test needs to be undertaken with several (two) separate hearing instruments, whereas the housing of these hearing instruments may differ. The subjects will not be informed about the setting or the sound changing principle in the specific hearing instrument.

If possible double blinding will be accomplished with help of computer controlled testing procedures (e.g. software tool for MUSHRA test).

Kind of comparators:

The comparators are different parameter setting of novel sound changing principles in recent hearing instrument (this may include a setting in which the sound changing principle is switched off) as well as sound changing principles in previous hearing instruments.

Method of assignment to treatment/intervention:

This study will be a controlled cross-overs study. Each subjects will receive the intervention to be tested (hearing systems with novel sound changing principles) as well as the respective comparator and serves therefore as his or her own control. The order of the investigational settings and/or products will be randomized. For home trials a respective wash-out period of one week is considered and applied if possible and meaningful.

Sequence of duration of all study periods:

The studies shall take place within the timeframe from 01.07.2016 to 30.06.2026 after approval by CEC. Each study part will take about 6 months and may overlap with other sub studies. The detailed duration of the appointments are listed in the study schedule.

6.2 Methods of minimising bias

(ICH/E6 6.4.3; AGEK 4.3; SPIRIT #16, 17)
ICH: A description of the measures taken to minimize/avoid bias, including: Randomization, Blinding.

In order to minimize bias, the following measures will be taken:

6.2.1 Randomisation

As this is a controlled cross-over study each subject serves as his or her own control. For the reduction of order effects the sequence of the tested settings (and/or tested devices) will be randomized. To do so block randomization will be used. The randomization is applied to all investigational settings for both the laboratory trials and the trials in real world environment. For sub-studies with several test methods the order of the test methods will be also randomized with help of block randomization. Randomization and concealment of randomization list is generated by the Principle Investigator. For laboratory tests where several individual ratings are executed with help of computer controlled testing procedures (e.g. software tool for MUSHRA test) simple randomization is applied to the sequence of the respective settings. This simple randomization is done automatically by the tool, the individual simple randomization can be examined afterwards.

6.2.2 Blinding procedures

Trial participants will be blinded after assignment to interventions. The subjects will not know which hearing instrument technology they are wearing or which hearing instrument setting is activated during the respective testing (Please refer to section 6.1 General study design and justification of design). If possible double blinding will be executed with help of computer controlled testing procedures (e.g. software tool for MUSHRA Test).

6.2.3 Other methods of minimising bias

In addition the following methods will be carried out:

- Sensitizing the investigators to bias (e.g. Halo-Effects).
- Application of standardized test methods according to their instructions to avoid training effects
- Usage of validated questionnaires to the greatest possible extent. However, specifically adapted questionnaires are inevitable to validly capture the appropriate information needed
- Orthogonal design of the questionnaires to fulfil the criteria for test quality (objectivity, validity, reliability)
- Limited information will be given to the subjects regarding the products and the sound changing principles being tested
- In order to ensure a high satisfaction of the subject, the physical position in and on the ear must be comfortable and it must be ensured that the subject can operate the device well (e. g. putting the hearing instruments on, changing batteries, switching on/off). These aspects will be observed and checked throughout the study sections so that they are not the form factor to cause any bias in results, especially subjective results

6.3 Unblinding Procedures (Code break)

(ICH/E6 6.4.8; AGEK 4.2; SPIRIT #17b)
ICH: Maintenance of trial treatment randomization codes and procedures for breaking codes.

N/A

7. STUDY POPULATION

(ICH/E6 6.2.6, 6.4.6; AGEK 3.2, 5; SPIRIT #9, 10, 15, 16, 21)
ICH: Description of the population to be studied.

This section describes the population to be studied.

7.1 Eligibility criteria

(ClinO, Art 25d5; ICH/E6 6.5.1&6.5.2; AGEK 5.2&5.3; SPIRIT #10)
ICH: Subject inclusion and exclusion criteria.

Only adult subjects will participate. Hearing impaired subjects as well as normal hearing subjects will participate, the latter as a control group.

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Adult (minimum age: 18 years) hearing impaired subjects both with and without (experience with) hearing aids
- Adult normal hearing subjects (minimum age: 18 years)
- Healthy outer ear (without previous surgical procedures)
- Ability to fill in a questionnaire conscientiously
- Informed Consent as documented by signature

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Contraindications to the MD in this study, e.g. known hypersensitivity or allergy to the investigational product
- Limited mobility and not in the position to attend weekly appointments
- Limited ability to describe listening impressions/experiences and the use of the hearing aid
- Inability to produce a reliable hearing test result
- Massively limited dexterity
- Known psychological problems
- Known central hearing disorders

7.2 Recruitment and screening

(ClinO, Art 25, Appendix 3, 1.4 & 1.6; AGEK 5.1; SPIRIT #15)

The recruitment will take place outside the study site for external subjects and will also take place internal (at Sonova) for internal subjects.

At Sonova AG Headquarters, a participant database is existing which is currently containing approx. 700 hearing impaired subjects (various degrees of hearing loss) from circumjacent cantons. Furthermore, this database is containing hearing impaired employees from Sonova AG (internal subjects). The database is permanently extended (study independently) with new subjects recruited via different paths and screened by qualified Audiologists employed at Sonova AG. One examples for this recruiting is a flyer for Phonak Field studies (see attachment: Flyer_Phonak_Feldstudie.pdf).

Recruitment and screening outside:

The pre-selection of suitable participants will be done by the principal investigator after receiving the study approval of the responsible CEC by using the participant database belonging to the study site.

The preselected participants will be listed in a password locked file. Only the study personal will have access to this file. The preselected potential participant will be contacted via telephone. At this initial contact, the time expenditure and the availability period will be discussed. If a participant is interested in participating in the study, the screening appointment for a preliminary clarification will be arranged and the participant information and informed consent will be sent to the potential participant by post or email at least one week before the screening appointment takes place. The assessment of the screening serves to judge the inclusion criteria (e. g. pure tone audiometry), giving answers to any questions which the subjects may have, giving information about the study and sign of the informed consent.

For all study related appointments at Sonova AG, the participants will receive a compensation of 25 CHF/hour and a SBB train ticket (2nd class) from their home address to Sonova AG, Laubisrütistrasse

28, 8712 Stäfa, by the end of the study.

Recruitment and screening inside:

The participants are recruited by the study team in the according study site (Sonova AG). The participants are employees at the study site. The pre-selection of suitable hearing impaired participants will be done by the principal investigator after receiving the study approval of the responsible CEC by using the participant database belonging to the study site.

The time expenditure and the availability period will be directly discussed with the participant. If a participant is interested in participating in the study, the screening appointment for a preliminary clarification will be arranged and the participant information and informed consent will be sent to the potential participant by email at least one week before the screening appointment takes place. The assessment of the screening serves to judge the inclusion criteria (e. g. pure tone audiometry), giving answers to any questions which the subjects may have, giving information about the study and sign of the informed consent.

The participants participate on a voluntary basis and contribute to an investigational benefit for the company.

7.3 Assignment to study groups

(AGEK 5; SPIRIT #16)

This study will be a controlled cross-overs study with active comparator whereas each subjects will receive the intervention to be tested (hearing systems with novel sound changing principles) as well as the respective comparator and serves therefore as his or her own control. For the reduction of order effects the sequence of the test procedures as well as the sequence of the tested settings (and/or tested devices) will be randomized. The randomization is applied to all investigational settings for both the laboratory trials and the trials in real world environment . (refer to 6.2.1 Randomisation).

7.4 Criteria for withdrawal / discontinuation of participants

(ClinO, Art 9; ICH/E6 6.5.3; SPIRIT #21b)
Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying: a) When and how to withdraw subjects from the trial/ investigational product treatment. c) Whether and how subjects are to be replaced.

If a subject will be withdrawn (e. g. withdrawal of informed consent, non-compliance, disease progression, safety etc. or study or routine procedure must be stopped, e. g. due to safety concerns), a final assessment of the ear and ear canal will be carried out and all products as well as all study material that had been used have to be returned by the participant to the study site. The participants participate on a voluntary basis and can abort the participation on the study at any point of the study. The withdrawn participant will be replaced by another voluntary participant, if needed. The measurement results of the withdrawn participants will be excluded of the evaluation if the results are not complete to be included in the analysis. A new participant has to pass each study trial from the beginning.

8. STUDY INTERVENTION

(SPIRIT #11)

8.1 Identity of Investigational Products (treatment / medical device)

(ICH/E6 6.2.1, 6.4.2, 6.4.4; AGEK Checklist 2, item 3)
ICH: A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s).

This section describes all trial treatments for each arm of the study.

8.1.1 Experimental Intervention (treatment / medical device)

ICH: Name and description of the investigational product(s).

All investigational devices are CE marked and based on the Sonova brand hearing system portfolio. This includes hearing systems comprising hearing instruments with hearing instrument software and respective acoustic coupling, fitting software and wireless accessories. The application is done according to the specialised information.

8.1.2 Control Intervention (standard/routine/comparator treatment / medical device)

ICH: Name and description of the investigational product(s).

Same as in 8.1.1, whereas the respective sound changing principle is disabled (switched off or switched to a parameter setting with weakest effect) as well as previous hearing instrument technology (containing comparable previous sound changing principles).

8.1.3 Packaging, Labelling and Supply (re-supply)

ICH: Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

N/A

8.1.4 Storage Conditions

All MD and MD supplies have to be stored according to standard procedures as mentioned in the manufacturer directions. The hearing instruments will be stored in their hearing instrument cases (dry and dust-free). There are no special environmental conditions necessary for storage.

8.2 Administration of experimental and control interventions

(ICH/E6 6.4.4)

8.2.1 Experimental Intervention

ICH: Description of and justification of the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

The study is an clinical trial with medical devices.

All medical devices in this trial are CE marked and the application is done according to the specialized information.

Description of route, dose and the rationale for timing of the investigational medical devices, see the following chapters:

- 3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)
- 6.1 General study design and justification of design

Description of study procedures, use and estimated exposure to humans, see the following chapters:

- STUDY SCHEDULE
- 5 STUDY OUTCOMES
- 6.1 General study design and justification of design

8.2.2 Control Intervention

ICH: Description of and justification of the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

Same as in 8.2.1

8.3 Dose / Device modifications

(SPIRIT #11b)

N/A

8.4 Compliance with study intervention

(ICH/E6 6.6.3; AGEK Checklist 2, item 2; SPIRIT #11c)
ICH: Procedures for monitoring subject compliance.

N/A

8.5 Data Collection and Follow-up for withdrawn participants

(ICH/E6 6.5.3; AGEK 9.2; SPIRIT #18b)
ICH: .....b) The type and timing of the data to be collected for withdrawn subjects. d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

The subjects participate on a voluntary basis and can abort the participation on the study at any point of the study. The withdrawn subject will be replaced by another voluntary subject. The measurement results of the withdrawn subject will be included to the evaluation if data are complete for the appropriate trial. The new subject has to pass each study trial from the beginning.

8.6 Trial specific preventive measures

(ICH/E6 6.6.2; AGEK 9; SPIRIT #11d)
ICH: Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

To avoid discomfort through too loud output levels of the hearing instruments which could harm the subjects ear, the uncomfortable level (UCL) will be measured within the pure tone audiogram during the screening appointment. The UCL will be used for the fitting of the hearing instruments to ensure a comfortable maximum power output.

After fitting the hearing instruments to the individual hearing loss of the subject, the subjective acceptance of loud input signals will be tested (tolerance test) to ensure that the individual maximum power output (based on the UCL measurement) of the hearing instruments is guaranteed and accepted by the subject.

8.7 Concomitant Interventions (treatments)

(ICH/E6 6.6.2; AGEK 9; SPIRIT #11d)
ICH: Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

N/A

8.8 Study Drug / Medical Device Accountability

(ICH/E6 6.4.7; AGEK Checklist 2, item 1; SPIRIT 11c)
ICH: Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

N/A

8.9 Return or Destruction of Study Drug / Medical Device

(AGEK Checklist 2, item 1; SPIRIT 11c)

At the end of the study during the final appointment, all study devices will be returned to the according PI.

9. STUDY ASSESSMENTS

(ICH/E6 6.7, 6.8; AGEK 6, 7; SPIRIT #18a)

This section includes a description of the procedures, measurements, collections and storage of samples taken.

9.1 Study flow chart(s) / table of study procedures and assessments

Each study is a combination of a pre-study and a main study. Each study part consists of a screening, study appointments and one follow-up appointment.

Several pre-studies may be necessary and conducted. The Schedule for a pre-study is visualized in Table 7Table 1. The number of the pre-study appointments may vary whereas a minimum of 3 appointments and a maximum of 6 appointments is considered. The main study represents the actual study for the investigation of one sound changing principle. The results from the pre studies are used to specify the main study. The Schedule is visualized in Table 8. The number of the study appointments may vary depending on the number of tests and test methods being executed for a respective sound changing principle. For a main study a minimum of 4 and a maximum of 8 study appointments is considered. Please note the following tables repeat those of the section STUDY SCHEDULE.

Table 7: Pre-Study schedule

Study Period	Screening	Pre-study appointments				Follow-up (final appointment)
Visit Number	1	2	(3)	(4)	(5)	3…6
Time [hrs]	1.5	2	(2)	(2)	(2)	2
Subject Information and Informed Consent	x					
Audiological History	x					
Physical Examination of Ear and Ear Canal	x	x	(x)	(x)	(x)	x
Audiogram	x					x
Check In- /Exclusion Criteria	x					
Decision Subject Participation	x					
Encoded Subject ID	x					
Fitting HI		x	(x)	(x)	(x)	(x)
Objective Measurements		x	(x)	(x)	(x)	(x)
Subjective Measurements		x	(x)	(x)	(x)	(x)
Introduction to Handling (depending on randomisation list for home trials)		x	(x)	(x)	(x)	
Scheduling Next Visit	x	x	(x)	(x)	(x)	
Capture of Adverse Events and Device Deficiencies		x	(x)	(x)	(x)	x

Table 8: Main study schedule

Study Period	Screening	Main study appointments						Follow-up (final appointment)
Visit Number	1	2	3	(4)	(5)	(6)	(7)	4…8
Time [hrs]	1.5	2	2	(2)	(2)	(2)	(2)	2
Subject Information and Informed Consent	x							
Audiological History	x							
Physical Examination of Ear and Ear Canal	x	x	x	(x)	(x)	(x)	(x)	x
Audiogram	x							x
Check In- /Exclusion Criteria	x							
Decision Subject Participation	x							
Encoded Subject ID	x							
Fitting HI		x	x	(x)	(x)	(x)	(x)	(x)
Objective Measurements		x	x	(x)	(x)	(x)	(x)	(x)
Subjective Measurements		x	x	(x)	(x)	(x)	(x)	(x)
Introduction to Handling (depending on randomisation list for home trials)		x	x	(x)	(x)	(x)	(x)	
Scheduling Next Visit	x	x	x	(x)	(x)	(x)	(x)	
Capture of Adverse Events and Device Deficiencies	x	x	x	(x)	(x)	(x)	(x)	x

9.2 Assessments of out comes

ICH: Specification of the efficacy parameters. Specification of safety parameters.

This section includes a description of each endpoint, what variables will be assessed/observed and how it will be done, including any related processes to promote data quality.

9.2.1 Assessment of primary outcome

ICH: Methods and timing for assessing, recording, and analysing of efficacy & safety parameters.

The primary outcomes are the laboratory test results (Reference to section 5.1 Primary Outcome). These tests intend to determine the hearing performance provided by the device. They are conducted with help of corresponding measurement tools, whereas the results are stored automatically in an appropriate format (e.g. xls file). Depending on the investigated sound changing principle the suited outcome measurement is chosen. The respective measurements are carried out at each study appointment. In general the content of these assessments in one sub-study includes measurements to investigate one of the three hearing performance dimensions (speech intelligibility, signal clarity, sound quality / hearing comfort). The respective other hearing dimensions may be investigated additionally to examine trade-off aspects. As well the investigational application and the comparator have to pass the same measurements to get comparable data. With help of the received data it can be concluded whether the experimental condition is superior to the comparator with regard to hearing performance.

9.2.2 Assessment of secondary outcomes

ICH: Methods and timing for assessing, recording, and analysing of efficacy & safety parameters.

The secondary outcomes are the subjective test results of questionnaires during tests in real world environment (Reference to section 5.2 Secondary Outcomes). This includes home trials and may include guided walks. This assessment will be done between the appointments (home trials) and/or at specifically defined study appointments (guided walks). Depending on the investigated sound changing principle the suited outcome measurement is chosen. With the questionnaire as well the investigational application and the comparator are subjectively evaluated by the participants. Depending on the study part, the questionnaire will be filled out directly in the laboratory or in an home trial.

9.2.3 Assessment of other outcomes of interest

ICH: Methods and timing for assessing, recording, and analysing of efficacy & safety parameters.

Other outcomes of interest like side-effects will be carefully investigated, evaluated and documented. This outcome will also be documented in the form of questionnaires. Additional further measurements (investigating basic psychoacoustic function for instance) will be done at specifically defined study appointments if necessary (Reference to section 5.3 Other Outcomes of Interest).

9.2.4 Assessment of safety outcomes

ICH E6 6.8: Specification of safety parameters. The methods and timing for assessing, recording, and analysing safety parameters

9.2.4.1 Adverse events

Basically, all participants will be instructed to immediately report any problems, oddness or difficulties which occurred with or through the testing devices by contacting the appropriate investigator. Additionally, the investigator will request the same after each home trial at the beginning of the subject appointment. Any feedback will be recorded in the appropriate eCRF.

9.2.4.2 Laboratory parameters

N/A

9.2.4.3 Vital signs

N/A

9.2.5 Assessments in participants who prematurely stop the study

Withdraw without Adverse Event: If a subject is withdrawn from the study without having an Adverse Event (AE), an audiogram will be recorded in a final appointment and the outer ear will be controlled to ensure that there are no damages through the study.

Withdraw with Adverse Event: If a subject is withdrawn in case of an AE, a referral to an independent doctor will be carried out. In accordance with the subject and the doctor, an additional appointment will be arranged to record a status update.

9.3 Procedures at each visit

Each study part follows the same pattern:

- Pre-Study
  - Screening
  - Pre-study appointments
  - Follow Up
- Main study

- Screening
- Main study appointments
- Follow Up

This pattern ensures the best method to not unnecessarily extend the study and to not perform tests with subjects, which are not needed. For that reason first a pre-study is conducted with only a few participants to test and determine sensitive outcome measures and promising parameter adjustments of the sound changing principle. The aim of the pre-study is to proof the study concept and the scientific interrogation behind it. Several pre-studies may be carried out. If the results of the pre-study are promising, the main study will start.

9.3.1 Screening Appointment

- Mapping to an encoded and randomized subject ID
- Discussion of the subject information and signing of the informed consent which were sent in advance by post or email
- Recording of the subject's audiological history
- Ear and ear canal assessment (otoscopy)
- Hearing test (pure tone and speech audiometry)
- In case of tinnitus: Tinnitus Pitch and Loudness Matching
- Explanation of in-/exclusion criteria
- Decision if patient can participate in the trial regarding to the in-/exclusion criteria
- Scheduling of the next visit

9.3.2 Pre-study appointment

- Ear canal assessment
- Fitting of hearing instrument (randomized)
- Measurements objective and subjective (randomized), see section 9.2.1 and 9.2.2
- Fine tuning hearing instrument, if necessary
- Introduction to handling of hearing system (randomized)
- Signing of the device delivery form
- Schedule next visit

9.3.3 Main study appointments

A main study appointment will only be executed if the pre-study results were promising. The procedure for the main study appointments is the same as for the pre-study appointments (see section 9.3.2).

9.3.4 Final appointment

- Ear canal assessment
- Measurements objective and subjective (randomized), see section 9.2.1 and 9.2.2
- Hearing test (pure tone)
- Calculation and signing of the compensation form
- Signing of the device return form
- Collecting all study material
- Hand out of study feedback form

10. SAFETY

(Clin O Art. 37-43; ICH/E6 6.8; ISO14155 8.2.5, A.14; AGEK 4.1; SPIRIT # 22, 30)

Description of plans for collecting, documenting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.

10.1 Drug studies

N/A

10.2 Medical Device Category C studies

N/A

10.3 Medical Device Category A studies

10.3.1 Definition and Assessment of safety related events

All hearing systems are CE-labelled, i.e. the safety of the user is granted. However, the hearing instrument can reach a high maximum power output (MPO) which can be louder than the user's threshold of uncomfortable levels is. For this reason, the MPO will always be set accordingly to clinical expertise at a level so that no injuries can occur (Refer to 8.6 Trial specific preventive measures). Consequently, neither during the measurements nor in the daily routine the safety of the participants will be compromised.

In order to ensure that each MD works correctly, every device will be checked before each application by the appropriate investigator. Furthermore, the participant is instructed to take note of any unexpected incidences (e.g. redness or swelling of the outer ear) and to document these in the questionnaires. Pressure points are also controlled by the investigator at the beginning and at the end of an appointment. In the case that wearing the test devices in the time between the appointments becomes uncomfortable or even painful, the subjects are instructed not to wear the devices anymore and to contact the investigator for information and, if necessary, a doctor.

Furthermore, the participants are advised not to wear the device if a setting is not acceptable or tolerable, but to contact the investigator for an additional appointment. If any unexpected incidences occur during the lab trials the participant will be encouraged to immediately report the issue to the investigator.

In all cases of undesirable events the responsible supervising investigator within Sonova must be informed immediately. Where appropriate the test subject will be forwarded to an independent fiduciary doctor for further clarification.

10.3.2 Reporting of Safety related events

Reporting to Sponsor:

Health hazards that require measures are reported to the Sponsor within 24 hours upon becoming aware of the event. If any unexpected AEs are to occur (e.g. chronic pain in the ear canal after MD application), the event has to be documented in the AE eCRF. Depending on the event, a decision needs to be made whether the participation in the study has to be interrupted or even cancelled. If required, a referral to an independent doctor is to be carried out. An additional appointment will be arranged with the test participant (e.g. after one to two weeks) in order to record and document the status update.

Reporting to authorities:

In Category A studies it is the investigator's responsibility to report health hazards requiring measures to the local Ethics Committee within 2 days.

11. STATISTICAL METHODS

(ICH/E6 6.9; AGEK 8; SPIRIT # 14, 20)
Statistical considerations
ICH: A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

This section describes the statistical considerations done for the study and the level of significance that will be used. The traceability of the study data is warranted for both the pre-study and the main study at any time.

11.1 Hypothesis

This is a methodical evaluation in which different parameter settings of novel sound changing principles in hearing instruments shall be investigated and new hardware and software technologies of Sonova brand products shall be compared with previous outstanding Sonova brand hearing systems. Hence, this study will not test a specific hypothesis.

11.2 Determination of Sample Size

ICH: The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

Based on numerous publications in the field of audiology research using standardized measurement methods testing hearing impaired subjects as well as on Sonova AG's extensive study experience, a number of maximum 20 - 25 subjects per study is sufficient to obtain statistically significant results on a significance level of 5%.

In the case of the pre-study a maximum of 5 subjects is included, since merely the study concept needs to be proven, and no inferential but only descriptive statistics is carried out. Later, during the main study, both descriptive and inferential statistics are executed. In the past, typically 20 subjects participated per study leading to significant results approaching the primary objective (determine and assess the performance of novel sound changing principles in hearing instruments). To tackle the secondary objective (investigate and assess the effect of the respective sound changing principles in real world environment) mainly descriptive statistics is carried out.

11.3 Statistical criteria of termination of trial

ICH: A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.

After each pre-study an analysis is performed. The corresponding results are the basis for the further progress of either an additional pre-study or the main study which might be adjusted accordingly, if necessary. If the study design has to be adjusted severely or changed based on former results this will be reported to the ethics commission via an amendment.

11.4 Planned Analyses

ICH: A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

In a first step, the distribution of the collected subjective and objective data is verified. Based on this outcome (normally distributed yes/no) and depending on the scale level (nominal, ordinal, interval or rational) of the variables, descriptive statistics is executed in the form of determining the mean value and standard deviation or the median and quartile, respectively. Furthermore, diagrams for visualization are compiled such as boxplots, histograms and scatterplots.

Then, after a determination of the measurement variables regarding their relationship or their difference, inference statistics is executed by applying the appropriate parametric or non-parametric test depending on the data's distribution either using the correlation coefficient (Pearson, Spearman), t-Test, ANOVA, MANOVA, Mann-Whitney-U-Test, or the Wilcoxon-Test. Generally, a significance level of 5% is pursued.

11.4.1 Datasets to be analysed, analysis populations

ICH: The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

The data of all participants and measurement methods will be analysed. Subgroups typically composed are hearing loss dependent groups (mild, moderate, severe, profound) and groups depending on their experience level wearing hearing instruments or using accessories (non-experienced, short-term, experienced, long-term user). In case of a subject withdrawal, the statistician will decide if the data can be used for a part of the statistical analysis or if the data will be dropped out completely.

11.4.2 Primary Analysis

The primary analysis will be done by the statistician with help of appropriate software programs (e.g. Matlab, Statistica) by the end of the study (end of the pre-study and end of the main study).

11.4.3 Secondary Analyses

The secondary analysis is done in the same way as the primary analysis.

11.4.4 Interim analyses

ICH 6.9.1: ..... including timing of any planned interim analysis(ses).

The procedure for each study is, to first make a pre-study with a small group of participants. After the pre-study an analysis is done, which can be also named interim analysis. Several pre-studies may be carried out. If the results of the pre-study (the pre-studies) do not look promising, it is decided whether to review the study design or to discontinue the study completely. If the results of the pre-study are sufficient one will continue with the main study.

11.4.5 Safety analysis

The safety analysis will be done permanently during the study by the PI.

11.4.6 Deviation(s) from the original statistical plan

(ICH/E6 6.9.6)
ICH: Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

Deviation(s) from the original statistical plan will be described and justified in a protocol and in a final report, as appropriate.

11.5 Handling of missing data and drop-outs

(ICH/E6 6.9.5; AGEK 8.5; SPIRIT 20c)
ICH: Procedure for accounting for missing, unused, and spurious data.

If data records are complete from subjects who dropped out of the study early, these data will also be used in the analysis. If the data sets are not complete, they will not be integrated in the analysis.

12. QUALITY ASSURANCE AND CONTROL

(ICH/E6 6.11, 6.13; AGEK 12; SPIRIT #19, 23, 27)
ICH: Quality Control and Quality Assurance Procedures

This section describes how quality is assured and controlled.

12.1 Data handling and record keeping / archiving

(ClinO, Art. 18, 45, 57, 62; ICH/E6 6.13; AGEK 12; SPIRIT #19, 27)
ICH: Data Handling and Record Keeping

All data and documents recorded during the study are only accessible to the clinical study team and to the monitor. Results from the laboratory measurements are stored automatically by the corresponding measurement tool in an appropriate format (e.g. xls file). The personal data, the source data of measurements, the documents inclusive all notes get coded and monitored. The code list for the codification is safely kept within the clinical study team.
All listed clinical investigators have access to the code list. This code list is not accessible to other people. The whole original data and personal data are accessible to the whole clinical study team. The study data are to undergo a comprehensive analysis. A written final report containing all phases of the study as well as a summary is to be written after the study is finished and is available to Sonova headquarters. The participants names have to be coded when they have to be used in an analysis.
At the end of the study all of the collected data, either collected in paper form or electronically, will be saved in an investigator site file (ISF) on CD or DVD. The ISF will be archived at Sonova AG Stäfa. The final data export will be stored electronically and in paper form.

12.1.1 Case Report Forms

(ICH/E6 6.4.9)
ICH: The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

Study data is recorded both with paper and with electronic Case Report Forms (p/eCRF). For each enrolled study participant a CRF is maintained. All CRFs are kept current to reflect the subject's status at each phase during the course of study. Participants cannot be identified in the CRF by name or initials and birth date but an appropriate coded identification is used, e.g. VP10SL15 containing the subject number and the study identifier. All study team members are authorized for the CRF entries and it is assured that any authorised person can be identified both for pCRFs and eCRFs. If pCRFs are used, the investigator's acronym as well as the subject ID is filled in and data are entered into an electronic file for analysis by the respective investigator and data get monitored by the assigned monitor. In case of a self-evident corrections, either the subject does it by himself or the investigator undertakes the correction by crossing out the word/sentence with a single horizontal line and by adding the correction including his personal identifier and the date.

12.1.2 Specification of source documents

(ICH/E6 6.4.9)
ICH: The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

Source data are available at the site to document the existence of the study participants and can be found as described in section 12.1. The source data include the original documents relating to the study as follows:

- Demographic data / audiological history
- Visit dates
- Informed Consent Forms
- Randomisation number
- AEs/SAEs
- Device Deficiencies (DD)
- Results of relevant measurements
- Directly recorded data in p/eCRFs

12.1.3 Record keeping / archiving

(ICH/E6 6.13)
ICH: Data Handling and Record Keeping

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. The location of storage is on SharePoint as well in the archive at Sonova AG, Stäfa, as explained in section 12.1.

12.2 Data management

(ICH/E2; AGEK 12.2; SPIRIT #19)

This section describes plans for data entry, coding, security, and storage, including any related processes to promote data quality.

12.2.1 Data Management System

The data management is carried out as described in section 12.1 with help of a data management system. Data management systems that may be applied are the database IBM Clinical Development (former eClinicalOS), the SharePoint Web Application (Microsoft) and the SQL server (Microsoft). The EDC system gets verified and validated by the study team in the form of User Acceptance Tests (UAT) prior to each study start to ensure a proper working of the solution for the user. In addition, the study team accesses a permanent SharePoint site which is verified as well as validated and the filing of the documents follows a predefined scheme. The SQL server working in the background is controlled by the IT at Sonova AG, Stäfa.

12.2.2 Data security, access and back-up

Data security is fully granted, the access is limited to specified persons and both systems IBM Clinical Development and SharePoint undergo a daily backup on appropriate servers.

12.2.3 Analysis and archiving

Data are extracted via the Microsoft SQL server and can be converted to an arbitrary format, e.g. xls file. For the data analysis, different programs are used such as Microsoft Excel, SPSS, Statistica and MatLab. Archiving is done according to section 12.1 for a minimum of 10 years.

12.2.4 Electronic and central data validation

The data is validated by the monitor.

12.3 Monitoring

(AGEK 12.1; SPIRIT #23)

During this Study the Monitor will perform the Monitoring on a regular base - including the initiation visit, the routine visit and the close-out visit - in order to ensure that the study is conducted in accordance to the clinical investigation plan, further written procedures (if applicable), the ISO 14155:2011 as well as further applicable requirement. The extent and nature of the monitoring appropriate for the particular sub-study is assessed separately, including the strategy for source data verification. This will be based on considerations such as the objective, design, complexity, size critical data points and endpoints of the particular sub-study.

12.4 Audits and Inspections

(ClinO, Art. 58, 59; AGEK 12.1; SPIRIT #23)

The study documentation and the source data/documents are accessible to auditors/inspectors and questions are answered during inspections. All involved parties have to keep the participants data strictly confidential.

12.5 Confidentiality, Data Protection

(ClinO, Art. 18, 58; SPIRIT #27, 29)

Direct access to source documents will be permitted for purposes of monitoring (12.3), audits and inspections (12.4) (ICHE6, 6.10). Confidentiality and data protection is granted since access to the original data is only allowed to the study team, the monitor and the auditor. In case of publications by Sonova AG, the data is anonymized and no conclusion can be made to the subjects.

12.6 Storage of biological material and related health data

(ClinO, Art. 18; HVF Art. 28-32; SPIRIT #33)

N/A

13. PUBLICATION AND DISSEMINATION POLICY

(ICH/E6 6.15)
ICH: Publication policy, if not addressed in a separate agreement.

The results are documented in a final report and will be communicated to relevant employees of the Sonova AG. Occasionally parts of the results could be published in internal papers, specialised press (industry magazine), or in respective journals.

14. FUNDING AND SUPPORT

(ClinO, Art. 25i; ICH/E6 6.14; SPIRIT #4)

This section provides a brief statement of sources and types of financial, material, and other support for the trial.

14.1 Funding

(ClinO, Art. 25i)
ICH: Financing and insurance if not addressed in a separate agreement.

All sources and types of financial support for the study is provided by the Sponsor, Sonova AG.

14.2 Other Support

(ClinO, Art. 25i)
ICH: Financing and insurance if not addressed in a separate agreement.

All material is provided by the Sponsor, Sonova AG.

15. INSURANCE

(ClinO Art 12, 13; ICH/E6 6.14, AGEK 10.3; SPIRIT #30)
ICH: ….and insurance if not addressed in a separate agreement.

Category A studies are exempt hence no insurance is required. However, insurance will be provided by the Sponsor, Sonova AG: Police (Nr. CHCANA00770) „Versicherung für klinische Versuche in der Humanforschung“ from the insurance broker KESSLER & CO AG Forchstrasse 95, CH-8032 Zürich. A copy of the specific certificate for each study part is filed in the ISF.

16. REFERENCES

(ICH/E6 6.2.7)
ICH: References to literature and data that are relevant to the trial, and that provide background for the trial.

List of the references cited in the protocol:

1. Declaration of Helsinki, Version October 2013, (http://www.wma.net/en/30publications/10policies/b3/index.html)
2. International Conference on Harmonization (ICH, 1996) E6 Guideline for Good Clinical Practice. (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf)
3. International Conference on Harmonization (ICH, 1997) E8 Guideline: General Considerations for Clinical Trials http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf)
4. Humanforschungsgesetz, HFG Bundesgesetz über die Forschung am Menschen (Bundesgesetz über die Forschung am Menschen, HFG) vom 30. September 2011/ Loi fédérale relative à la recherche sur l'être humain (loi relative à la recherche sur l'être humain, LRH) du 30 septembre 2011. (http://www.bag.admin.ch/themen/medizin/00701/00702/07558/index.html?lang=de)
5. Verordnung über klinische Versuche in der Humanforschung (Verordnung über klinische Versuche, KlinV) vom 20. September 2013 / Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain (Ordonnance sur les essais cliniques, OClin) du 20 septembre 2013. (http://www.bag.admin.ch/themen/medizin/00701/00702/12310/index.html?lang=de)
6. Heilmittelgesetz, HMG Bundesgesetz über Arzneimittel und Medizinprodukte (Heilmittelgesetz, HMG) vom 15. Dezember 2000/Loi fédérale sur les médicaments et les dispositifs médicaux (Loi sur les produits thérapeutiques, LPT) du 15 décembre 2000. (http://www.admin.ch/ch/d/sr/8/812.21.de.pdf)
7. ISO 14155:2011 Clinical investigation of medical devices for human subjects -- Good clinical practice (www.iso.org)
8. ISO 10993 Biological evaluation of medical devices (www.iso.org)
9. WHO, International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
10. Kochkin, S. (2010). MarkeTrak VIII, Consumer satisfaction with hearing aids is slowly increasing, Hearing Journal, Vol. 63, No. 1, 2010
11. Kochkin, S. (2011). MarkeTrak VIII, Patients report improved life with hearing aid usage, Hearing Journal, Vol. 64, No. 6, 2011
12. Aazh, H. and Moore, B.C.J (2007). The Value of Routine Real Ear Measurement of the Gain of Digital Hearing Aids. J. Acoust. Soc. Am., 18: 653-664(12).
13. Kollmeier, B. (1992), Moderne Verfahren der Sprachaudiometrie, Band 1. Medianverlag von Killisch-Horn GmbH
14. Wagener, K., Kühnel, V. & Kollmeier, B. (1999a). Entwicklung und Evaluation eines Satztestes für die deutsche Sprache Teil III: Evaluation des Oldenburger Satztestes. Zeitschrift für Audiologie 38, 1999. p: 86-95
15. Wagener, K., Brand, T. & Kollmeier, B. (1999b). Entwicklung und Evaluation eines Satztestes für die deutsche Sprache Teil I: Design des Oldenburger Satztests. Zeitschrift für Audiologie 38(1), p: 4-14
16. Wallenberg v., E. & Kollmeier, B. (1989). Sprachverständlichkeitsmessungen für die Audiologie mit einem Reimtest in deutscher Sprache: Erstellung und Evaluation von Testlisten. Audiologische Akustik, 28(2):50-65.
17. Sukowski H., Brand T., Wagener K.C., Kollmeier B. (2010). Vergleich des Göttinger Satztests und des Einsilber-Reimtests nach Wallenberg und Kollmeier mit dem Freiburger Sprachtest. HNO Volume 58 Nr. 6
18. Bolia R. S., Nelson W. T., Ericson M. A., Simpson B. D. (2000). A speech corpus for multitalker communications research. Journal of the Acoustical Society of America, 107, 1065–1066;
19. Marrone N. L., Mason C. R., Kidd G., Jr. (2008c) Evaluating the benefit of hearing aids in solving the cocktail party problem. Trends in Amplification 12: 300–315.
20. Helfer and Freyman (2009), "Lexical and indexical cues in masking by competing speech,"

JASA
21. Carroll, R., Meis, M., Schulte, M., Vormann, M., Kießling, J., & Meister, H. (2015). Development of a German Reading Span Test with dual task design for application in cognitive hearing research. International Journal of Audiology, 54(2), 136-141.
22. Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatric Society, 53(4), 695-699.
23. Mishra, S. (2014). Exploring cognitive spare capacity: executive processing of degraded speech. Linköping University.
24. Rudner, M., Ng, H.N.E., Rönnberg, N., Mishra, S., Rönnberg, J., Lunner, T., and Stenfelt, S. (2011). Cognitive spare capacity as a measure of listening effort. Journal of Hearing Science 1, 47-49.
25. Wickens, C.D. (2008). Multiple resources and mental workload. Hum Factors 50, 449-455.
26. Lehnhardt, E. and Laszig, R. (2000). Praxis der Audiometrie, 8. überarbeitete und erweiterte Auflage. Thieme-Verlag Stuttgart.
27. Wolfe, J., John, A., Schafer, E., Nyffeler, M., Boretzki, M., & Caraway, T. (2010). Evaluation of nonlinear frequency compression for school-age children with moderate to moderately severe hearing loss. Journal of the American Academy of Audiology, 21(10), 618-628. doi: 10.3766/jaaa.21.10.2.
28. Wolfe, J., John, A., Schafer, E., Nyffeler, M., Boretzki, M., & Caraway, T., et al. (2011). Long-term effects of non-linear frequency compression for children with moderate hearing loss. International Journal of Audiology, 50(6), 396–404. doi: 10.3109/14992027.2010.551788.
29. Phoneme Perception Test: URL (status: 04.06.2015) https://www.phonakpro.com/com/b2b/de/professional_tools/diagnostic/phoneme-perception-test/overview.html
30. Schmitt, N.; Winkler, A.; Boretzki, M.; Holube, I. (2015). A Phoneme Perception Test Method for High-Frequency Hearing Aid Fitting. Journal of the American Academy of Audiology, 00:1-13(2015). DOI: 10.3766/jaaa.15037
31. Mueller, M.F., Meisenbacher, K., Lai, W., Dillier, N. (2014). Sound localization with bilateral cochlear implants in noise: how much do head movements contribute to localization? Cochlear Implants Int.: 15(1):36-42. doi 10.1179/1754762813Y.0000000040. Epub 2013 Nov 25.
32. Kirchberger, M. J. & Russo, F. A. (2015). Development of the adaptive music perception test. Ear and Hearing, 36(2), 217-228.
33. Borg, I. and Staufenbiel, T. (1997). Theorien und Methoden der Skalierung: eine Einführung. Bern: Huber, Auflage 4. ISBN-10: 34568444476.
34. Hellbrück, J. and Ellermeier, W. (2004). Hören – Physiologie, Psychologie und Pathologie. Hogrefe, 2. aktualisiert und erweiterte Auflage.
35. David, H.A. (1988). The Method of Paired Comparisons. New York: Oxford University Press
36. MUSHRA: ITU-R recommendation BS.1534
37. Gustav H. Blanke (1973). Einführung in die semantische Analyse. Hueber, München, 135–137.
38. Freyaldenhoven, M.C., Nabelek, A.K., Burchfield, S.B., & Thelin, J.W. (2005). Acceptable noise level (ANL) as a measure of directional benefit. Journal of the American Academy of Audiology 16, 228-236.
39. Nabelek, A.K., Freyaldenhoven, M.C., Tampas, J.W., Burchfield, S.B., & Muenchen, R.A. (2006). Acceptable noise level as a predictor of hearing aid use. Journal of the American Academy of Audiology,17, 626-639.
40. Brand, T. and Hohmann, V. (2002). An adaptive procedure for categorical loudness scaling. J. Acoust. Soc. Am., 112(4): 1597-604.
41. Blau, M., Sankowsky, T., Oberdanner, H., Stirnemann, A. (2008). Einfluss des Otoplastikprofils auf den objektiven Okklusionseffekt. DAGA, 2008.
42. Schulte, M., Krüger, M., Meis, M., Wagener, K.C., (2015) Subjective listening effort. The Journal of the Acoustical Society of America, 137(4), 2236-2236.
43. Neumann, W.L. (2005). Social Research Methods: Qualitative and Quantitative Approaches (6th Edition), ISBN-13: 978-0205457939.
44. Larson, R. and Csikszentmihalyi, M. (1983). The Experience-Sampling method. Naturalistic Approaches to Studying Social Interaction: New Directions for Methodology of Social and Behavioral Science. San Francisco, CA: Jossey-Bass.
45. Stone, A. and Shiffman, S. (1994). Ecological momentary assessment (EMA) in behavorial medicine. Annals of Behavioral Medicine, Vol 16(3), 199-202.

46. Intille, S.S., Rondoni, J., Kukla, C., Iacono, I., Bao, L. (2003). A Context-Aware Experience Sampling Tool. 5-10, Ft. Lauderdale, Florida, USA. ACM 1-58113-630-7/03/0004
47. Gatehouse, S., and Noble, W. (2004). "The Speech, Spatial and Qualities of Hearing Scale (SSQ)," Int. J. Audiol. 43, 85-9. (https://www.ihr.mrc.ac.uk/pages/products/ssq)
48. Moore, B.C.J. (2012). An Introduction to the Psychology of Hearing. Sixth edition. Emerald Group Publishing Limited.
49. Moore, B.C., Huss, M., Vickers, D.A., Glasberg, B.R., Alcántara, J.L. (2000). A test for the diagnosis of dead regions in the cochlea. Br. J. Audiol., Aug, 34(4):205-24.
50. Hoare, D.J., Edmonson-Jones, M., Gander, P.E., Hall, D.A. (2014). Agreement and Reliability of Tinnitus Loudness Matching and Pitch Likeness Rating. PloS ONE 9(12): e114553. doi:10.1371/journal.pone.0114553.
51. Strelcyk, O.; Dau, T. (2009). Relations between frequency selectivity, temporal fine-structure processing, and speech reception in impaired hearing. The Journal of the Acoustical Society of America 125 (5), 3328-3345;
52. Bartosinski. 2017. Hemoencephalography (HEG) Biofeedback as a method of stress control among healthy subjects. International Journal of Humanities and Social Science Invention. 6(12), 12-16.
53. Serra-Sala et al. 2012. Evaluating Prefrontal Activation and Its Relationship with Cognitive and Emotional Processes by Means of Hemoencephalography (HEG). Journal of Neuropathy. 16(3), 183-195.
54. Serra-Sala et al. 2016. Clinical usefulness of Hemoencephalography beyond the neurofeedback. Neuropsychiatric Disease & Treatment. 12, 1173-1180.

17. APPENDICES

ICH: (NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

N/A