ALICE

Assistant for LIstening and Communication Enhancement

STUDY PROTOCOL

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Clinical investigation plan

ALICE: ASSISTANT FOR LISTENING AND COMMUNICATION ENHANCEMENT

VERSION 5 – 07/02/2024

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Sponsor

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3.5.1. General introduction

3.5.1.1. Applicable, Law, guidance and standards

This document has been written in accordance with the **EU MDR** and is compliant with the **ISO 14155 standard for Clinical investigation of medical devices for human subjects — Good clinical practice** and ISO 14791 Risk Management

Additionally the MDCG (2020-1) Guidance on clinical evaluation (MDR) / Performance evaluation (IVDR) of medical device software is used.

3.5.1.2. Summary of the project

Aim

This study is set-up as a pre-market clinical investigation of a non-CE marked medical device. The main goal of the study is to measure the efficacy of the ALICE app (Assistant for Listening and Communication Enhancement), a newly developed software application that will function as an added service in the aural rehabilitation of persons with HI, by providing remote monitoring, training and follow-up.

Medical device & classification

The software application is considered to be a medical device type IIa, because it is an active device that monitors a persons' hearing disability and provides a personalized rehabilitation program to alleviate (some of) the experienced hearing difficulties (and could be used to take decisions with a therapeutic purpose of low risk impact, which falls under rule 11 of the MDR).

3.5.1.3. Background

Hearing impairment (HI) is listed as one of the most common health problems in the world and one of the largest sources of years lived with disability (WHO, 2021). More than 5% of the world population has disabling HI, about 466 million people worldwide (WHO, 2021). HI places a burden on human health, society and healthcare expenditure. Without appropriate follow-up, a person with HI will experience difficulties with communication, learning, social-emotional functioning, employment and quality of life (Davis et al. 2016). Moreover, HI has been related to cognitive decline and is also a potentially modifiable risk factor for dementia (Livingston et al., 2020).

To overcome the risks and difficulties associated with HI, different rehabilitation and treatments option exist. The overarching term for the treatment of persons with HI is called **Aural rehabilitation (AR)**. AR consists of 4 cornerstones (Boothroyd, 2007):

- Sensory management (hearing aids, cochlear implants, assistive listening devices...) to enhance auditory function;
- Knowledge and skills (to improve the outcome);
- Perceptual training;
- Counselling (motivational engagement).

This multidisciplinary and holistic approach is recommended as best practice in hearing health care, but not all persons with HI have access to these four cornerstones.

⇨ Adults with severe to profound HI receive the four different cornerstones of AR at rehabilitation centers for a defined period of time. This defined period encompasses only a few years. After this initial treatment period, adults are not reimbursed for further follow-up at rehabilitation centers and have to find multidisciplinary follow-up elsewhere. Moreover,

due to the limited capacity at rehabilitation centers, many persons end up on waiting lists and lose their motivation to manage their HI.

- ⇨ Adults with mild to moderate HI are often referred to hearing aid centers, where rehabilitation is mainly focused on sensory management (technological solutions, such as hearing aids and assistive listening devices). However, the uptake of hearing technology remains low, with an adoption rate of only 20-40% of those who seek help (Abrams & Kihm, 2015; Laureyns et al. 2015; Hougaard et al., 2016; van Leeuwen et al., 2021). Hearing aids manage sensory loss, but do not restore hearing to normal (Davis et al. 2016). As a result, low satisfaction is reported in challenging listening situations, such as understanding speech in noise or over a distance.
- ⇨ Adults with perceived hearing difficulties, without diagnosed HI do not receive any AR.

In summary, many persons with HI do not receive optimal treatment at the right time, due to many barriers and difficulties in the standard hearing health care. These difficulties and barriers are mostly related to time constrictions, lack of knowledge and limited reimbursement.

Adherence and uptake of hearing aid technology could be higher with additional AR services (low-friction; easy to access), which would also alleviate the current rehabilitation centers.

Ideally, AR could be provided through a remote online application that provides perceptual training, counselling and additional information, in order to enhance the listening and communication strategies of persons with perceived hearing difficulties.

Previous research with LUISTER (S59845)

During a previous study, ExpORL developed the LUISTER app ("Leuven Interactief Schema voor gehoorTraining, Evaluatie en gehoorRevalidatie"; EC number: S59845).

The LUISTER programme consists of different tests to evaluate listening and communication skills (the validated digit triplet test and the phoneme discrimination test) and more than 500 automated training tasks on a tablet (van Wieringen et al., 2021 and Magits et al., 2023). The LUISTER app was developed and validated with adults with a profound HI and a cochlear implant (Magits et al., 2023). The results of this study provided the scientific evidence for the added benefit of the LUISTER training for persons with HI.

LUISTER was an important first start to greater accessibility, interactivity, and personalisation of hearing care, which can lead to improvements in self-management of HI, at home whenever convenient. However, LUISTER still depended on a hearing care professional (HCP) informing a client on what to do next. This is partly because the results of the training paradigm are not self-explanatory and partly due to a lack of guidance and counselling offered in the programme. In addition, the HCP cannot serve multiple clients simultaneously with LUISTER.

Therefore, LUISTER was further developed into an optimized app called ALICE (Assistant for Listening and Communication Enhancement), containing a closed loop system and additional features to address the aforementioned gaps.

3.5.2. Identification and description of the investigational device

3.5.2.1. Description of the investigational device

See IB for a more detailed description.

ALICE

The ALICE app consists of two software units:

- The *ALICE-Client* app for persons with HI or listening difficulties. The app provides remote monitoring, training and counselling.

- The *ALICE-Pro* dashboard for hearing care practitioners (HCP) involved in the aural rehabilitation process of persons with HI or persons with listening difficulties. ALICE-Pro provides the audiologists with data and analytics of their clients.

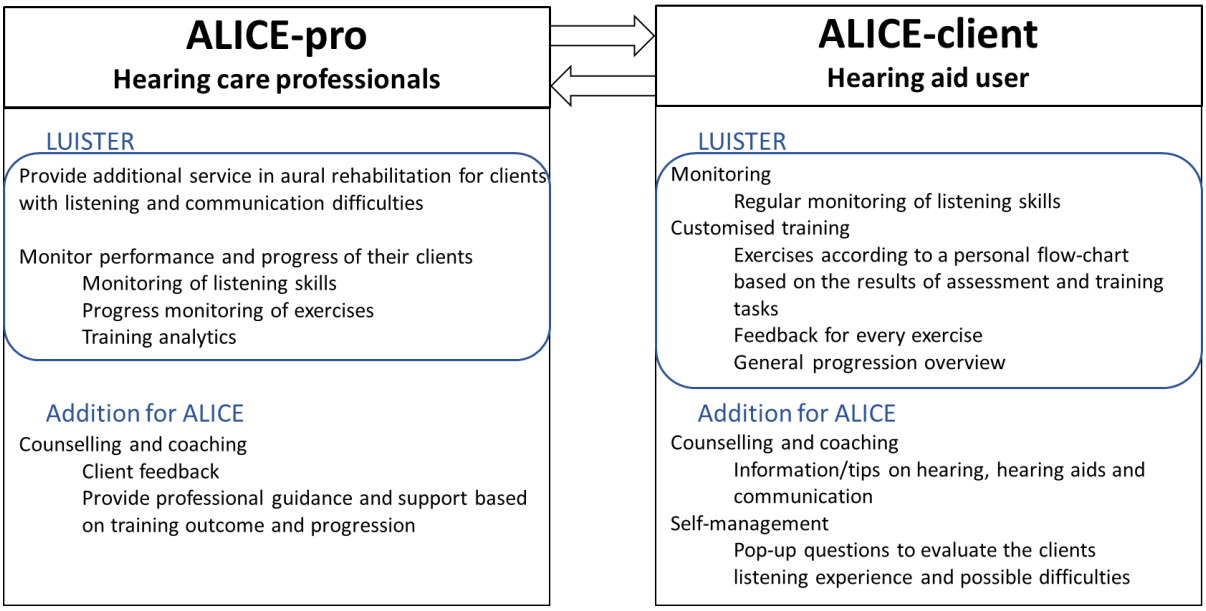


Figure 1. Overview of ALICE-Pro (left) and ALICE-Client (right) including the incorporation of the existing (and validated) LUISTER app

ALICE-Client

The ALICE-Client app can be downloaded onto the client's personal smart device (smartphone or tablet). Similar to LUISTER, the app contains different monitoring tasks and a large number of listening training exercises. For the ALICE app a counselling module was added (see below).

- The ***monitoring tests,*** (cfr. LUISTER app) consist of the validated digit triplet test (DTT) and the phoneme discrimination test. Both are speech perception tests: the DTT is used to monitor the level of speech understanding in noise, the phoneme discrimination test determines how well a person can discriminate between different phonemes. The outcome of the DTT determines the starting level of the first speech in noise exercise. The outcome of the phoneme discrimination test determines which phoneme exercises will be trained first.
- The ***listening training exercises*** (cfr. LUISTER app) consist of a range of auditory-cognitive tasks. Five types of listening training exercises are available: vowels, consonants, exercises according to a theme, recognition of voices and emphasis, clock and cognitive sentences. Exercises are performed in quiet and in various types/levels of background noise. The client can choose their answer from a closed set of options (3-6-9). Feedback is provided in a targeted way (not only 'correct' or 'wrong', but with information on the type of errors that are made).

    ⇨ *Both monitoring tasks and training exercises have been researched (cfr. S59845) and documented in van Wieringen et al., 2021 and Magits et al., 2023, van Wilderode et al., 2023).*

- The ***counselling module*** consists of different questions about the clients' listening experience and difficulties. These questions are based on validated questionnaires such as the Speech Spatial and Quality of hearing questionnaire (SSQ; Gatehouse and Noble, 2004), the Hearing Handicap Inventory for Adults/the Elderly (Ventry and Weinstein, 1982) and the Fatigue Assessment Scale (De Vries et al., 2004) among others. Clients will be presented with 3

questions every other day to inventory their daily experiences. Questions can be answered on a 5-point Likert scale.

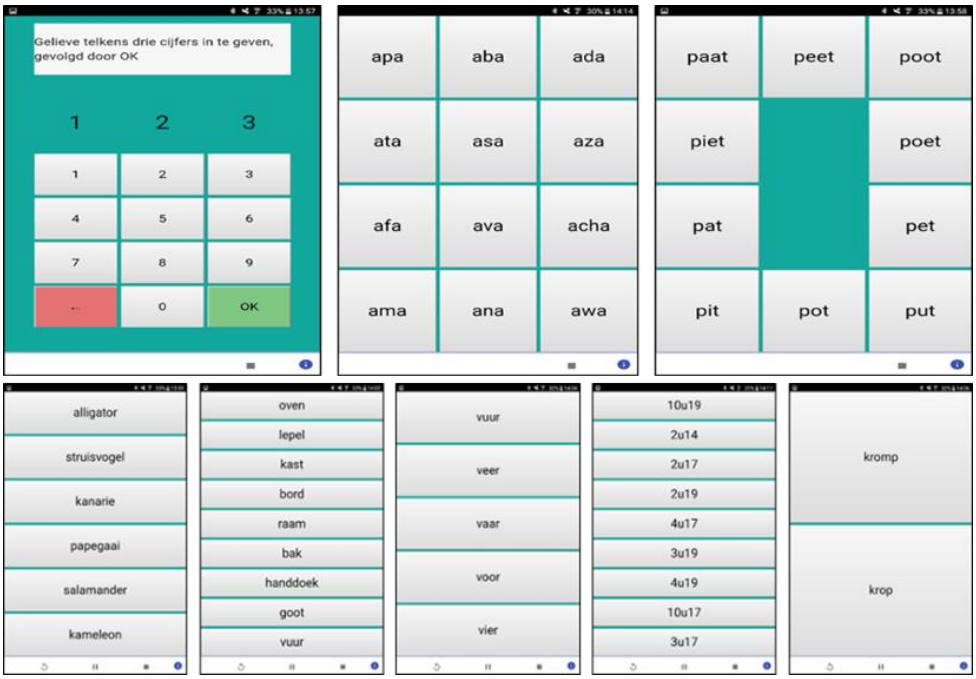


Figure 2: Screenshots of the ALICE-Client app, very similar to the LUISTER app. On top: monitoring tasks, DTT and phoneme discrimination tests. Below listening training exercises.

ALICE-Pro

The ALICE-Pro dashboard is accessible from a website on a dashboard computer.

ALICE-Pro allows the HCP to gain insight in the listening and communication skills of their clients based on the data and results of the client app, i.e. results of monitoring tasks, listening training exercises (Pro Portal; Figure 2) and on daily life experiences of their clients (counselling module). The output of the counselling module includes information about the clients' well-being, their degree of self-management and difficulties they encounter in daily life.

This information provides the HCP with a systematic overview of the clients' results and needs that can be uses as guidance during follow-up consultations.

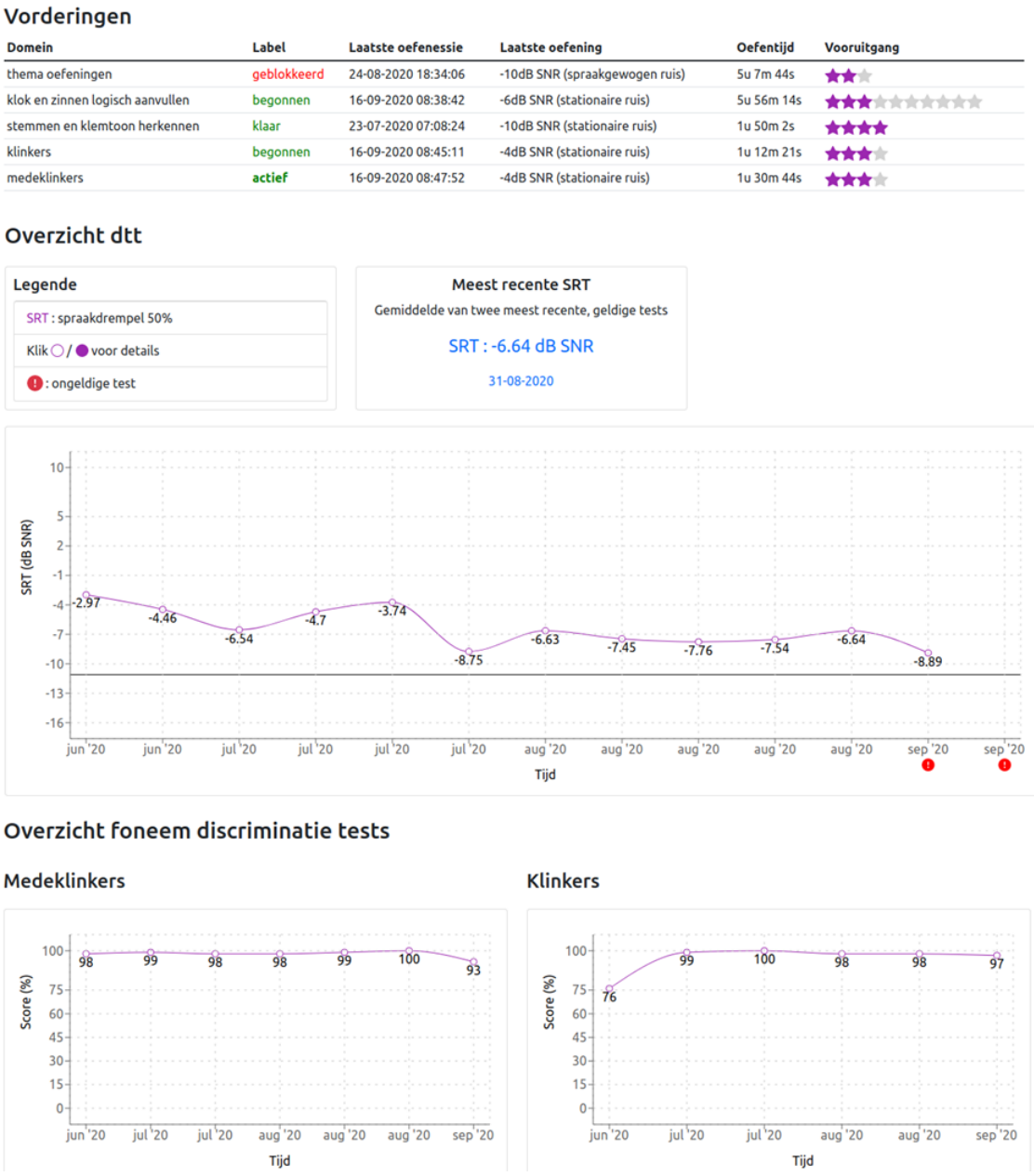


Figure 3: screenshots of the ALICE-Pro dashboard showing one clients results, i.e.: the progress on the training tasks, the results of the digit triplet tests and the results of the phoneme discrimination tests (left: consonants, right: vowels)

3.5.2.2. Intended purpose of the investigational device

ALICE (Assistant for Listening and Communication enhancement) is a software application that will function as an added service in the aural rehabilitation of persons with HI, by providing remote monitoring, training and follow-up .

The software application is considered to be a medical device type IIa, because it is an active device that monitors a persons' hearing disability and provides a personalized rehabilitation program to alleviate (some of) the experienced hearing difficulties.

3.5.2.3. The populations and indications for which the investigational device is intended

- Population = ALICE will be used in Dutch speaking individuals, who are able to read and follow instructions on a smartphone or tablet;
- Indication and intended users = the ALICE-Client app will be used by persons with or without HI who experience listening difficulties. In the clinical study the clients will be monitored closely by their HCPs by using the ALICE-Pro dashboard (see section 3.5.6. for further details).

3.5.2.4. Details concerning the manufacturer of the investigational device.

The ALICE app is developed by the Research Group Experimental Oto-rhino-laryngology (ExpORL). ExpORL is part of the Department of Neurosciences of the Catholic University in Leuven (KU Leuven).

Over the years, the ExpORL research group has developed a number of products (research purpose only). These products cover the entire hearing care trajectory from screening (quickly testing a large population without detailed diagnostics), to detailed and ecologically valid diagnostics and intervention. The ALICE app is the first product that will be launched commercially as stand-alone software. The ALICE app is defined as software as a medical device (SaMD).

3.5.2.5. Name or number of the model/type, including software version and accessories, if any, to permit full identification.

Name	Software version
ALICE	v.0.12.0

3.5.2.6. Description as to how traceability shall be achieved during and after the clinical investigation, for example by assignment of lot numbers, batch numbers or serial numbers.

In accordance with Annex VI, Part C of the Medical Device Regulation (EU) 2017/745 (MDR), only software which is commercially available on its own as well as software which constitutes a device in itself shall be subject to Unique Device Identifier (UDI) requirements.

For the clinical investigation, traceability shall be achieved by restricted access to the app, only subjects who are enrolled in the study and have signed the informed consent will be granted access (see section 3.5.6. for further details on the enrolment procedure)

3.5.2.7. Summary of the necessary training and experience needed to use the investigational device based on risk management.

Both the ALICE-Client, as the ALICE-Pro software are developed following the applicable ISO standards, including ISO 62366 Application of Usability Engineering to Medical Devices, and are considered to be easy to use.

At the start of the clinical investigations, a workshop will be organized to provide (See in more details in onboarding procedure (3.5.4.3)):

- A general introduction about the intended use of the app,
- Information about the compatibility of the app with personal (streaming) devices,
- The safety measures that should be taken into account by both HCP and their clients:
    - Procedure to control the loudness of the stimuli provided by the app

- Procedure to follow to ensure safe data management (compliant with GDPR)
- Procedure to follow in case of adverse events and/or device malfunction

The app provides a onboarding process, to get the user familiar with the interface of the app, the intended use and its functionalities. For every functionality, clearly written instructions are provided within the app.

3.5.3. Justification for the design of the clinical investigation

3.5.3.1. Evaluation of the results of the relevant pre-clinical testing/assessment and prior clinical investigations carried out to justify the use of the investigational device in human subjects

LUISTER

The monitoring and training tasks included in the ALICE app were previously evaluated by the ExpORL research group. This evaluation was performed as part of the LUISTER program in 40 persons with profound HI and a cochlear implant in a randomized control trial (Magits et al., 2023).

The LUISTER training program yielded significant improvements in outcomes provided during the trial (based on the monitoring tests: DTT and phoneme identification in quiet). Training also improved speech understanding in noise (based on a sentence in noise test) and health-related quality of life (based on a quality-of-life questionnaire; NICQ). The magnitude of training-induced transfer to speech in noise understanding was greater than 2 dB for half of the participants. Moreover, adherence to the program was very high, as was the (technical) usability (median 91, IQR=5°).

At the end of the study trial, participants rated the usefulness of the LUISTER program on a Likert scale: 77% reported to find the training useful (= 4 or 5 on the Likert scale) and 88% of the participants would recommend the program to someone else. During the use of the LUISTER training tasks, no adverse events were reported, which indicates the software is safe to use in our participants.

mHealth for AR

ALICE is not the first programme to deliver AR to clients by using mHealth. Different apps or websites are already available on the market (Olson 2015, 2018) (e.g. www.clearworks4ears.com; www.cogmed.com; www.laceauditorytraining.com). These apps or websites deliver AR to the client in different languages (mostly English) and offer different types of exercises. Interestingly, none have a CE-mark and none have been evaluated as an app. Part of these materials have been researched in different studies but results of these studies show a high degree of variability in outcome.

Little evidence is available on auditory training improving outcomes for persons with HI. A very comprehensive systematic review on the efficacy of computerized auditory training for persons with HI by Henshaw and Ferguson (2013) is cautiously positive. However, the authors identified several scientific, methodological, and study quality issues that preclude solid conclusions and highlight the need for higher-level evidence.

3.5.3.2. Evaluation of clinical data relevant to the proposed clinical investigation

To date, no consensus exists on how effectiveness of AR should be assessed and a comparison across apps is impossible due to differences between languages. In the current study, a validated measure for speech understanding in noise is used as the main outcome, complemented with non-auditory outcomes to evaluate effectiveness in a broader context of functioning and participation.

Justification for the chosen materials:

- *A speech in noise test* (Dutch: LIST sentences or BLU words, French: Lafon's dissyllabic words) will evaluate the persons' ability to perceive speech in noise, in a clinically controlled condition.

Speech in noise understanding has been reported as the number one difficulty that persons with HI encounter in daily life.
We should keep in mind that sentence testing in noise only partly resembles real-life listening difficulties (well-articulated sentences in speech-weighted noise, whereas in real life, speech understanding is also influenced by high paced speech, interruptions by other talkers, and other acoustical factors such as background noise, reverberation, and cognitive factors). However, it is not possible to account for all real-life factors in a testing environment.

- Besides the clinically validated measures we will evaluate the daily life listening with *questionnaires* that tap into the listeners' daily life experience:
    - We will evaluate perceived listening difficulties with the Speech Spatial and Quality of hearing questionnaire (SSQ12) which evaluates typical listening situations and is commonly used in clinical practice and the Client Oriented Scale of Improvement (COSI) which evaluates an individual's listening difficulties reported by the listener over time.
    - We will also evaluate the benefit of AR with non-auditory outcomes to gain insight in how listening difficulties are perceived and experienced by the listener and how it influences their participation and functioning in society. We will use the effort assessment scale (EAS) which evaluates the amount of effort needed by an individual and the communication and acceptance scale (CAS) which measures clinical changes in "communication strategies and the emotional consequences, knowledge and acceptance of HI". Additionally we will use the International Outcome Inventory for Hearing Aids (IOI-HA) which evaluates the satisfaction of the clients with their hearing aids in daily life situations.

3.5.4. Benefits and risks of the investigational device and clinical investigation

3.5.4.1. Anticipated clinical benefits

FOR Experienced CI/HA users:

We hypothesise that 75% of our subjects will:

- Indicate an enhancement in their daily life listening and/or communication strategies (primary)
    - Enhanced speech understanding in difficult listening situations
    - Reduced listening effort
- Indicate to be more knowledgeable about their HI and recognize the emotional consequences of their HI and (secondary)
- Indicate to be more satisfied with the delivered care and/or their hearing aid/cochlear implant in daily life (secondary).

FOR first-time HA users:

We hypothesise that 75% of our subjects will:

- Indicate an enhancement in their daily life listening and/or communication strategies (primary)
    - Enhanced speech understanding in difficult listening situations
- Indicate to be more knowledgeable about their HI and recognize the emotional consequences of their HI and (secondary)

- Indicate to be more satisfied with the delivered care and/or their hearing aid in daily life (secondary)
- Indicate to habituate faster to their hearing aids (secondary).

3.5.4.2. Residual risks associated with the investigational device, as identified in the risk analysis report

(See Risk analysis in IB). In summary, only 1 risk remains significant after implementation of the control measures. The occurrence of (small) software failures remains high, but the severity of the harm is in our case considered to be minimal as the device is used as an additional service on top of the standard of care. As the risks are associated with negligible potential harms, we consider the harm and the risk as acceptable, and we can, with certainty, say that the benefits of the app (as already demonstrated in section 3 of the IB) outweigh these minimal risks.

3.5.4.3. Risks associated with participation in the clinical investigation and mitigations

See Safety section (3.5.14).

3.5.5. Objectives and hypotheses of the clinical investigation

3.5.5.1. The purpose of the clinical investigation, claims for clinical performance or effectiveness and safety of the investigational device that are to be verified

Claims

ALICE-Client

- **Enhancement** - the app enhances daily life listening and the ability to manage difficult listening situations

ALICE-pro

- **Data-driven hearing care –** the HCP will be able to deliver an additional rehabilitation service, that will be evidenced-based and data-driven and it will enforce valued based hearing care.

Hypotheses on the clinical performance & effectiveness of the ALICE app

User-oriented outcomes for experienced HA/CI users

After 8 weeks of continued use of the ALICE-Client app persons with HI will:

- Indicate enhancement in their daily life listening and/or communication strategies (primary)
  - Enhanced speech understanding in difficult listening situations
  - Reduced listening effort
- Indicate to be more knowledgeable about their HI and recognize the emotional consequences of their HI (secondary)
- Indicate to be more satisfied with the delivered care and/or their hearing aid/cochlear implant in daily life (secondary).

User-oriented outcomes for persons in their hearing aid trial (first time HA users):

- Indicate an enhancement in their daily life listening and/or communication strategies (primary)
  - Enhanced speech understanding in difficult listening situations
- Indicate to be more knowledgeable about their HI and recognize the emotional consequences of their HI and (secondary)

- Indicate to be more satisfied with the delivered care and/or their hearing aid in daily life (secondary)
- Indicate to habituate faster to their hearing aids (secondary).

3.5.5.2. Effect sizes and equivalence limits, where applicable

The effect size is discussed in detail under 'statistical design and analysis'.

3.5.5.3. Risks and anticipated adverse device effects that are to be assessed

Risks and anticipated adverse effects during the clinical trial are discussed in detail under 'Adverse events, adverse device effects and device deficiencies'. For a more detailed overview of all risks related to the investigational device we refer the reader to the IB.

3.5.6. Design of the clinical investigation

3.5.6.1. General

The main goal of this clinical study is to evaluate the efficacy of the ALICE app.

We will prove efficacy in two distinctive user groups:

- Experienced hearing aid/CI users (Dutch speakers: Research ARM 1, approved by EC on 25/08/2022 – ref. CIV-22-06-039801, French speakers: Research ARM 3)
- First-time hearing aid users (Dutch speakers: Research ARM 2, approved by EC on 20/02/2023 – ref. CIV-22-06-039801)

This clinical study is a multicenter study that takes place in different hearing aid centers and one university hospital. All investigational sites are geographically spread across Belgium.

The duration of the study is estimated between 12 and 26 months, between October 2022 and December 2024 (see procedures for the overview of the time lines).

3.5.6.2. Research ARM 1 (approved by EC on 25/08/2022 – ref. CIV-22-06-039801)

Description of the design type of clinical investigation to be performed (e.g. comparative double-blind, parallel design, with or without a comparator group) with rationale for the choice

The study design is a randomized controlled clinical trial (RCT) which is the golden standard for ascertaining the efficacy and safety of a new treatment or intervention. The goal of the current RCT is to demonstrate the superiority of the ALICE app, as a new intervention over the existing standard of care.

In this RCT two groups will be compared:

(1) A group that receives the standard of care, which is defined as followed:
    a. Persons with a moderate to profound HI who are provided with a hearing aid
    b. Persons with a profound to severe HI who are provided with a cochlear implant and concomitant rehabilitation. Most persons with a cochlear implant receive intensive rehabilitation during the first 6 months after their implantation. Afterwards, they mainly return for mapping of the device but not for listening training therapy.

(2) A group that receives the standard of care, supplemented with the ALICE app, to be used as a home-based monitoring, training and counselling tool.

Description of the measures to be taken to minimize or avoid bias, including randomization, concealment of allocation, blinding/masking, assessment of blinding plan and management of potential confounding factors

For each investigator site clients will be recruited by the local principal investigator (PI) of the study (HCPs working in the hearing centre or university hospital). Once the HCP has recruited the required number of clients, they will send the list of clients to the KU Leuven researcher who will divide the clients randomly across the two groups (standard of care/additional use of ALICE). Randomisations of these two groups will be stratified according to age and will be done automatically with an automatic seed generator.

We foresee a few possible confounding factors:

- Medical confounding factors
    - Type and degree of HI
    - Comorbidities such as high blood pressure, diabetes, stroke, visual acuity, cognitive abilities
- Methodological confounding factors
    - For sentence understanding in noise, procedural effects are believed to be minimal. The LIST sentence materials will be offered twice, at first and final appointment. Lists of sentences are counterbalanced and never presented twice.
    - Potential procedural effects for the questionnaires may occur and will be controlled for by administering the questionnaires twice prior to the participants starting the training and at the end of the 8 week training period.
- Other confounding factors such as lifestyle factors

Primary and secondary endpoints, with rationale for their selection and measurement

The outcome measures that will be used as an endpoint to determine the clinical benefit of the ALICE app are:

- Effectiveness of the app is ensured
    - Enhanced speech understanding in difficult listening situations
    - Enhanced communication strategies
    - Reduced reported listening difficulties and reduced experienced listening effort
    - Increased knowledge/acceptance of the non-auditory consequences of HI
    - Increased satisfaction with hearing aid/cochlear implant

Methods and timing for assessing, recording, and analyzing variables

Table 1. Overview of outcome measures of assessment during the study

ALICE-Client			
	Outcome measure	*Type of test*	*Name of test/questionnaire*
Effectiveness	Speech understanding in difficult listening situations	Speech in noise test	LIST *(van Wieringen et al. 2008)*
		Questionnaires	SSQ12 *(Gatehouse and Noble, 2004)* COSI *(Dillon et al., 1997))*
	Listening effort		EAS *(Alhanbali et al., 2017)*
	Emotional consequences /acceptance of HI		CAS *(Öberg et al., 2021)*
	Use of hearing aid		IOI-HA *(Kramer et al., 2002)*

Overview of the tests and questionnaires used

(all materials are added to the folder CIP materials)

The **LIST** (Leuven intelligibility sentences test) is a validated speech test, using sentences that can be used in quiet or in noise (van Wieringen & Wouters, 2008). Each set consists of 10 sentences that are equally difficult. In the literature the initial test is sometimes performed at two different times to minimise the risk of procedural learning. This LIST is included in the investigation because its commonly used int the standard clinical practice and is able to demonstrate off-task training effects for speech understanding in noise after using the ALICE app.

The **COSI** questionnaire (Client Oriented Scale of Improvement) is a validated clinical tool that can assist in measuring the impact of hearing aid fitting on a person's life and the benefit that is obtained after intervention (Dillon et al., 1997). Administering the COSI questionnaire is also part of the RIZIV application to receive a refund for hearing aids. The COSI questionnaire allows the audiologist to measure improvements in listening situations important for their client. Before fitting the hearing aids, together with their client, they list their client's needs/goals. After hearing aids have been fitted and the client has had time to experience the hearing aids, they evaluate the progression/satisfaction in these situations together with their client.

The **CAS** (Communication and Acceptance Scale) is a validated scale that consist of 18 items (Öberg et al., 2021). The CAS scale is a reliable instrument that can be used to measure the effect of a rehabilitation programme. Each question is scored on a 5-point Likert scale (completely agree to completely disagree). It was developed to detect clinical changes in "communication strategies and the emotional consequences, knowledge and acceptance of HI". This questionnaire has been translated from Swedish to Dutch (and back translated to ensure correct translation).

EAS (Effort Assessment Scale) is a validated scale to measure listening effort (Alhanbali et al., 2017). The EAS consists of 6 items that are scored by the client on a 10-point scale, no effort to lots of effort. The EAS questions were translated to Dutch for this study.

The **SSQ12** is a short version of the validated Speech, Spatial and Qualities of Hearing Scale. This short form was developed for use in clinical research and rehabilitation settings. (Noble et al., 2013). Participants score each questions on a ruler (visual analogue scale) from 0 to 10. Questions were translated to Dutch.

The **IOI-HA** (International Outcome Inventory for Hearing Aids) evaluates the daily use of the hearing aid, as well as the perceived benefit and satisfaction with the hearing aids or cochlear implants. The IOI-HA consist of 7 questions and has been validated in Dutch (Kramer et al., 2002).

Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration

Equipment used/needed to perform test protocol

- Speech in noise testing: part of the standard of care
    - Audiometer (calibrated): available at the investigational sites
- Questionnaires: online/tablet
    - Clients will be able to fill out the questionnaires on a tablet (provided by the KU Leuven researchers to the investigational sites) or on their own computer through a website.
- The app will be used on the clients' personal smart device (device compatibility will be described in IB)
- Feedback: documented in word files

Clinical investigation sites: number, location and if appropriate differences in clinical investigation site characteristics

A list of participating clinical investigation sites and their locations will be provided at a later stage.

Subjects

Subjects will be recruited by their HCP (see recruitment procedure) in accordance with the following criteria:

Inclusion criteria

- Clients who are using a hearing aid (N = 150) or cochlear implant (N = 30). Which is more than necessary according to the power analysis (3.5.7).
    - Clients with a hearing aid must have completed the hearing aid trial period and must have decided to purchase the hearing aid.
    - Clients with a cochlear implant must have at least 6 months of experience with the cochlear implant.
- Clients who experience listening and communication difficulties
- Clients with a hearing aid may not have any experience with auditory training yet.
- Able to operate the training programme as an app on a mobile device/tablet (e.g. clients have a mobile device or table; clients have sufficient eyesight to see the exercises; clients must be able to operate the programme).
- At least 18 years old.
- Dutch-speaking as all training material and counselling questions will be presented in Dutch.
- Clients need to have an Android or iPhone smartphone and connection to internet

Exclusion criteria

- Visually impaired
- Motorically impaired
- Cognitively impaired

Criteria and procedures for subject withdrawal or loss to follow up

When and how to withdraw a subject from the clinical investigation or stop the use of the investigational device

Clients participate in this study voluntarily and have the right to withdraw from the study at any time they want. If they choose to withdraw they will be asked to delete the ALICE app from their smartphone or tablet.

Documentation of efforts to be made to trace subjects that are lost to follow up and possible reasons

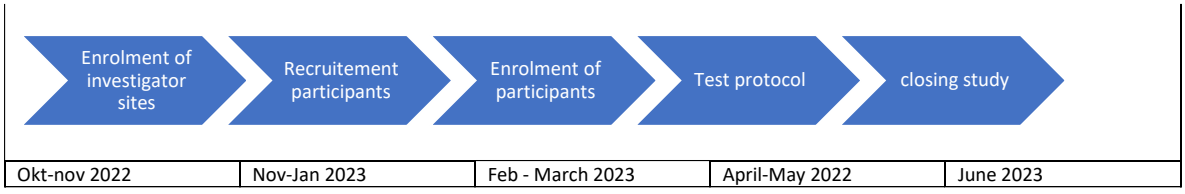
When clients withdraw from the study, they will be asked to provide a reason as this may be of interest to the study. However, they are not obligated to provide a reason for their withdrawal.

Whether and how subjects are to be replaced.

In case of withdrawal or loss to follow up, we will report this but the client will not be replaced since we have sufficient participants for the study.

Procedures

Overview and estimated timing



Enrolment of investigator sites

- 6 hearing centres and 1 university hospital (UZ Leuven) will be enrolled as an investigator site in this multicentric study. The sites will be assessed based on adequate resources, a qualified investigation team and access to an adequate number of subjects.

- For every investigator site, one local PI will be appointed. The local PI will be responsible to execute the investigation (following the study protocol) and to perform the local coordination for the study.
- In order to know if the local PI is eligible to coordinate the study, the following criteria apply
  - Experienced professionals (> 5 years of working experience) in the field of aural rehabilitation of adults with hearing impairment
  - Dutch speaking
  - Willing to become familiar with research and good clinical practice
- Once the local PI has been assigned (and approved by FAGG and EC), the protocol will be discussed and the clinical trial agreement (see Annex 8) will be signed by the local PI.
- All local PI's will have to follow an initiation training, in which following details of the study are presented and/or discussed
  - Intended use of the app
  - Content of the investigator's brochure (IB)
  - Instructions for use of the ALICE app, with aids on training with the app, including set-up and internal calibration
  - Recruitment protocol
  - Enrolment protocol with ICFs for the clients
  - Study programme with study protocol (=CIP), in which instructions are included to uniformly assess and document clinical findings (eCRF)
  - GCP (see GCP protocol)
  - Quality check of the in-house equipment that will be used
  - Coordination & assistance
  - Risk management

Recruitment of clients

- Local PIs will be responsible for the recruitment of patients. Before they start with recruiting they will be instructed with clear inclusion and exclusion criteria (see 3.5.6.2 Subjects)
- The number of clients that should be enrolled will be in the range of 20-30 for every investigator site
- The recruitment period is a fixed period over a time span of 12 weeks or when 20 to 30 clients are recruited (start of the study + 12W), after that period no clients can enter the study.

Enrolment of clients

- Clients who match the criteria, will receive a brief introduction about the study, which may or may not include the ALICE app. If they are interested to participate in the study, they will receive an information brochure about the study programme, in which a more detailed description is provided (details about the course of the study, the 2 visits (at 0 and 8 weeks), the duration of the study and their rights and responsibilities.) They will also be informed that they will be assigned randomly to one of the two groups.
- If clients agree to participate in the study they will sign an informed consent form.
- A complete list of clients who wish to participate for each investigational site is sent to the KU Leuven researchers at the end of the recruitment period.
- After being stratified by age clients will be randomly assigned to one of the two groups by a KU Leuven researcher using an automatic seed generator:
  - 1 group will receive the standard of care

- 1 group will receive the standard of care with additional support of the ALICE app

	Responsible	Accountable
Clients match the criteria	Local PI	KUL PI
Clients get a brief introduction about the app and the goals of the study; when interested they receive a detailed information brochure	Local PI	
Clients sign an Informed Consent	Local PI	KUL PI
Clients are enrolled in the study	Local PI	KUL PI
Allocation of groups and randomization	KUL PI	KUL PI

The study program and test protocol

- Onboarding procedure: once the clients are enrolled they will receive a standard onboarding procedure, which will be led by the local PI. Within this procedure following points/formalities will be discussed with their client:
  - The study programme/course of the study
  - Appointment schedule to perform the tests
  - Procedure to follow in case of change
  - Contact information in case of questions
  - Risk & Safety management (see safety section), with special attention to following procedures:
    - Procedure to control the loudness of the stimuli provided by the app
    - Procedure to follow to ensure safe data management (compliant with GDPR)
    - Procedure to follow in case of adverse events and/or device malfunction
  - Rights and responsibilities
- Installation of the app
  - Intended use of the app
  - Compatibility of the app with personal (streaming) devices,
  - Instruction to use the app
  - First installation and set-up of account
- Test protocol (see below and Fig. 4)

Description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation including any deviation from normal clinical practice

Below, the timeline of the test protocol is presented: After allocation to a treatment group, a client will be assessed with speech in noise and questionnaires (Figure 4), followed by 8 weeks use of the ALICE app. The same outcome measures will be assessed at the final appointment to evaluate the benefit of the intervention.

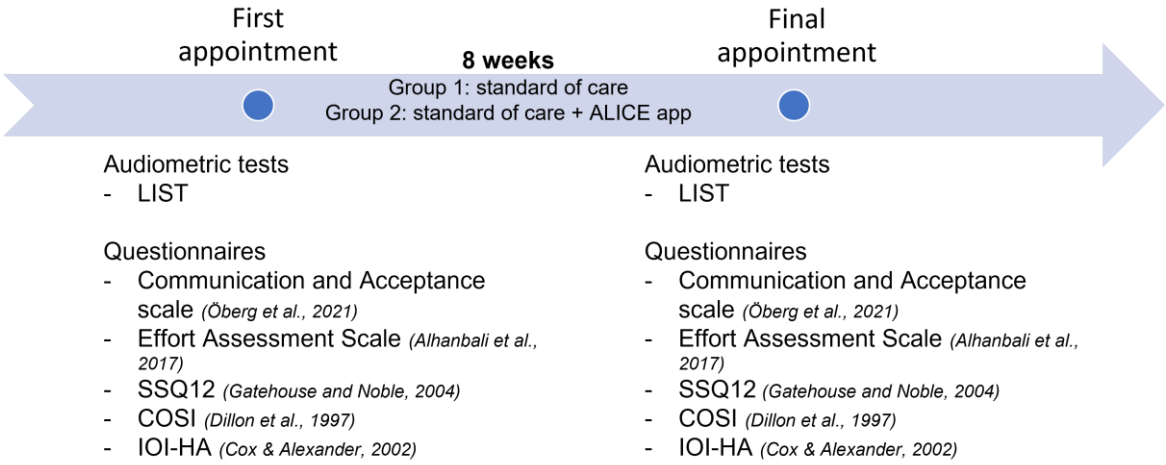


Figure 4. Timeline of the test protocol.

Monitoring plan

General outline of the monitoring plan to be followed, including access to source data and the extent of source data verification planned

In accordance with ICH-GCP E6(R2) the Sponsor is responsible for monitoring the Trial to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the Trial procedures have been followed as shown in the approved protocol, and that relevant Trial data have been collected and reported in a manner that assures data integrity. To this end Source Data will be compared with the data recorded in the (e)CRF. A risk-based approach will be applied to determine the extent of monitoring activities and monitoring of the Trial will be performed by qualified individuals (independent from the site Trial staff), as applicable.

- **Coordination & monitoring plan**
    - Project management and on-site monitoring visits
      The Coordinating Investigator (Andrea Bussé, KUL) will supervise: the recruitment and the enrolment of the study participants (including the verification of the ICF procedure), the implementation of the study protocol at the investigational sites, the quality of the data collection, the achievement of the study goals, and the use of the ALICE app according to the CIP.
      The test protocol will be performed by the local PI. The local PI can rely on support and assistance of the Coordinating Investigator at any given time. The Research Manager will schedule regular monitoring visits with the local PI. All monitoring activities will be documented in a written report according to ISO14155.
    - Project support
      When clients need additional support their first contact point will be their local PI. When the support needed is related to their hearing or hearing aids, the local PI will help them out through their standard of practice (standard care path).
      When the support needed is related to the use of the app, the local PI will contact the Coordinating Investigator. The Coordinating Investigator will provide the local PI with additional support, if needed technical support will be provided by our in-house developers.
    - Safety evaluation & reporting

Adverse events, device deficiencies, and withdrawals will be reported and documented (see section 'Subjects' + withdrawal procedure section 3.5.6.2).

- Data collection
  - To ensure/guarantee quality of the data collection the Coordinating Investigator will perform a quality check of the data (samples) on regular basis.
  - Safety = See data management plan

3.5.6.3. Research ARM 2 (approved by EC on 20/02/2023 – ref. CIV-22-06-039801)

The main goal of the second arm of the clinical study is to evaluate the performance (and viability) of the ALICE app in a specific part of the hearing care path, i.e. during the first 4 to 8 weeks of hearing aid adoption, commonly referred to as the 'hearing aid trial period'. This period is mandatory before purchasing a hearing aid.

The hearing aid trial period starts once the client has chosen a suitable hearing aid together with his or her HCP. It is therefore not possible to create a waiting list for enrolled participants. For this reason we will facilitate a rolling start with eligible participants during 9 consecutive months in 6 hearing aid centers geographically spread across Flanders, Belgium.

As the enrolment rate of this arm is expected to be lower than in the first research arm, the duration of the study will be longer. The duration of the study is estimated between 10 and 12 months (see procedures for the overview of the time line).

Description of the design type of clinical investigation to be performed (e.g. comparative double-blind, parallel design, with or without a comparator group) with rationale for the choice

The study design is a randomized controlled clinical trial (RCT) which is the golden standard for ascertaining the efficacy and safety of a new treatment or intervention. The goal of the current RCT is to demonstrate the superiority of the supplementary use of the ALICE app, as a new intervention over the existing standard of care.

In this RCT two groups will be compared:

(1) A group that receives the standard of care, which is defined as followed:
    a. Persons with a moderate to profound HI who are provided with a hearing aid
(2) A group that receives the standard of care, supplemented with the ALICE app, to be used as a home-based monitoring, training and counselling tool.

Description of the measures to be taken to minimize or avoid bias, including randomization, concealment of allocation, blinding/masking, assessment of blinding plan and management of potential confounding factors

For each investigator site clients will be recruited by the local principal investigator (PI) of the study (HCPs working in the hearing centre or university hospital). The recruited participants will be divided randomly across the two groups (standard of care/additional use of ALICE). Randomisations of these two groups will be stratified according to age and will be done automatically with an automatic seed generator.

We foresee a few possible confounding factors:

- Medical confounding factors
  - Type and degree of HI
  - Comorbidities such as high blood pressure, diabetes, stroke, visual acuity, cognitive abilities
- Methodological confounding factors

    - Potential procedural effects for the questionnaires may occur and will be controlled for by administering the questionnaires twice prior to the participants starting the training and at the end of the 8 week training period.
- Other confounding factors such as lifestyle factors

Primary and secondary endpoints, with rationale for their selection and measurement

The outcome measures that will be used as an endpoint to determine the clinical benefit of the ALICE app are:

- Clients - Effectiveness of the app is ensured
    - Enhanced outcome measures at the end of the hearing aid trial period (Primary)
        - Enhanced speech understanding in noise
        - Enhanced speech understanding in daily life
    - Increased knowledge of the consequences of HI (Secondary)
    - Increased satisfaction of care delivery (Secondary)
    - Increased habituation to hearing aids (Secondary)
        - Satisfaction with hearing aid
        - Duration of daily hearing aid use

- HCP - Effectiveness of the app is ensured
    - Enhanced care delivery (Secondary)
        - Reduced F2F time with HCP (reduction in time, appointments, hearing aid fittings, tests, …)

Methods and timing for assessing, recording, and analyzing variables.

Table 2. Overview of outcome measures administered in clients

ALICE-Client			
	Outcome measure	*Type of test*	*Name of test/questionnaire*
Effectiveness	Speech understanding in difficult listening situations	Speech in noise test	BLU *(Bosman, Woutes & Damman)*
		Questionnaires	SSQ12 *(Gatehouse and Noble, 2004)* COSI *(Dillon et al., 1997))*
	Emotional consequences /acceptance of HI		CAS *(Öberg et al., 2021)*
	Care delivery		ALICE-Specific questionnaire
	Use of hearing aid		IOI-HA *(Kramer et al., 2002)*
		Datalog	Daily hearing aid use

Table 3. Overview of outcome measures administered in HCPs

HCPs			
	Outcome measure	*Type of test*	*Name of test/questionnaire*
Effectiveness	Care delivery	Datalog	F2F time between HCP and client
			Number of tests, fittings and appointments needed during hearing aid trial period

Overview of the tests and questionnaires used

(all materials are added to the folder CIP_materials)

The **BLU** (Brugge-Leuven-Utrecht list) is a validated speech test during which Dutch words are provided in quiet or in noise. Each list contains 10 2-sylable words. (Damman, 1994)

The **COSI** questionnaire (Client Oriented Scale of Improvement) is a validated clinical tool that can assist in measuring the impact of hearing aid fitting on a person's life and the benefit that is obtained after intervention (Dillon et al., 1997). Administering the COSI questionnaire is also part of the RIZIV application to receive a refund for hearing aids. The COSI questionnaire allows the audiologist to measure improvements in listening situations important for their client. Before fitting the hearing aids, together with their client, they list their client's needs/goals. After hearing aids have been fitted and the client has had time to experience the hearing aids, they evaluate the progression/satisfaction in these situations together with their client.

The **CAS** (Communication and Acceptance Scale) is a validated scale that consist of 18 items (Öberg et al., 2021). The CAS scale is a reliable instrument that can be used to measure the effect of a rehabilitation programme. Each question is scored on a 5-point Likert scale (completely agree to completely disagree). It was developed to detect clinical changes in "communication strategies and the emotional consequences, knowledge and acceptance of HI". This questionnaire has been translated from Swedish to Dutch (and back translated to ensure correct translation).

The **SSQ12** is a short version of the validated Speech, Spatial and Qualities of Hearing Scale. This short form was developed for use in clinical research and rehabilitation settings. (Noble et al., 2013). Participants score each questions on a ruler (visual analogue scale) from 0 to 10. Questions were translated to Dutch.

The **IOI-HA** (International Outcome Inventory for Hearing Aids) evaluates the daily use of the hearing aid, as well as the perceived benefit and satisfaction with the hearing aids or cochlear implants. The IOI-HA consist of 7 questions and has been validated in Dutch (Kramer et al., 2002).

A specific **ALICE-questionnaire** was developed for the purpose of this study. The questions of this questionnaire were based on 3 different questionnaires. First, the SUS (system usability scale) to determine the usability of the ALICE app. Second, the SADL (Satisfaction with Amplification in Daily Living) which was designed to evaluate the satisfaction that people experience with their hearing aids. Third, the PREM (Patient Reported Experience Measures) as is used to evaluate audiological centres in the Netherlands. A total of 20 questions were selected to evaluate the participants' experience with the usability of the ALICE app, their satisfaction with their hearing aids and their satisfaction with their audiologist/hearing centre.

Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration

Equipment used/needed to perform test protocol

- Speech in noise testing: part of the standard of care
    - Audiometer (calibrated): available at the investigational sites
- Questionnaires: online/tablet
    - Clients will be able to fill out the questionnaires on a tablet (provided by the KU Leuven researchers to the investigational sites) or on their own computer through a website.
- The app will be used on the clients' personal smart device (device compatibility will be described in IB)
- Feedback: documented in word files

Clinical investigation sites: number, location and if appropriate differences in clinical investigation site characteristics

A list of participating clinical investigation sites and their locations will be provided at a later stage.

Subjects

Subjects will be recruited by their HCP (see recruitment procedure) in accordance with the following criteria:

Inclusion criteria

- Clients who are starting their hearing aid trial as a first time hearing aid user (N= 120). Which is more than necessary according to the power analysis (3.5.7).
- Clients who experience listening and communication difficulties
- Able to operate the training programme as an app on a mobile device/tablet (e.g. clients have a mobile device or table; clients have sufficient eyesight to see the exercises; clients must be able operate the programme).
- At least 18 years old.
- Dutch-speaking as all training material and counselling questions will be presented in Dutch.
- Clients need to have an Android or iPhone smartphone and connection to internet

Exclusion criteria

- Visually impaired
- Motorically impaired
- Cognitively impaired

Criteria and procedures for subject withdrawal or loss to follow up

When and how to withdraw a subject from the clinical investigation or stop the use of the investigational device

Clients participate in this study voluntarily and have the right to withdraw from the study at any time they want. If they choose to withdraw they will be asked to delete the ALICE app from their smartphone or tablet.

Documentation of efforts to be made to trace subjects that are lost to follow up and possible reasons

When clients withdraw from the study, they will be asked to provide a reason as this may be of interest to the study. However, they are not obligated to provide a reason for their withdrawal.

Whether and how subjects are to be replaced

In case of withdrawal or loss to follow up, we will report this but the client will not be replaced since we have sufficient participants for the study.

Procedures

Overview and estimated timing

Enrolment of investigator sites

- 6 hearing centres will be enrolled as an investigator site in this multicentric study. The sites will be assessed based on adequate resources, a qualified investigation team and access to an adequate number of subjects.

- For every investigator site, one local PI will be appointed. The local PI will be responsible to execute the investigation (following the study protocol) and to perform the local coordination for the study.
- In order to know if the local PI is eligible to coordinate the study, the following criteria apply
  - Experienced professionals (> 5 years of working experience) in the field of aural rehabilitation of adults with hearing impairment
  - Dutch speaking (Flemish side)
  - Willing to become familiar with research and good clinical practice
- Once the local PI has been assigned (and approved by FAGG and EC), the protocol will be discussed and the clinical trial agreement (see Annex 8) will be signed by the local PI.
- All local PI's will have to follow an initiation training, in which following details of the study are presented and/or discussed
  - Intended use of the app
  - Content of the investigator's brochure (IB)
  - Instructions for use of the ALICE app, with aids on training with the app, including set-up and internal calibration
  - Recruitment protocol
  - Enrolment protocol with ICF's for the clients
  - Study programme with study protocol (=CIP), in which instructions are included to uniformly assess and document clinical findings (eCRF)
  - GCP (see GCP protocol)
  - Quality check of the in-house equipment that will be used
  - Coordination & assistance
  - Risk management

Recruitment of clients

- Local IPs will be responsible for the recruitment of patients. Before they start with recruiting they will be instructed with clear inclusion and exclusion criteria (see 3.5.6.3 Subjects)
- The number of clients that should be enrolled will be in the range of 20-30 for every investigator site
- To be able to recruit 120 first time hearing aid users, the recruitment period will be spread out from April 2023 to August 2024, employing a rolling start strategy. Enrolment of clients
- Clients who match the criteria, will receive a brief introduction about the study, which may or may not include the ALICE app. If they are interested to participate in the study, they will receive an information brochure about the study programme, in which a more detailed description is provided (details about the course of the study, the 3 visits, the duration of the study and their rights and responsibilities.) They will also be informed that they will be assigned randomly to one of the two groups.
- If clients agree to participate in the study they will sign an informed consent form.
- After being stratified by age clients will be randomly assigned to one of the two groups by a KU Leuven researcher using an automatic seed generator:
  - 1 group will receive the standard of care
  - 1 group will receive the standard of care with additional support of ALICE app

	Responsible	Accountable
Clients match the criteria	Local PI	KUL PI

Clients get a brief introduction about the app and the goals of the study; when interested they receive a detailed information brochure	Local PI	
Clients sign an Informed Consent	Local PI	KUL PI
Clients are enrolled in the study	Local PI	KUL PI
Allocation of groups and randomization	Local PI	KUL PI

The study program and test protocol

- Onboarding procedure: once the clients are enrolled they will receive a standard onboarding procedure, which will be led by the local PI. Within this procedure following points/formalities will be discussed with their client:
  - The study programme/course of the study
  - Appointment schedule to perform the tests
  - Procedure to follow in case of change
  - Contact information in case of questions
  - Risk & Safety management (see safety section), with special attention to following procedures:
    - Procedure to control the loudness of the stimuli provided by the app
    - Procedure to follow to ensure safe data management (compliant with GDPR)
    - Procedure to follow in case of adverse events and/or device malfunction
  - Rights and responsibilities
- Installation of the app
  - Intended use of the app
  - Compatibility of the app with personal (streaming) devices,
  - Instruction to use the app
  - First installation and set-up of account
- Test protocol (see below and Fig. 4)

Description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation including any deviation from normal clinical practice

Below, the timeline of the test protocol is presented after allocation to a treatment group a client will be assessed with speech in noise and questionnaires (Figure 5). Followed by 4 to 6 weeks use of the ALICE app. The same outcome measures will be assessed at the end of the hearing aid trial period to evaluate the benefit of the intervention.

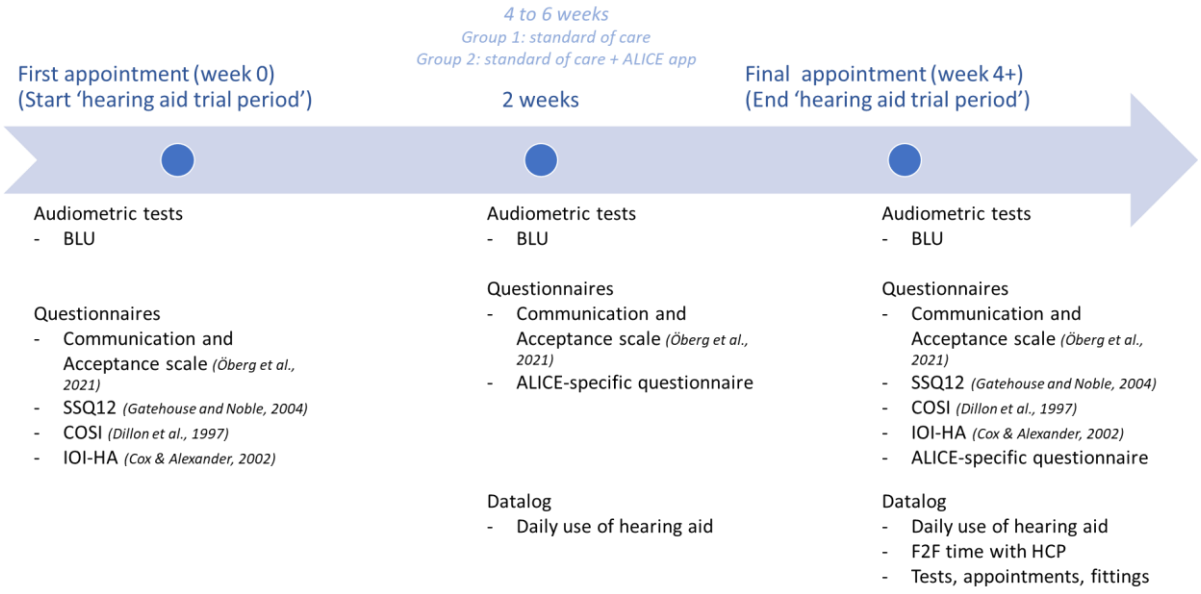


Figure 5. Timeline of the test protocol of the second research arm

Monitoring plan

General outline of the monitoring plan to be followed, including access to source data and the extent of source data verification planned

In accordance with ICH-GCP E6(R2) the Sponsor is responsible for monitoring the Trial to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the Trial procedures have been followed as shown in the approved protocol, and that relevant Trial data have been collected and reported in a manner that assures data integrity. To this end Source Data will be compared with the data recorded in the (e)CRF. A risk-based approach will be applied to determine the extent of monitoring activities and monitoring of the Trial will be performed by qualified individuals (independent from the site Trial staff), as applicable.

- **Coordination & monitoring plan**
  - Project management and on-site monitoring visits
    The Coordinating Investigator (Andrea Bussé, KUL) will supervise: the recruitment and the enrolment of the study participants (including the verification of the ICF procedure), the implementation of the study protocol at the investigational sites, the quality of the data collection, the achievement of the study goals, and the use of the ALICE app according to the CIP.
    The test protocol will be performed by the local PI. The local PI can rely on support and assistance of the Coordinating Investigator at any given time. The Research Manger will schedule regular monitoring visits with the local PI. All monitoring activities will be documented in a written report according to ISO14155.
  - Project support
    When clients need additional support their first contact point will be their local PI. When the support needed is related to their hearing or hearing aids, the local PI will help them out through their standard of practice (standard care path).
    When the support needed is related to the use of the app, the local PI will contact the Coordinating Investigator. The Coordinating Investigator will provide the local PI with additional support, if needed technical support will be provided by our in-house developers.

- Safety evaluation & reporting
  Adverse events, device deficiencies, and withdrawals will be reported and documented (see section 'Subjects' + withdrawal procedure section 3.5.6.2).
- Data collection
  - To ensure/guarantee quality of the data collection the Coordinating Investigator will perform a quality check of the data (samples) on regular basis.
  - Safety = See data management plan

3.5.6.4. Research ARM 3 (NEW!)

The main goal of the third arm of the clinical study is to evaluate the performance (and viability) of the French version of the ALICE app. This arm will be carried out in 8 hearing aid centres geographically spread across the French-speaking part of Belgium (the Walloon Region and Brussels). The duration of the study is estimated around 9 months (see procedures for the overview of the time line).

Description of the design type of clinical investigation to be performed (e.g. comparative double-blind, parallel design, with or without a comparator group) with rationale for the choice

The study design is a randomized controlled clinical trial (RCT), which is the golden standard for ascertaining the efficacy and safety of a new treatment or intervention. The goal of the current RCT is to demonstrate the superiority of the supplementary use of the ALICE app, as a new intervention, over the existing standard of care.

In this RCT two groups will be compared:

(1) A group that receives the standard of care, which is defined as followed:
   a. Persons with a moderate to profound HI who are provided with a hearing aid
(2) A group that receives the standard of care, supplemented with the French version of the ALICE app, to be used as a home-based monitoring, training and counselling tool.

Description of the measures to be taken to minimize or avoid bias, including randomization, concealment of allocation, blinding/masking, assessment of blinding plan and management of potential confounding factors

For each investigator site, clients will be recruited by the local study team (HCPs working in the hearing centre). Once the HCP has recruited the required number of clients, they will send the list of clients to the KU Leuven researcher, who will then divide the clients randomly across the two groups (standard of care/additional use of French ALICE). Randomisation of these two groups will be stratified according to age with an automatic seed generator.

We foresee a few possible confounding factors:

- Medical confounding factors
  - Type and degree of HI
  - Comorbidities such as high blood pressure, diabetes, stroke, visual acuity, cognitive abilities
- Methodological confounding factors
  - Potential procedural effects for the questionnaires may occur and will be controlled for by administering the questionnaires twice prior to the participants starting the training and at the end of the 8 week training period
- Other confounding factors such as lifestyle factors

Primary and secondary endpoints, with rationale for their selection and measurement.

The outcome measures that will be used as an endpoint to determine the clinical benefit of the ALICE app are:

- Effectiveness of the app is ensured
    - Enhanced speech understanding in difficult listening situations
    - Enhanced communication strategies
    - Reduced reported listening difficulties and reduced experienced listening effort
    - Increased knowledge/acceptance of the non-auditory consequences of HI
    - Increased satisfaction with hearing aid(s) and the delivered care

Methods and timing for assessing, recording, and analyzing variables

Table 4. Overview of outcome measures of assessment during the study

ALICE-Client			
	Outcome measure	*Type of test*	*Name of test/questionnaire*
Effectiveness	Speech understanding in difficult listening situations	Speech in noise test	Lafon disyllabiques
		Questionnaires	SSQ12 *(Gatehouse and Noble, 2004)* COSI *(Dillon et al., 1997)*
	Listening effort		EAS *(Alhanbali et al., 2017)*
	Emotional consequences /acceptance of HI		CAS *(Öberg et al., 2021)*
	Use of hearing aid and care delivery		ALICE-Specific questionnaire (custom made)

Overview of the tests and questionnaires used:

(all materials are added to the folder CIP_materials)

The **"listes disyllabiques de Lafon"** is validated speech material consisting of French disyllabic words that can be presented in quiet or in noise (Marie-Haps procedure). This speech material is included in the investigation because it is commonly used in the standard clinical practice in the Walloon region and Brussels. Administering this test is also a part of the RIZIV/INAMI application process to receive a reimbursement for hearing aids.

The **SSQ12** is a short version of the validated Speech, Spatial and Qualities of Hearing Scale, developed for use in clinical research and rehabilitation settings (Noble et al., 2013). The SSQ questionnaire has also been validated in French (Moulin et al., 2015). For the purpose of this research arm, we have constructed a French short version.

The **COSI** questionnaire (Client Oriented Scale of Improvement) was explained in detail in the context of ARM 1 (3.5.6.2) and ARM 2 (3.5.6.3) and will be administered in French in ARM 3. The administration of this questionnaire is also a part of the RIZIV/INAMI application process to receive a reimbursement for hearing aids.

The **CAS** (Communication and Acceptance Scale) and **EAS** (Effort Assessment Scale) have been explained in the context of ARM 1 (3.5.6.2) and/or ARM 2 (3.5.6.3) and have been translated from Dutch to French for the purpose of this arm of the clinical trial.

The **ALICE-questionnaire** was developed for the purpose of this study. The questions of this questionnaire were based on 3 different questionnaires. First, the SUS (system usability scale) to determine the usability of the ALICE app. Second, the SADL (Satisfaction with Amplification in Daily Living) which was designed to evaluate the satisfaction that people experience with their hearing aids. Third, the PREM (Patient Reported Experience Measures) as is used to evaluate audiological centres in the Netherlands. A total of 20 questions were selected to evaluate the participants' experience with the usability of the ALICE app, their satisfaction with their hearing aids and their satisfaction with their audiologist/hearing centre.

Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration.

Equipment used/needed to perform test protocol

- Speech in noise testing: part of the standard of care
    - Audiometer (calibrated): available at the investigational sites
- Questionnaires: online/tablet
    - Clients will be able to fill out the questionnaires on a tablet (provided by the KU Leuven researchers to the investigational sites) or on their own computer through a website
- The app will be used on the clients' personal smart device (device compatibility is described in the IB)
- Feedback: documented in word files

Clinical investigation sites: number, location and if appropriate differences in clinical investigation site characteristics.

A list of participating clinical investigation sites and their locations will be provided at a later stage.

Subjects

Subjects will be recruited by their HCP (see recruitment procedure) in accordance with the following criteria:

Inclusion criteria

- Clients who are using a hearing aid (N = 120), which is more than necessary according to the power analysis (3.5.7). Clients must have completed the hearing aid trial period and must have decided to purchase the hearing aid.
- Clients who experience listening and communication difficulties
- Clients with a hearing aid may not have any experience with auditory training yet.
- Able to operate the training programme as an app on a mobile device/tablet (e.g. clients have a mobile device or table; clients have sufficient eyesight to see the exercises; clients must be able operate the program).
- At least 18 years old.
- French-speaking as all instructions and counselling questions will be presented in French.
- Clients need to have an Android or iPhone smartphone and connection to internet.

Exclusion criteria

- Visually impaired
- Motorically impaired
- Cognitively impaired

Criteria and procedures for subject withdrawal or lost to follow up

When and how to withdraw a subject from the clinical investigation or stop the use of the investigational device

Clients participate in this study voluntarily and have the right to withdraw from the study at any time they want. If they choose to withdraw they will be asked to delete the ALICE app from their smartphone or tablet.

Documentation of efforts to be made to trace subjects that are lost to follow up and possible reasons

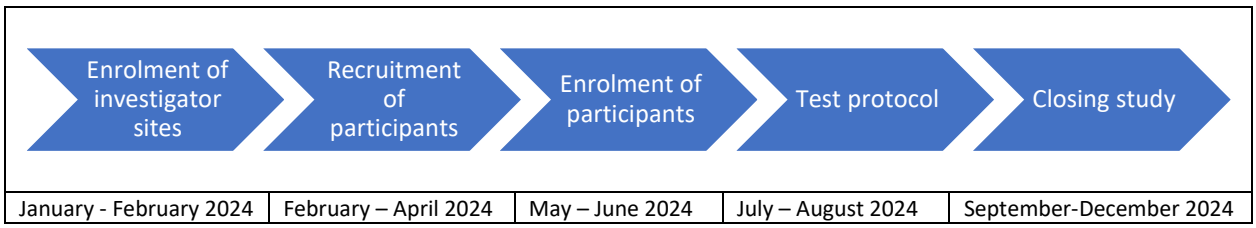
When clients withdraw from the study, they will be asked to provide a reason as this may be of interest to the study. However, they are not obligated to provide a reason for their withdrawal.

Whether and how subjects are to be replaced

In case of withdrawal or loss to follow up, we will report this but the client will not be replaced since we have sufficient participants for the study.

Procedures

Overview and estimated timing



January - February 2024	February – April 2024	May – June 2024	July – August 2024	September-December 2024

Enrolment of investigator sites

- 8 hearing centres will be enrolled as an investigator site in this multicentric study. The sites will be assessed based on adequate resources, a qualified investigation team and access to an adequate number of subjects.
- For every investigator site, one local PI will be appointed. The local PI will be responsible to execute the investigation (following the study protocol) and to perform the local coordination for the study.
- In order to know if the local PI is eligible to coordinate the study, the following criteria apply
  - Experienced professionals (> 5 years of working experience) in the field of aural rehabilitation of adults with hearing impairment
  - French speaking
  - Willing to become familiar with research and good clinical practice
- Once the local PI has been assigned (and approved by FAGG and EC), the protocol will be discussed and the clinical trial agreement (see Annex 8) will be signed by the local PI.
- All local PI's will have to follow an initiation training, in which following details of the study are presented and/or discussed
  - Intended use of the app
  - Content of the investigator's brochure (IB)
  - Instructions for use of the ALICE app, with aids-on training with the app, including set-up and internal calibration
  - Recruitment protocol
  - Enrolment protocol with ICFs for the clients
  - Study programme with study protocol (= CIP), in which instructions are included to uniformly assess and document clinical findings (eCRF)
  - GCP (see GCP protocol)
  - Quality check of the in-house equipment that will be used
  - Coordination & assistance
  - Risk management

Recruitment of clients

- The local study team (HCPs working in the hearing centre) of each investigator site will be responsible for the recruitment of patients. Before they start with recruiting they will be instructed with clear inclusion and exclusion criteria
- The number of clients that should be enrolled will be in the range of 15 to 20 persons for every investigator site

- The recruitment period is a fixed period over a time span of 12 weeks or when approximately 15 to 20 clients are recruited, after that period no clients can enter the study.

Enrolment of clients

- Clients who match the criteria, will receive a brief introduction about the study, which may or may not include the ALICE app. If they are interested to participate in the study, they will receive an information brochure about the study program, in which a more detailed description is provided (details about the course of the study, the 2 visits at 0 and 8 weeks, the duration of the study and their rights and responsibilities). They will also be informed that they will be assigned randomly to one of the three groups.
- If clients agree to participate in the study they will sign an informed consent form.
- A complete list of clients who wish to participate for each investigational site is sent to the KU Leuven researchers at the end of the recruitment period.
- After being stratified by age, clients will be randomly assigned to one of the two groups by a KU Leuven researcher using an automatic seed generator:
  - 1 group will receive the standard of care
  - 1 group will receive the standard of care with additional support of the ALICE app (French version)

	Responsible	Accountable
Clients match the criteria	Local PI	KUL PI
Clients get a brief introduction about the app and the goals of the study; when interested they receive a detailed information brochure	Local PI	
Clients sign an Informed Consent Form	Local PI	KUL PI
Clients are enrolled in the study	Local PI	KUL PI
Allocation of groups and randomization	KUL PI	KUL PI

The study program and test protocol

- Onboarding procedure: once the clients are enrolled they will receive a standard onboarding procedure, which will be led by the local PI. Within this procedure following points/formalities will be discussed with their client:
  - The study program/course of the study
  - Appointment schedule to perform the tests
  - Procedure to follow in case of change
  - Contact information in case of questions
  - Risk & Safety management (see safety section), with special attention to following procedures:
    - Procedure to control the loudness of the stimuli provided by the app
    - Procedure to follow to ensure safe data management (compliant with GDPR)
    - Procedure to follow in case of adverse events and/or device malfunction
  - Rights and responsibilities
- Installation of the app
  - Intended use of the app
  - Compatibility of the app with personal (streaming) devices,
  - Instructions to use the app

        - First installation and set-up of account
    - Test protocol (see below and Fig. 6)

Description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation including any deviation from normal clinical practice

Below (Figure 6), the timeline of the test protocol is presented: After allocation to a treatment group a client will be assessed with a speech in noise test and questionnaires, followed by 8 weeks use of the ALICE app. The same outcome measures will be assessed at the final appointment to evaluate the benefit of the intervention.

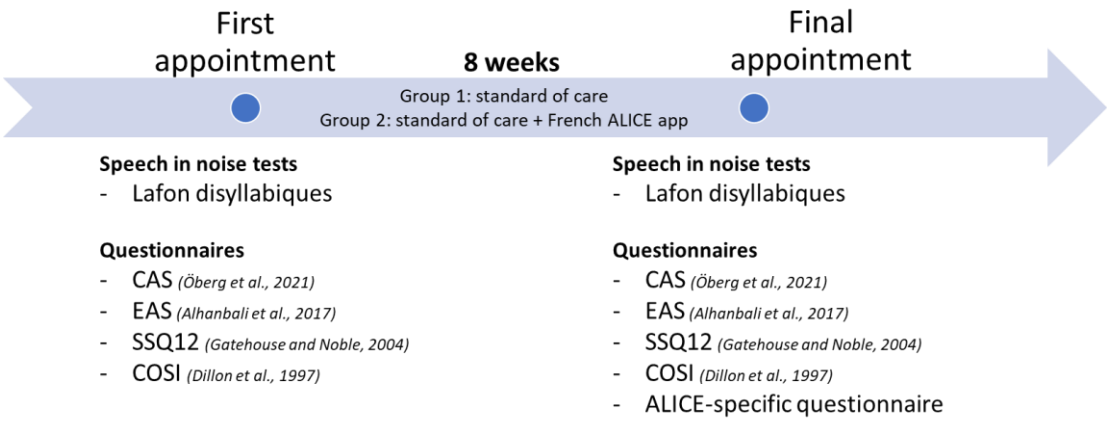


Figure 6. Timeline of the test protocol.

Monitoring plan

General outline of the monitoring plan to be followed, including access to source data and the extent of source data verification planned

In accordance with ICH-GCP E6(R2) the Sponsor is responsible for monitoring the Trial to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the Trial procedures have been followed as shown in the approved protocol, and that relevant Trial data have been collected and reported in a manner that assures data integrity. To this end Source Data will be compared with the data recorded in the (e)CRF. A risk-based approach will be applied to determine the extent of monitoring activities and monitoring of the Trial will be performed by qualified individuals (independent from the site Trial staff), as applicable.

- **Coordination & monitoring plan**
    - <u>Project management and on-site monitoring visits</u>
      The Coordinating Investigator (Andrea Bussé, KUL) will supervise: the recruitment and the enrolment of the study participants (including the verification of the ICF procedure), the implementation of the study protocol at the investigational sites, the quality of the data collection, the achievement of the study goals, and the use of the ALICE app according to the CIP.
      The test protocol will be performed by the local PI. The local PI can rely on support and assistance of the Coordinating Investigator at any given time. The Research Manager will schedule regular monitoring visits with the local PI. All monitoring activities will be documented in a written report according to ISO14155.
    - <u>Project support</u>

When clients need additional support, their first contact point will be their HCP of the local study team.
When the support needed is related to their hearing or hearing aids, the local study team will help them out through their standard of practice (standard care path).
When the support needed is related to the use of the app, the local study team will contact the Coordinating Investigator. The Coordinating Investigator will provide the local study team with additional support. If needed, technical support will be provided by our in-house developers.

- Safety evaluation & reporting
  Adverse events, device deficiencies, and withdrawals will be reported and documented (see section 'Subjects' + withdrawal procedure section 3.5.6.4).
- Data collection
  - To ensure/guarantee quality of the data collection, the Coordinating Investigator will perform a quality check of the data (samples) on regular basis.
  - Safety = See data management plan

3.5.7. Statistical design and analysis

3.5.7.1. Sample size

HCPs from the hearing centres participating in the first, second and third arm of the study will include a total of 390 hearing aid users (150 in the first arm, 120 in the second arm and 120 in the third arm). HCPs from UZ Leuven will include 30 CI users for the first arm only. Clients will be equally divided among participating investigation sites. After being stratified by age, they will be randomly assigned to two groups of approximately 195 hearing aid users (75 in the first arm, 60 in the second arm and 60 in the third arm), and two groups of 15 CI users (first arm only).One group will receive the standard of care, the other group will receive the standard of care supplemented with theALICE app (The Dutch version in both the first and second arm the French version in the third arm).

Scientific literature was consulted to estimate the group size needed for our RCT and a power analysis was conducted to confirm the effect size for this sample.

Power analysis conducted with the G*Power software (Erdfelder et al., 2009) indicated that a total sample of at least 76 persons is needed to detect differences in speech understanding in noise outcomes between the two treatment groups with a low to medium effect size (d = 0.25) to have statistical power of 95% using a repeated measures ANOVA ($\alpha = 0.05$). We will be able to recruit more clients via the hearing centers (between 15 and 30 persons per hearing center). We estimate that, for all three arms of the study, 390 persons with a HA will take part in the trial and, for the first arm of the study only, about 30 persons with a CI. This larger number accounts for clients being lost to follow-up during the study.

3.5.7.2. Statistical analysis

Statistical analyses will be performed using either the R programming language and statistical environment (R Core Team, 2017) or IBM SPSS 27. Potential missing data will be replaced using multiple imputation (in SPSS).

Data for hearing aid users and cochlear implant users will be analysed separately. Potential relations between outcomes will be determined in a within-subject design, i.e., baseline session outcomes will be compared to the final session outcomes, with a repeated measures ANOVA ($\alpha = 0.05$). We will correct for multiple comparisons using Dunn post-hoc tests with Holm correction (Dunn, 1961).

3.5.8. Data management

3.5.8.1. Data Collection Tools and Source Document Identification

Operational aspects

Data collection, handling, processing and transfer for the purpose of this Trial will be performed in compliance with applicable regulations, guidelines for clinical trials and internal procedures, as follows:

Data collection

Source Data will be collected and recorded in the Trial participant's files/medical records.

If applicable, worksheets may be used for capturing some specific data in order to facilitate completion of the (e)CRF. Any such worksheets will become part of the Trial participant's source documentation and will be filed together with or as part of the medical records (during but also following completion of the Trial).

It remains the responsibility of the Investigator to check that all data relating to the Trial, as specified in the Trial protocol (=CIP), are entered into the (e)CRF in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

(e)CRFs are provided by the Sponsor (hear the coordinating investigator) for each participant. The Trial data will be transcribed from the source records (i.e. participant's medical file or Trial-specific source data worksheets) into an (e)CRF by Trial Staff (here the local PI). Transcription to the (e)CRF will be done as soon as possible after a participant visit and in a pseudonymized manner using a unique identifier assigned by the Sponsor.

The (e)CRFs will be available for review at the next scheduled monitoring visit (as applicable) and shall under no circumstances capture personal data such as but not limited to the participant or their relative(s) name, home address, contact details, full date of birth medical record number (e.g. UZ Leuven EAD number), social security number etc.

Data Validation

All data relating to the Trial must be prepared and validated by the local PI and coordinating Investigator. Any (e)CRF entries, corrections and alterations must be made by the PI or other authorized Trial staff.

Proper audit trails must be available to demonstrate the validity of the Trial data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e. who made the correction/addition, when and why), without obliterating the original data entry information.

Data Management

The Trial Data Manager (here coordinating investigator) will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A Data Management Plan (DMP) will be developed to map data flows, data validation measures that will be taken, how (interim) database lock(s) will be managed and, as applicable, the role and responsibilities of the Data Safety Monitoring Committee (DSMB)

Data Transfer

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the Trial-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Trial must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor(see 8.1.2. legal requirements).

Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the EU General Data Protection Regulation 2016/679 (GDPR) and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Trial staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Trial disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Trial as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each Trial participant, and will maintain a Trial Master File (TMF)/Investigator Site File (ISF) containing all Trial documents as specified in ICH-GCP E6(R2) Chapter 8 entitled “Essential Documents for the Conduct of a Clinical Trial”, and as specified by applicable regulatory requirement(s).
The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the European General Data Protection Regulation). The receiving party will be bound by contractual agreement to keep the transferred data confidential at all times and to only process the data for the purpose of the Trial. To this end, appropriate Data Transfer Agreements (DTAs) will be established.

3.5.8.2. Audits and Inspections

The Investigator will permit direct access to Trial data and documents for the purpose of monitoring, audits and/or inspections by authorized entities such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such (e)CRFs, source records and other Trial related documentation (e.g. Investigator Site File, the Trial Master File, pharmacy records, etc.) must be kept current, complete and accurate at all times.

3.5.8.3. Datamanagement related to the use of the investigational device

Registration, authentication and verification

HCPs have to register to use ALICE-Pro before using the dashboard for the first time. They cannot log onto the dashboard without registration. Before clients can use the ALICE app, they first have to download it onto their smart device. The first time a client logs on to ALICE-Client, they will be asked to register and give permission to process personal data. No data can be accessed without being logged on to the app. After registration is completed, clients have to connect to a HCP dashboard and allow their data to be used and shared before an HCP can see their test and training data.

Permission

The client has to indicate that he/she allows the app to process their personal data when first registering on the app (including a privacy statement). This step is necessary for the HCP to identify who is using the app and for them to match training outcome to the right client.

Why

The data will be collected and processed based on 4 legal grounds:

1. Technical support from KUL to HCP and client
2. Medical service/treatment from HCP to client
3. Research purposes (efficacy, safety and usability of the app)
4. Future commercial activities (launch of the app through KUL spin off)

Data collection

All data collected throughout the study will be pseudonymised and coded for KU Leuven researchers. HCPs will have the key which connects the code to each client. This key is stored on a secure location on the KU Leuven server.

When registering on the app, clients receive an anonymous code. This can only be linked to the ALICE-Pro dashboard after clients agree to the terms and conditions of the app and after they agree that data can be shared with their HCP. The client app will collect data that origin from the monitoring tasks, listening training exercises, pop-up questions and data that origin from the use of the app (analytics). No personal data are saved on the smart device. Training data are only saved on the clients' smart device when they are using the device without an internet connection. The data are transferred to the KU Leuven server once internet connection is established. The data collected through the ALICE-Client app can only be accessed through the ALICE-Pro dashboard after HCPs log on to the website.

The KU Leuven confirms that collection and processing during clinical trials is done in full compliance with the European Regulation 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (GDPR).

Participant data will be processed in accordance with the European General Data Protection Regulation (AVG/GDPR) and the Belgian Law (30 July 2018) on the protection of natural persons with regard to the processing of personal data. Research data resulting from the current project will be discarded after 25 years, according to KU Leuven/UZ Leuven research data policy regulations.

As the commissioner of the study, KU Leuven is the data controller of the personal data, which will be processed in the context of this study. Participants will be informed through the ICF about the purpose of the study, the data collected, the period for which data will be stored and the participants' rights. These rights may be exercised at any time during the study. All PIs have acquired certificates of good clinical practice. Applicants and researchers involved in the project will ensure that all research is carried out in accordance to the rules and regulations of scientific integrity of the KU Leuven.

Storage

The file with the key to match each anonymised code to a specific client is stored on a secure location on the KU Leuven server. This key is used to automatically match the client with the training data in the pro portal.

All data input (from ALICE-Pro and ALICE-Client) will be safely stored on the KUL server. During the length of the study this data will not be encrypted based on the legal grounds that apply, to guarantee the technical and medical service will be delivered to the users of ALICE.

Procedures for data retention

The file with the key to match each anonymised code to a specific client is stored on a secure location on the KU Leuven server. This key is used to automatically match the client with the training data in the pro portal.

All data input (from ALICE-Pro and ALICE-Client) will be safely stored on the KUL server. During the length of the study this data will not be encrypted based on the legal grounds that apply, to guarantee the technical and medical service will be delivered to the users of ALICE.

Specified retention period

Research data resulting from the current project will be discarded after 25 years, according to KU Leuven/UZ Leuven research data policy regulations.

3.5.9. Amendments to the CIP

Unless for urgent reasons as specified in ICH-GCP E6(R2) section 4.5.4, amendments must not be implemented prior to EC and/or CA review and/or approval, as applicable.

In accordance with the Belgian law of May 7th 2004 regarding experiments on humans, the Sponsor may develop a non-substantial amendment at any time during the Trial. If a substantial amendment to the clinical Trial agreement or the documents that supported the original application for the clinical Trial authorisation is needed, the Sponsor must submit a valid substantial amendment to the Competent Authority (CA) for consideration, and to the EC for review and approval. The CA and/or EC will provide a response in accordance with timelines defined by applicable regulations. It is the Sponsor's responsibility to assess whether an amendment is substantial or non-substantial for the purpose of submission to the CA and/or EC.

Amendments to the Trial are regarded as 'substantial' when they are likely to have a significant impact on the safety or physical or mental integrity of the clinical Trial participants, or the scientific value of the Trial.

3.5.10. Deviations from the CIP

3.5.10.1. Protocol / GCP compliance

The Trial must be performed in accordance with the protocol, current ICH and ICH-GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of Trial participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the Trial data are credible, reliable and reproducible.

The Investigator and Trial team acknowledge and agree that prospective, planned deviations or waivers to the protocol are not permitted under applicable regulations on clinical studies. However, should there be an accidental protocol deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor. Deviations should also be reported to the EC as part of the EC's continued review of the Trial (e.g. through the ASR, APR, etc.). Protocol deviations which are found to frequently recur, will require (immediate) action. The Investigator acknowledges that such recurring protocol deviations could potentially be classified as a serious violation of ICH and/or the protocol.

It is understood that "a serious violation" is likely to affect to a significant degree:

- the safety or physical or mental integrity of the Trial participants; or
- the scientific validity of the Trial

The Investigator is expected to take any immediate action required to protect the safety of any participant included in the Trial, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action and the EC at the Trial site should be informed according to local procedures and regulations.

3.5.11. Device accountability

In accordance with Annex VI, Part C of the Medical Device Regulation (EU) 2017/745 (MDR), only software which is commercially available on its own as well as software which constitutes a device in itself shall be subject to Unique Device Identifier (UDI) requirements.

For the clinical investigation, traceability shall be achieved by restricted access to the app, only subjects who are enrolled in the study and have signed the informed consent will be granted access (see section 3.5.6. for further details on the enrolment procedure)

3.5.12. Statements of compliance

The Trial will be conducted in compliance with the principles outlined in the requirements for **the European Regulation (EU) 2017/745 on Medical Devices (MDR)**, the ISO14155 as well as in compliance with ICH-GCP E6(R2) guidelines, other GCP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) or the Belgian law of May 7th 2017 on clinical Trials with medicinal products for human use, as applicable, and with the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights and all other applicable legal and regulatory requirements.

This clinical trial will not begin until it is approved by the ethical commission.

3.5.12.1. Data protection and participant confidentiality

The Trial will be conducted in compliance with the requirements of the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR including the Belgian Privacy Act of 30 July 2018 on the protection of privacy in relation to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix). In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR. (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

Financing

This study is sponsored by the KU Leuven internal funds C3/21046 (PI: Prof. Astrid van Wieringen)

Financial arrangement: Investigational sites will not receive a reimbursement for participation in this study.

No fault insurance

The Participating Site, the Investigator and Sponsor shall have and maintain in full force and effect during the term of this Trial, and for a reasonable period following termination of the Trial, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

For Belgian Participating Sites

Art 29 of the Belgian Law relating to experiments on human persons dated May 7th, 2004 applies. Prior to the start of the Trial, the Sponsor shall enter into an insurance contract in order to adequately cover Trial participants from Belgian sites in accordance with art. 29 of the said law.

3.5.13. Informed consent process

The Trial will be conducted only on the basis of prior informed consent by the Trial participants and/or their legally authorized representative(s). As such, no Trial-related procedures will be conducted prior to obtaining written informed consent from potential Trial participants.

The process for obtaining and documenting initial and continued informed consent from potential Trial participants will be conducted in accordance with ICH-GCP E6(R2), applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the Investigator Site File (ISF) at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the protocol section entitled “Archiving”.

Participants may voluntarily withdraw consent to participate in the Trial for any reason at any time. The participant’s request to withdraw from the Trial must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant’s medical record.

Trial data and samples collected before withdrawal can be used in the trial. No new trial data or samples will be collected after withdrawal of the participant.

3.5.13.1. Description of the general process for obtaining informed consent, including the process for providing subjects with new information, as needed.

Before clients enter the study, they will be informed about the purpose of the study, its goals, what is expected from the participant, the data collected, the period for which data will be stored and the participants’ rights by their HCP/the researcher and also through the informed consent form (ICF). All clients receive an informed consent form and an informed consent signature is obtained for all clients who agree to participate in the study.

Clients will be informed that they can withdraw from the study without any reason (and without consequence for their follow-up in the hearing centre or at UZ Leuven, if applicable). These rights may be exercised at any time during the study. Clients cannot participate in the study without signing the informed consent form.

Besides an informed consent form, clients have to agree to the terms and conditions and the privacy statement of the ALICE app. These include information on how data are processed and stored. Clients have to indicate that they allow their data to be collected and shared within the study.

3.5.13.2. Description of the informed consent process in circumstances where the subject is unable to give it

No participants will be included in the study who are unable to give informed consent themselves.

3.5.14. Adverse events, adverse device effects and device deficiencies

3.5.14.1. Definitions

The definitions and reporting requirements adopted in this Clinical Investigation Plan (CIP) are based on the Medical Device Regulation (EU) 2017/745 and the MDCG 2020-10/1 European guideline.

Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device.

Note:

a. This definition includes events related that are anticipated as well as unanticipated events

b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

Serious Adverse Event (SAE)

A SAE is any adverse event that led to any of the following:

a) death

b) serious deterioration in health of the subject, that resulted in any of the following:

- life-threatening illness or injury
- permanent impairment of a body structure or a body function
- hospitalisation or prolongation of patient hospitalisation
- medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
- chronic disease

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device.

Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

An Unanticipated Serious Adverse Device Effect is an effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Device Deficiency (DD)

A DD is any in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Possible adverse events related to device deficiency

- Software malfunctions (bugs)
- Software compatibility/interoperability

Mitigation of adverse events related to malfunctions of the software

Software malfunction: software has been developed following the IEC 62304 standard, taking into account all possible risks in the design and development phase (risk-based approach, ISO 14791, see

IB). However the occurrence of small software malfunctions remains high, resulting in a significant risk of low harm for the users of the app.

If bugs or deficiencies occur clients can contact their hearing care professional at the hospital or hearing centre, or report the issue directly to the app developers by email. The developers are not directly involved in the clinical study. Moreover, continuity of the standard of care is always guaranteed by their HCP.

Software compatibility/interoperability: Software can only be used with other CE-marked devices (tablet or smartphone) to ensure a safe output level (which is regulated by EU standard EN 50332 in Europe since 2013[1]). This is clearly stated in the IFU.

Adverse Events of Special Interest

It is highly unlikely that the ALICE app produces adverse events. We identified a number of possible adverse events that may occur while using the app and described possible methods to avoid these adverse events.

The following adverse events are of special interest and should be reported within the same timelines as SAEs:

Clinical adverse events

- Since stimuli are played from a personal smart device, stimuli may be too loud or uncomfortable despite the measures that have been taken e.g. setting the volume at a comfortable level.

Privacy related adverse events

- Risks related to data/server security

Mitigation of adverse events related to use of the ALICE app

To avoid that a stimulus is presented too loud or that a stimulus sounds different to the client than expected several measures have been taken. Clients using the ALICE app are instructed to adjust the volume of the smart device at a comfortable level (not too loud, nor too quiet) before starting to use the app. The level that has been set by the client will determine the volume at which the training is done. The app will automatically adjust the volume of the smart device to this level every time the client opens the app. If the client tries to increase the volume of his/her device after the volume has been set at a comfortable level, a warning will appear and the client is instructed to go back to the page to set the volume at a comfortable level.

Clients will be instructed to not use the ALICE app for more than 45 minutes a day to avoid causing additional noise induced HI. Noise induced HI is caused by chronic and excessive exposure to hazardous levels of noise and is characterized by a reduced sensitivity (>20 dB HI or HL) in the 3-6 kHz range, with normal sensitivity at lower and higher frequencies. The extent of HI depends on the intensity of the noise and duration of noise exposure. According to the latest WHO guidelines[2] a sound intensity over 80 dB that is listened to for more than 40 hours a week can cause noise induced HI. Clients will use the app for 15 to 30 minutes each day on average, which should not be long enough to cause an additional noise induced HI even at the maximum volume. This rule is defined in the instructions for use.

[1] Standards for safe listening systems: Situational Analysis. Geneva: World Health Organization and International Telecommunication Union, 2017.
(https://www.who.int/pbd/deafness/Monograph_on_situation_analysis_and_background_for_standards_for_safe_listening_systems.pdf)

[2] World report on hearing. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
(file:///C:/Users/u0150004/Downloads/9789240020481-eng.pdf)

These risks and mitigations were investigated on effectivity (see CEP and IB for more info)

Mitigation of adverse events related to the use of the ALICE app in combination with personal devices

Speech materials can be streamed directly to the clients' hearing aid or cochlear implant, can be played in free field or can be played through headphones.

If clients stream directly to their hearing aid, clients are instructed to use the pre-set hearing aid or cochlear implant settings as programmed by their hearing care professional. The signals pass through the same algorithm as for the normal microphone inputs, with the same maximum output as is used in the participants daily life.

Similar precautions are taken for clients who use the ALICE app without streaming option. Clients who use headphones, earbuds or speakers are instructed to only use CE marked devices with the use of the ALICE app and to pay extra attention when setting the volume of the ALICE app. The ALICE app cannot control the quality or possible malfunctioning of the headphones, earbuds or speakers used by the client. However, CE-marked smart devices (tablet or smartphone) ensure a safe output level (which is regulated by EU standard EN 50332 in Europe since 2013[3]). Clients are instructed to not exceed the recommended maximum output level of their smart device.

Before clients take the ALICE app home to train their listening and communication skills , they will be given the opportunity to use the app together with their hearing care professional. During this session, they will be asked to indicate if any of the stimuli sound uncomfortable or if any of the stimuli are too loud. The hearing care professional will be available at any point if problems with the ALICE app occur.

Mitigation of privacy related adverse events

We confirm that the software has an inherent safe design and is developed taking into account all possible risks related to cybersecurity (ISO 14791 and MDCG 2019-16 - Guidance on Cybersecurity for medical devices) according to the CIA model.

All data is pseudomised and safely stored on the servers of the KUL. All GDPR regulations are followed.

A data management plan is filled out and the KUL safety measures are activated if a data leak would be reported.

In case a data breach would occur (for instance by personal error, eg. Loss of smartphone), the KU Leuven Privacy Policy & Data Management Procedure is followed.

3.5.14.2. Adverse Events that do not require reporting

In general, the following should <u>not be reported as AEs:</u>

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness.
- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.

The following events are commonly observed and are therefore not considered as adverse events for the purpose of the trial:

- All AEs or SAEs should be reported

[3] Standards for safe listening systems: Situational Analysis. Geneva: World Health Organization and International Telecommunication Union, 2017. (https://www.who.int/pbd/deafness/Monograph_on_situation_analysis_and_background_for_standards_for_safe_listening_systems.pdf)

Although these events should not be reported to the Sponsor, these should be recorded in the patient's medical notes according to routine practice.

The following events not to be considered as SAEs are:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Hospitalisation as part of a standard procedure for protocol therapy administration. However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

3.5.14.3. Recording and reporting of Adverse Events

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by trial staff, will be recorded in the patient's medical record and in the (e)CRF within a reasonable time after becoming aware. If available, the diagnosis should be reported on the AE form, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs using separate AE forms.

The following minimum information should be recorded for each AE:

- AE description
- start and stop date of the AE
- severity
- seriousness
- causality assessment to the Investigational Medical Device (IMD) and/or study procedures
- outcome
- what caused the AE
- possible solution

Possible adverse events that may occur during this study:

- The test used in the clinical protocol are standard clinical tests used in daily practice. These tests do not hold any risks for the participants in the study.
- Use of the training app can lead to a high cognitive load, which can result in feelings of fatigue.

Mitigation of possible adverse events

The audiometric tests that are used during the study do not contain any risks. The audiometric tests are administered by trained and licenced hearing care professionals in hospitals or hearing centres and are part of the standard of care.

Test sessions of 15 minutes per day are recommended to the participant. It is possible that a participant gets tired within this time. In that case they can take a break or stop the session. Participants are frequently reminded that a session can be paused or stopped at any time. Moreover, each test session is divided into short measurement blocks of 5 minutes. Participants may choose to train longer than the recommended time if they wish but will informed that the training should be continued the next day after 45minutes of subsequent training.

Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.
- **Severity:**

- Severity must be evaluated by an Investigator according to the following definitions:
  - *Mild* – no or transient symptoms, no interference with the subject's daily activities
  - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
  - *Severe* – considerable interference with the subject's daily activities, unacceptable

- **Causality:**

Not related	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event; - the event involves a body-site or an organ that cannot be affected by the device or procedure; - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.
Possible	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship	The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that • the investigational device or procedures are applied to; • the investigational device or procedures have an effect on; - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible); - other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Timelines for reporting

- After informed consent has been obtained but prior to first use of the IMD, only adverse events caused by a study specific procedure should be reported
- After first use of the IMD, adverse events will be reported as follows:
    - All AEs, SAEs, AESIs and Device Deficiencies will be reported until 7 days after last use of IMD or until last follow-up visit (whichever occurs first)

All SAEs and AESI as defined in the protocol must be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers.

SAE details will be reported by the Investigator to the sponsor:

- By completing a paper SAE form and sending it to the following email address:

Mail: andrea.busse@kuleuven.be

If an authorised Investigator from the reporting site is unavailable, initial reports without causality assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

Follow-up

The Investigator must record follow-up information by updating the patient's medical records and the appropriate forms in the (e)CRF. The worst case severity and seriousness of an event must be kept throughout the trial.

SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All *SAEs* must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due to the SAE) and until all related queries have been resolved, or until end of trial (whichever occurs first).
- *Non-serious AEs* must be followed up until the patient's last study visit, and until all related queries have been resolved.

SAEs after the end of the trial: If the Investigator becomes aware of an SAE with suspected causal relationship to the IMD or experiment after the subject has ended the trial, the Investigator should report this SAE within the same timelines as for SAEs during the trial.

Pregnancy

Female subjects must be instructed to notify the Investigator immediately if they become pregnant during the trial.

Death

All deaths will be reported without delay to the sponsor (irrespective of whether the death is related to disease progression, the IMD, study procedure or is an unrelated event). The sponsor will notify all deaths as soon as possible after becoming aware to the EC and provide additional information if requested.

3.5.14.4. Recording and reporting of Device Deficiencies

Each Device Deficiency must be documented by the Investigator in the source documents and reported to the Sponsor on a Device Deficiency form.

If the Device Deficiency lead to the occurrence of a (S)ADE, the (S)ADE must also be reported by the Investigator to the Sponsor on the appropriate forms and within the specified timelines.

3.5.14.5. Reporting requirements to Ethics Committees (ECs) and Competent Authorities (CAs)

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SAEs, AESIs and Device Deficiencies against medical experience to identify and expeditiously communicate possible new safety findings to Investigators, ECs and applicable CA's based on applicable legislation.

Sponsor's reporting of Serious Adverse Events and Device Deficiencies

The Sponsor is responsible to report to the CA's where the clinical investigation has commenced:

- Any SAE that has a **causal** relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
- Any Device Deficiency that might have led to a SAE if:
    a) Appropriate action had not been taken or,
    b) Intervention had not occurred or,
    c) If circumstances had been less fortunate
- New findings/update in relation to already reportable events.

These 'reportable events' must be reported within the following timelines:

- A reportable event which results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it must be reported immediately, but not later than **2 calendar days** after awareness by

the sponsor of a new reportable event or of new information in relation with an already reported event.

- Any other reportable event or a new finding/update to it must be reported immediately, but not later than **7 calendar days** following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	AE	AE form	sponsor	as defined in protocol
	SAE	SAE form	sponsor	asap, but no later than 3 calendar days after awareness
	Device Deficiency (DD)	DD form + AE/SAE form (if applicable)	sponsor	as defined in protocol (exception: within 3 calendar days if considered reportable event)
	death	SAE form	sponsor	asap
Sponsor	all reportable events (of all participating sites)	EU SAE report form (excel)[1]	- CA for Belgium -> FAGG: via mail to ct.rd@fagg.be - PI's of participating sites	asap, but no later than - 2 calendar days (in case of risk of death or serious injury/illness that requires prompt remedial action for other patients, users or other persons) - 7 calendar days (all other reportable events)
	death	SAE form + narrative	- CA for Belgium -> FAGG: via phone and mail	asap

[1] The SAE report form in excel format can be downloaded from the following web page: https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx?web=1

3.5.15. Vulnerable population

No vulnerable population will be involved in this study.

3.5.16. End, suspension or premature termination of the clinical investigation

The clinical investigation will not be suspended or terminated prematurely in any of the investigation sites unless the local PI of the study in an investigation site is unable to recruit or follow up the clients that participate in this study because of for example sickness.

The competent authority (CA) shall be notified by the PI of the KU Leuven at the end of the clinical investigation, and a justification shall be provided in case of a temporary study halt or early termination. The PI will provide the CA with a clinical investigation report.

This must be done in accordance with the MDR:

In accordance with MDR article 77 study end reporting is mandatory within 15 days (but 24 hours if based on safety grounds). In addition, a clinical investigation report needs to be submitted within one year of the end of the clinical investigation or within three months of the early termination or temporary halt. The end of a clinical investigation shall be deemed to coincide with the last visit of the last subject unless another point in time for such end was set out in the clinical investigation plan.

Participants of the clinical investigation are clients in the hearing centre/university hospital. Termination of the clinical investigation will not affect the relationship with their hearing care provider or their regular health care.

3.5.17. Publication policy

If the results of the clinical investigation will be submitted for publication, we will opt for a mix of gold and green open access for the produced results. Articles that are published in journals that do not grant open-access online will be self-archived after publication in the online repositories.

3.5.18. COVID related precautions

Our studies can be conducted safely when the right precautions are taken regarding COVID. Hearing centres and hospitals have very strict COVID regulations. In case any tests need to be performed in our lab, we have specific rules and a protocol to test participants during the COVID pandemic.

3.5.19. Bibliography

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