Study Title: "Pilot Validation of a Prototype Mobile Health Tympanometer"

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NCT#: NCT05666505

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Abbreviations

AC	Arkansas Children's
ADEs	Adverse Device Effects
AE	Adverse Event
APR	Annual Progress Report
CFR	Code of Federal Regulations
FDA	United States Food and Drug Administration
IEC	International Electrotechnical Commission
IRB	Institutional Review Board
LMICs	Low- and middle-income countries
mHealth	Mobile Health
ML	Machine Learning
ORRA	Office of Research Regulatory Affairs
PI	Principal Investigator
RCA	Root Cause Analysis
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SD	Secure Digital
UADE	Unanticipated Adverse Device Effect
UAMS	University of Arkansas for Medical Sciences
UPIRTSO	Unanticipated Problem Involving Risks to Subjects or Others

Background and Rationale

An estimated 1.6 billion people are living with hearing loss globally, making it the third leading impairment worldwide [1]. Unfortunately, over 80% of affected individuals reside in low- and middle-income countries (LMICs) with limited access to hearing care [2, 3]. Childhood hearing loss has well-known, lifelong implications for language development, school achievement, and future employment opportunities [4-12]. The World Health Organization estimates that up to 75% of childhood hearing loss in LMICs is preventable due to the high prevalence of infection-related hearing loss in low resource settings [3].

School health programs are well-known to be critical for delivery of preventive healthcare in LMICs and rural underserved settings. School hearing screening is especially critical for identification and management of childhood hearing loss in low resource settings, where newborn screening is often unavailable and the majority of hearing loss is due to ear infections [13, 14]. However, not all types of hearing loss can be identified by the screening methods commonly used in low-resource settings. To be effective, screening must account for the type and prevalence of hearing loss in a given population. Most screening programs only use pure-tone screening and are not equipped to identify middle ear disease common in populations with a high prevalence of infection-related hearing loss [15]. A major reason for this gap is that tympanometer, a device used to clinically identify middle ear disease, is not typically used for screening because it is expensive and designed for use and interpretation by trained professionals.

Our overarching goal is to develop and validate a mobile health (mHealth) based tympanometer with machine learning support for laypersons to transform this technology into a low-cost tool that could be broadly disseminated in LMICs and underserved rural areas, where the burden of hearing loss is greatest. In collaboration with Duke Biomedical Engineering team and hearX, a commercial partner and spin off company from the University of Pretoria, along with funding through the National Institutes of Health (R21), we have developed a prototype mHealth tympanometer that will be integrated with software on an Android smartphone. We have also developed a machine learning (ML) algorithm that will support lay users. Large clinical validation studies are required for commercialization of this device but a form factor evaluation and pilot validation study are first necessary to finalize the design of the device and complete the first testing in human ears. These critical steps will ensure the prototype and ML algorithm are ready for large-scale testing.

In this study, we will focus on the pilot evaluation of the prototype in adult and pediatric participants from University of Arkansas for Medical Sciences (UAMS) and Arkansas Children's (AC) respectively. UAMS and AC will be responsible for the pilot validation data collection; Duke University, where the prototype was developed, will be responsible for refinements based on data obtained from the study; and University of Pretoria/hearX, collaborators on the software development to run to mHealth tympanometer and experts in technology development, will provide guidance as needed for the hardware refinement and the impact on subsequent integration with the software.

Specific Aims

The study consists of two aims:

1. A pilot evaluation of the accuracy and performance of the prototype device compared to commercial tympanometer in pediatric and adult population [approximately 60 ears].
2. Testing of the ML algorithm using prototype data from the pilot validation study. Results from the ML algorithm will be compared with audiologist interpretation.

Investigational Device

The device under investigation is a lay friendly mHealth tympanometer, a medical device for objectively evaluating middle ear function. The tympanic membrane, or eardrum, facilitates hearing by transmitting sound vibrations from the outer ear to the middle ear. A tympanometer can evaluate if the eardrum is functioning normally by applying an acoustic tone and varying air pressure in a measured way. The result is a graphical display quantifying the properties of the eardrum known as a tympanogram (see Fig 1). A typical test takes about 10-15 seconds to complete.

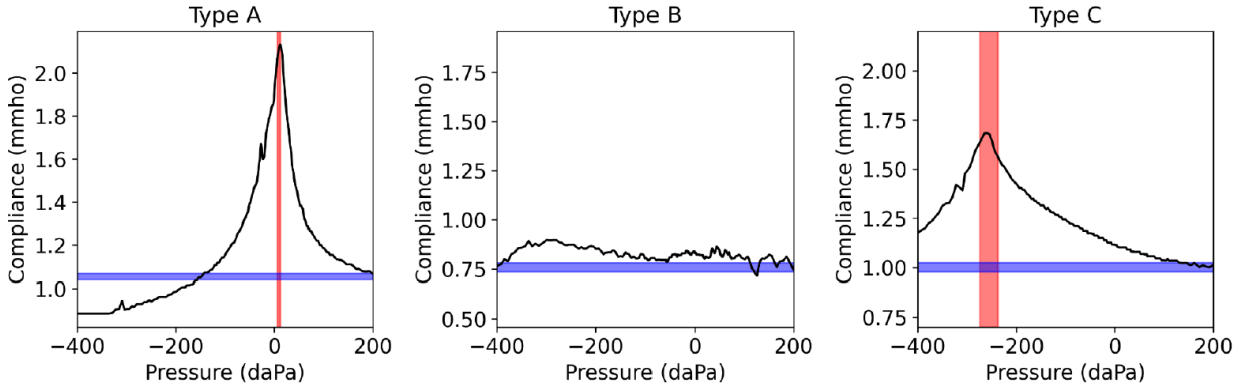

Fig 1. Example graphical display of tympanograms and the 3 common classifications.

Tympanograms can then be classified into types (Type A, B, C) that help to determine if an eardrum has fluid behind it, is retracted, or perhaps has a perforation, all common ear disease states. Type A indicates normal ear function, and types B and C indicate abnormal middle ear function.

Commercial tympanometers contain 4 main parts: a speaker, microphone, pump, and manometer. However, commercial tympanometers are expensive and designed to be used by highly trained hearing healthcare specialists, such as audiologists. The mHealth tympanometer being developed will function the same as a commercial device and contain the same core components. We will use a low-cost pump or replace the pump with a small syringe for applying controlled pressure (similar to the commercial tympanometer) to the ear canal to measure the pressure change of the eardrum (see Fig 2) [16]. The device will also be Bluetooth enabled for the wireless transmission of

tympanogram results to a smartphone device and/or UAMS laptop. This device is being designed to adhere to the international standards established by International Electrotechnical Commission (IEC) 60645-5 (ELECTROACOUSTICS – AUDIOMETRIC EQUIPMENT – Part 5: Instruments for the measurement of aural acoustic impedance/admittance).

Fig 2. Prototype mHealth tympanometer

Like all tympanometer devices, the mHealth tympanometer works by placing a probe into the outer portion of the ear canal where the measurement process will automatically initiate once a hermetic or airtight seal is obtained. The mHealth tympanometer has been designed to work with commercially available probe tips (see Fig 3a and 3b).

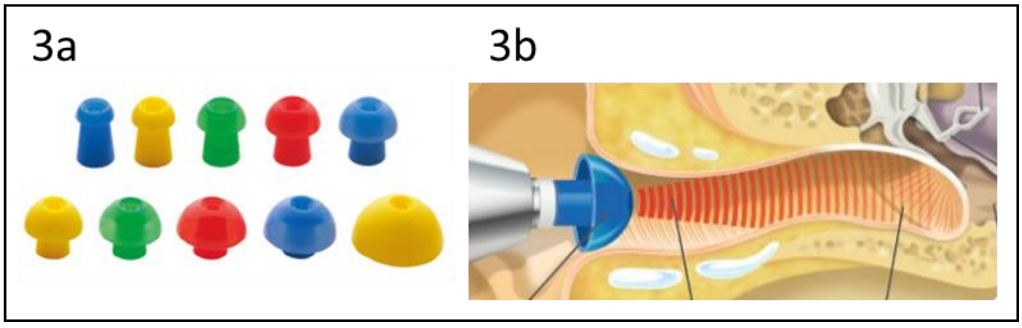

Fig 3. Commercial tympanometry ear tips and visual of placement in outer ear canal.

Once a seal is obtained with the probe gently placed in the outer portion of the ear, the speaker will generate a calibrated tone into the ear canal, as specified by IEC 60645-5. The reflected sound in the ear canal will be measured by the microphone in the device and the values transmitted via Bluetooth to an Android based smartphone and/or UAMS laptop will display the tympanogram result (see Fig 4). The tympanogram will be generated using an application (app) developed by our hearX collaborators. This display is similar to that generated by commercial tympanometers, and it is this graphical display that will be reviewed and interpreted by the audiologist.

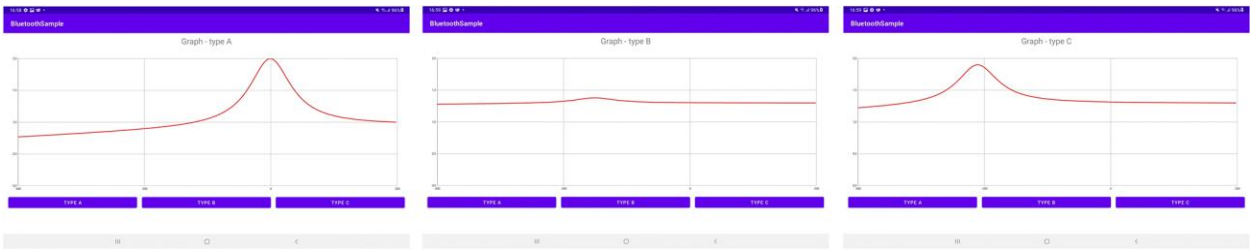

Fig 4. Beta graphical output from the hearX application on the Android smartphone for each of the common tympanogram classifications.

All prototypes will be tracked by a unique label that will allow a comprehensive, retrospective analysis to be performed.

Study Design and Procedures

Pilot Validation: The proposed pilot validation study at UAMS and AC audiology clinics involves a comparative investigation of a commercially available tympanometer with a minimal risk lay-friendly (mHealth) tympanometer prototype. The pilot validation will be conducted in consented adults and children presenting to the Audiology Clinics of UAMS and AC. The study will evaluate device performance compared to a commercial tympanometer in patients with various middle ear pathologies, including occluding cerumen, effusion, perforation, retraction, otosclerosis, cholesteatoma, ossicular chain discontinuity, myringitis, and tympanosclerosis. Data acquired from the pilot validation will also be used with our machine learning algorithm to determine how well it works with prototype data and the if there will be a need for further refinement.

Convenience sampling will be used to recruit patient participants. We will recruit approximately 20 adult patients who present to the UAMS clinic and approximately 10 pediatric patients presenting to audiology at AC. We will enroll participants until we have complete data from 60 ears. Patients with various middle ear pathologies (see above) will be selected to evaluate if the prototype is able to provide the expected tympanogram output, type A, B, and C.

Eligible patients will be invited to participate, and the consent form reviewed. Consented participants will receive their audiological services as scheduled, with the addition of prototype measurements to their appointment. The audiology appointment will include routine ear and hearing measures, such as otoscopy (visual ear exam) and pure tone

testing. The prototype device will be conducted before the commercial tympanometry. Audiologists will be asked to complete the prototype measurement and interpretation prior to the commercial device to limit bias in study results. We anticipate approximately 3 audiologists from UAMS and 2 audiologists from AC being involved in the study. Audiologists will be provided initial training and a demonstration of the prototype device and given instruction on how to troubleshoot and who to contact should an unanticipated problem occur. The tympanometric measurement takes roughly 10-15 seconds per ear to collect. We anticipate the prototype measurement and data entry will take no more than 5 minutes to complete during the audiological appointment.

The resulting tympanograms from the prototype device and the clinical tympanometer will be interpreted by the audiologist and entered in a secure Research Electronic Data Capture (REDCap) database. The audiologist will also answer a few brief questions during/after testing each participant in a REDCap form on device performance for both the prototype and commercial tympanometers.

Specifically, the order of events will be as follows:

1. Audiologist will test each ear of the participant with the prototype device and interpret the tympanogram. These findings will be entered in a secure Research Electronic Data Capture (REDCap) database in real time using a tablet or computer.
2. Next, the audiologist will test each ear of the participant with a commercial tympanometer, interpret the results and enter them in the database as described above.
3. The audiologist will complete 4 questions on each device performance between testing with each device (steps 1 and 2) if time permits, or after completion of testing with both the devices, and document it in a secure REDCap database.

Testing machine learning algorithm: The performance of the machine learning algorithm will be tested by using raw data from the prototype mHealth tympanometer obtained from the pilot validation study. The ML will interpret the raw tympanometric data and classify the results into Type A, B, and C. The classification by the ML algorithm will be compared to audiologists' interpretation, and concordance will be assessed. The audiologists interpreting the data will be blind to the ML algorithm and the ML algorithm will not be provided the audiologist interpretation.

Study Population

The study population consists of patient participants presenting to the UAMS and AC Audiology Clinics for audiological evaluation. The goal is to enroll enough participants to have a total of 60 ears (40 adult ears and 20 pediatric ears) with data from both the prototype and commercial tympanometers. If test results cannot be obtained, which can happen in some ears with tympanometry, then we will enroll additional participants until we reach 40 adult ears with data from both devices and 20 pediatric ears with data from both devices. This may involve inviting up to 20 adults and 20 children to participate in the study.

Inclusion Criteria

- Individuals, 1-year old and older
- Presenting to the UAMS or AC Audiology Clinics for evaluation where tympanometry is warranted for testing at the discretion of the audiologist
- Presence of various middle ear health states/pathologies that result in Type A, B, C tympanograms; examples include normal, occluding cerumen, effusion, perforation, retraction otosclerosis, cholesteatoma, ossicular chain discontinuity, myringitis, and tympanosclerosis
- English-speaking

Exclusion Criteria

- Children or adults with cognitive disabilities
- Unable to provide consent/assent
- Individuals who are unable to sit still
- Any other condition, that, in the opinion of the investigator, might interfere with the safe conduct of the study or place the participant at increased risk

Recruitment

Qualifying patients presenting for audiology evaluation will be approached by study staff, prior to their appointment inquiring about their interest in study participation. The study team will review the clinical schedule in partnership with the clinical team for eligible participants. Eligibility will be determined by review of the reason for visit on audiology schedules, as well as presenting findings on otoscopy suggestive of middle ear pathology and the need for tympanometry. Findings suggestive of middle ear pathology include ear symptoms, such as pain, pressure, fullness, and draining. Tympanometry is also indicated in any patients with present or history of ear surgery and/or mixed/conductive hearing loss. Study personnel will review the informed consent form and enroll those who express interest (adults 18 years of age and older). In the case of eligible children, interested parents/guardians will be similarly approached by study staff, and an informed consent form will be reviewed, and signature obtained from parent/guardian. A written assent form will be reviewed with children aged 7 and older, along with informed consent of parent/guardian. For children aged 6 and younger, informed consent will be obtained from the parent/guardian and no consent will be obtained from the child.

Risks and Benefits

This mHealth tympanometer prototype is designed to function the same as commercially available technology, which are Class II medical devices. Our prototype is being designed to adhere to the relevant IEC standards. Commercial tympanometers are considered minimal risk devices. Our investigational device has implemented best design practices to maintain that minimal risk classification, including safeguards in hardware and software to limit pressure excursions. The prototype devices will be manufactured by a medical device development company with approved Quality

Management Systems and International Organization for Standardization 13485:2016 compliance.

A risk to participants is the potential for loss of confidentiality of study data. Measures to protect the confidentiality of study data will be implemented as described in the *Data Handling and Recordkeeping* section below.

There will be no direct benefits to participants; however, knowledge gained from the study could potentially benefit patients in the future.

Data Safety Monitoring Plan

The Principal Investigator (PI) has overall responsibility for assuring safety, conducting the study, gathering study data, overseeing the data safety plan, and complying with reporting requirements with assistance from the sub-investigators and study staff, under the guidance of the Institutional Review Board (IRB) and the study Sponsor (UAMS Office of Research Regulatory Affairs, ORRA). Safety will be monitored by assessment of adverse events AEs throughout the study. The PI Susan Emmett, MD MPH or designated sub-investigator Samantha Robler, PhD AuD will assess all AEs for seriousness, relatedness (attribution), and expectedness. (See *Safety and Adverse Experiences* section below).

John Dornhoffer, MD will serve as the Medical Monitor and will be a resource to the clinical investigators and the Sponsor for advice about management of all AEs (serious and non-serious). He will not be involved in other aspects of the study. The Medical Monitor will independently review all Grade 3 or higher AEs as well as all serious adverse events (SAEs) related to the investigational device submitted by the study team in real time to ensure good clinical practice and to identify safety concerns quickly. Grade 3 AEs are severe or medically significant (but not immediately life-threatening), resulting in hospitalization, or prolongation of hospitalization. The Medical Monitor's review will include AEs and SAEs with the PI's assessments of attribution and severity as well as any quality assurance issues that have emerged. These reviews will examine whether risks of participation remain acceptable under the present protocol, modifications are needed, or the study needs to be halted.

The Medical Monitor may choose to halt the study temporarily if serious concerns arise regarding participant safety. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule. If only suspended the study may resume once all concerns have been addressed, and satisfy the Sponsor, IRB, and/or the United States Food and Drug Administration (FDA).

Data Handling and Recordkeeping

No identifying information will be collected about the participant other than their signed consent. The consent form, which will be collected electronically, will be stored separately in a secure REDCap database. Participants will be assigned a unique study code that will be used to identify all study data. Participant information such as age,

gender, race, date of test, type of ear pathology present, if any, and prototype details, such as device ID number and ID numbers of major components of the prototype, will be recorded in secure REDCap database. The tympanometric data from the prototype device will be read by an Android app and/or UAMS laptop for the audiologist to interpret the result in real time. The Android devices and/or UAMS laptop will adhere to UAMS/AC mobile device requirements for research.

Data collected will be stored in internal storage as well as on a secure digital (SD) card and will be copied daily to a secure REDCap database and/or UAMS Box account. Data from the prototype and the Android app and/or UAMS laptop will contain no identifying information. Only the appropriate study staff will have access to study data. These de-identified data will be stored separately from the Informed Consent Forms, which will be the only source linking unique study identifiers with participants' identities. Data will be stored on a UAMS password-protected server accessible only by the PI and study staff.

The PI will carefully monitor study procedures to ensure the quality of the data and the integrity of the study.

Participant study data collected using the devices will be destroyed after completion of the study. Audit documentation, consents, and other related records will be kept for 7 years. Records will be kept for 7 years after final reporting or publication and then destroyed by shredding or deletion from computers per all applicable UAMS institutional policies and federal regulations. Deidentified data will be stored electronically indefinitely.

Safety and Adverse Experiences

Following consent, safety will be measured by assessment of AEs (serious and non-serious) through the duration of the study. All corroborative information related to the AEs will be documented in the electronic medical record of the participant and filed with the source documents in secure REDCap database.

Definitions

Adverse Event (AE)

An AE is any untoward, unintended, unfavorable, or undesirable medical occurrence, symptom, sign (including an abnormal laboratory finding), illness/disease, or experience that develops or worsens in severity during the course of the study, regardless of relatedness to the investigational device. This includes any new medical problem, or exacerbation of an existing problem, experienced by a participant while enrolled in the study, whether or not it is considered device related. Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

Serious Adverse Event (SAE)

SAEs are a subset of AEs. AEs are classified as serious or non-serious. An event is "serious" if it involves considerable detriment or harm to one or more persons (who may or may not be participants) or required intervention to prevent one or more persons from experiencing considerable detriment or harm. An SAE is any untoward medical occurrence that results in any of the following:

- Death - (i.e., the AE actually causes or leads to death),
- Life-threatening experience - (i.e., the AE, in the investigator's opinion, places a participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death),
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the participant's ability to conduct normal life functions),
- Congenital anomaly/birth defect in participant's offspring,
- Any other important medical event that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.

The term AE encompasses all adverse events. AEs are either serious (SAE) or non-serious (non-SAE). To avoid confusion, as the terms "serious" and "severe" are not synonymous, the following clarification is given: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself; however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on participant/event outcome or action usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations [ICH-E2A(II)(B)].

Unanticipated Adverse Device Effects (UADEs)

A UADE is any serious adverse effect on health or safety, or any life-threatening problem, or death caused by, or associated with, a device; if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or application (including supplementary application); or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants [21 CFR 812.3(s)]. Adverse device effects (ADEs) include any event that is a result of a use error or intentional misuse as well as any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational device.

Relatedness

An AE is related if more likely than not it was caused by the research activity or if there is evidence to suggest a causal relationship to the study. Attribution categories are as follows:

- Definite - The AE is clearly related to study treatment. The AE onset occurs in a

plausible time relationship to study treatment and other contributing factors (e.g. concurrent disease or concomitant medications/treatments) can be ruled out.

- Probable - The AE is likely related to study treatment. The AE onset occurs in a plausible time relationship to study treatment and the influence of other contributing factors (e.g., concurrent disease or concomitant medications/treatments) is unlikely.
- Possible - The AE may be related to study treatment. The AE onset occurs in a plausible time relationship to study treatment; though, other factors (e.g., concurrent disease or concomitant medications/treatments) may have contributed to it.
- Unlikely - The AE is doubtfully related to study treatment. The AE onset does not occur in a plausible time relationship to study treatment, and other contributing factors (e.g., concurrent disease or concomitant medications/treatments) are likely.
- Unrelated - The AE is clearly NOT related to study treatment. There is not a causal relationship between the AE and the study treatment.

Expectedness

Unexpected AEs are those not listed in the device manual, protocol, or not identified. This includes AEs for which the specificity, nature, intensity, severity, incidence, or frequency is not consistent with the description in the device manual or protocol.

Study Period

Following consent, baseline/pre-existing conditions will be recorded and assessed until initiation of use of the study intervention. All AEs will then be recorded and assessed from the time of the initiation of study intervention through the end of the study visit in AE Case Report Forms. All AEs will be documented in the participant record (captured in source documents, including but not limited to the electronic medical record).

Monitoring, Recording, and Reporting of AEs

All participants will be monitored for AEs (serious and non-serious) during their participation in the study. AE data collection and reporting, which are required as part of every study, are done to ensure the safety of participants enrolled in the studies and those who will enroll in future protocols.

All AEs occurring during the study period whether volunteered by the participant; discovered by study personnel during questioning; or detected through physical examination, observation of clinical symptoms, laboratory, pathological, radiological, or surgical findings, or other appropriate means must be recorded and reported appropriately. AEs are to be reported in a routine fashion and at scheduled times during the study. Certain AEs must be reported in an expedited fashion to allow for timely monitoring of participant safety and care.

Pre-existing Conditions

A pre-existing medical condition is any condition, laboratory abnormality, or physical finding with an onset date at the start of the study (prior to the initiation of the use of any

study intervention).

Pre-existing medical conditions should be reported as part of the participant's medical and surgical history. All relevant historical medical conditions (as determined and documented by Investigator/ Clinician) that are known/diagnosed prior to the start of study procedures are to be recorded in the medical record. For the purposes of this study, pre-existing conditions may include presence of ear symptoms such as ear pain, draining, pressure, fullness, tinnitus, otorrhea, and/or presence of middle ear disease such as perforation, otosclerosis, cerumen impaction, retraction, effusion, ossicular chain discontinuity, cholesteatoma, myringitis, or tympanosclerosis. Any medical condition that is present at the time that the participant is consented will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates or exacerbates at any time during the study period, it will be recorded as an AE. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches"). All AEs, which completely resolve and then recur, should be recorded as a new AE, regardless of relatedness. In addition to new AEs, any increase in the severity or frequency of a pre-existing condition that occurs during the study period is considered an AE.

Diagnosis versus Signs and Symptoms

If known at the time of reporting that a sign or symptom is one component of a diagnosis or syndrome, the diagnosis or syndrome should be reported as the AE (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Hospitalizations for Medical or Surgical Procedures

If a participant is hospitalized to undergo a medical or surgical procedure as a result of an AE, document the event responsible for the procedure, not the procedure itself, as the SAE. For example, if a participant is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations or prolonged hospitalization required to allow efficacy measurement for the study, for scheduled therapy of the target disease, or for diagnostic or elective surgical procedures for pre-existing conditions do not require reporting.

Follow-Up of AEs

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that study participation is not the cause. If an AE does not return to baseline, the resolution date is recorded as "ongoing". Any AEs/SAEs that are still ongoing at the end of the study period must be followed for up to 30 days to determine the final outcome. Any SAE occurring more than 30 days after the study period and is considered possibly/probably/definitely attributable to the investigational

device must be recorded and reported immediately to the Sponsor.

After testing with the prototype mHealth tympanometer and at the end of the scheduled audiology visit, participants will be evaluated for any potential AEs related to the device or study. This will be documented in the participant record. Any AEs discovered during this contact will be assessed, documented and reported according to the investigational plan as outlined in this section.

Assessment of AEs

Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the investigational device (see following guidance), and actions taken. To ensure consistency of AE causality assessments, investigators should apply the following general guideline.
The reporting of these events depends on the characteristics of the event:

1. Seriousness (grading of event)
2. Relatedness to use of the investigational device or study procedure
3. Expectedness

Steps to Determine if the Event Requires Expedited Reporting:

1. Identify/describe the type of event.
2. Grade the severity of the event as follows: Mild, Moderate, Severe.
3. Determine whether the AE is related to the investigational device. Attribution categories are as follows: Definite, Probable, Possible, Unlikely, and Unrelated.
4. Determine expectedness of event. Expected events are those previously identified resulting from use of the investigational device. An AE is considered unexpected when the type or severity of the event is not listed in the protocol or device manual.

Expedited Reporting of AEs

The PI is responsible for ensuring that all AEs/SAEs observed or reported during the study are collected and reported to the Sponsor and the UAMS IRB in accordance with 21 CFR 812.

The PI/study staff should immediately report to the Sponsor any SAE, regardless of relatedness to the study, including those listed in the protocol or device manual, along with an assessment of whether there is a reasonable possibility that the device caused the event. Investigators should immediately notify the Sponsor of any adverse device effect within 24 hours of first learning of the event. UADEs should be reported using the MedWatch Form FDA 3500A. Although an event may be considered ‘serious’ based on previous criteria and should be reported to ORRA immediately, not all SAEs or ADEs meet IRB expedited reporting criteria.

IRB Reporting

Any serious or immediately life-threatening AE, including those resulting in death, occurring while the participant is actively participating in the study will be reported to the UAMS IRB. Only AEs meeting the Unanticipated Problem Involving Risks to Participants or Others (UPIRTSO) criteria will need to be reported to the UAMS IRB within the required 10-day allotment of being notified of the event. UPIRTSO requires

that an unanticipated problem meet the following qualifications: a) unanticipated or unexpected; b) related to the research; and c) involves new or increased risk to the participant(s) (including physical, psychological, economic, or social harm). Examples of other UPIRTSOs include theft of a computer containing participant information or incarceration of a participant (if not approved for research on prisoners). UPIRTSO may or may not result in actual harm.

All other AEs should be recorded and reported to the UAMS IRB at Continuing Review and on the Annual Progress Report (APR).

The Investigators must report any UADE to the IRB within 10 working days after learning of it.

Sponsor Reporting

The Sponsor will be promptly notified of all potential SAEs/UADEs by the investigator/study staff using the MedWatch Form FDA 3500A. The Sponsor will evaluate all potential SAEs/UADEs and report these evaluations in accordance with 21 CFR 812.

The results of any UADE evaluation by the Sponsor, regardless of the findings, must be reported to the FDA and the IRB 10 working days after the Sponsor learns of the potential UADE.

All other SAEs not expeditiously reported will be reported to the Sponsor for the APR and submitted to the IRB at the time of Continuing Review.

All deaths that occur during the study period will be reported to the Sponsor as soon as possible, preferably within 24 hours, but no later than 48 hours, of learning of the participant's death, regardless of relatedness to the device or the study. A death due to a terminal condition of the research participant would be considered anticipated and not related to the research.

The Sponsor will report deaths in accordance with 21 CFR 812.

Clinical Site Monitoring

Clinical site monitoring will be conducted by the UAMS ORRA to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable from source documents, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), International Council of Harmonisation good clinical practices, and applicable regulatory requirements.

Monitoring specialists from the UAMS ORRA will conduct periodic, comprehensive monitoring (either on-site or remote) as determined by a protocol specific monitoring plan, which will be provided to the Investigator by ORRA Monitoring Unit.

Deviations and Violations

Protocol Deviation

Any unintentional change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations will be tracked and compiled in a Protocol Deviation Log. Deviations that potentially cause concern for the participant's health, safety, or rights will be reported to the Sponsor as soon as possible for guidance on reporting.

Protocol Violation

A change to, or non-compliance with, the IRB-approved procedures without prior Sponsor and IRB approval (excluding changes made to eliminate apparent immediate hazard to participants). A violation may affect health, safety, or rights of a participant. Any violation will be reported immediately to the Sponsor for guidance on reporting.

If the protocol deviation/protocol violation does not represent a significant alteration in the approved protocol and/or affect the safety or welfare of the participant, it will be reported to the UAMS IRB at the time of Continuing Review. If the protocol deviation/violation represents a significant alteration in the approved protocol and/or if it affects the safety or welfare of the participant, it must be reported to the Sponsor and UAMS IRB immediately.

Study Stopping/Pausing

This study is low risk, and no adverse experiences are anticipated. The device is being designed with adherence to all the safety considerations established in IEC 60645-5. Each device will be labeled with a unique identifier that will correlate with specific hardware and firmware versions to allow performance and any adverse events to be recorded and a full root cause analysis (RCA) to be performed. If there are concerns during measurement such as discomfort reported by the patient, or device malfunction reported by the clinician, testing will be stopped immediately. The issue will be documented, reported to the PI, and the device will no longer be used until a full RCA has been performed. If this issue can be resolved immediately, then testing will be restarted with the participant. If the issue cannot be resolved immediately (i.e., within the duration of the clinical appointment), then the data will be considered incomplete and additional participants will be recruited in order to meet recruitment goal of 40 adult ears with complete data and 20 child ears with complete data. The participant will still receive the $20 gift card. While both ears will be tested, if data can only be obtained in one ear, the participant will still be considered to have completed the study as long as results from both the devices can be obtained for that ear. Any safety concerns will be reported to the PI, ORRA, and the UAMS IRB. Any event related to changes in consent form, protocol, or inadvertent disclosure of confidential information will be reported to the IRB.

Data Analysis

Pilot Validation Analysis

Analyses for the pilot validation will include: 1) comparison of categorical classifications of tympanogram types for the commercial vs prototype devices; 2) evaluating potential intra-participant correlation between ears; 3) assessing differences in numerical measures between the commercial and prototype tympanometer; and 4) evaluating performance of mHealth tympanometer and commercial tympanometer.

1) For each device, commercial and prototype, tympanograms with be categorized into one of 3 categories: A, B and C. To assess the agreement between the two devices with respect to categories, Bowker's test of symmetry and the Kappa coefficient conventional methods to assess agreement, will be used. For the initial analysis, both tympanograms will be performed for each ear and no adjustments will be made for participants (i.e., most will have both ears included).
2) To assess the potential effect of participant and ear status (normal, diseased) for participants where both ears are included, each participant's ears will be characterized as (both normal, both diseased, one diseased and one normal). Within those categories, the number of ears for which there is concordance between the two tympanograms for each participant will be 0, 1 or 2. Pearson's chi-square test will be used to compare the three groups defined by ear status with respect to the distributions of the number of ears with concordance.
3) The Wilcoxon signed rank test will be used to determine if the differences in the numerical measures (ear canal volume, static admittance and tympanometric peak pressure) obtained from the commercial and prototype devices are significantly different from zero. No adjustment for multiple testing is planned.
4) Audiologist assessment of the mHealth and commercial tympanometers will be captured through questionnaires which assess 4 performance measures using a 5-point Likert scale. For each performance measure, the Kappa coefficient and Bowker's test of symmetry will be used to assess agreement between the two mHealth and commercial tympanometers with respect to responses.

A minimum of 30 participants will be enrolled. Both ears will be used for each patient enrolled, with enrollment remaining open until 60 ears (40 adult and 20 pediatric ears) are accrued to ensure that there are sufficient number of ears for analysis. It is possible that more than 30 participants will be required to accrue 60 ears if we are unable to obtain a tracing on one or both ears in certain patients (such as due to a draining ear, which inhibits formation of a seal). We anticipate consenting no more than 40 individuals to reach the enrollment goal of 30 participants. With a sample size of 30 participants (60 ears), a null hypothesis where kappa is 0 (no correlation between devices) can be tested against the alternative hypothesis of kappa of 0.3 using a two-sided 0.05 significance level with a power of 0.89.

Machine Learning Algorithm Analysis

The categorizations of the tympanogram (Type A, B, C) classified by the algorithm will be compared with the audiologists' interpretations. To assess agreement between the audiologist and the algorithm, Kappa analysis and Bowker's test of symmetry will be performed.

Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and UAMS research policies and procedures. This protocol and any amendments will be submitted and approved by the IRB as required.

For recruitment and eligibility determination, a partial HIPAA waiver will be obtained. PHI access under the partial HIPAA waiver will entail using the clinic schedule to screen for potential participants by their age and reason for visit. Reason for visit will be used to determine middle ear status and whether tympanometry is likely to be performed as part of the clinical visit.

For eligible participants and parents/guardian of eligible children, informed consent using IRB-approved consent materials, will be obtained before the participant begins any study procedures and will be performed electronically using a secure REDCap database. All participants for this study will be provided an electronic informed consent form (e-consent) describing this study in language understandable to the study population.

Consent materials will provide sufficient information for participants/parent/guardian to make an informed decision about participation in this study. The person obtaining consent will thoroughly explain what the participants/parent/guardian need to know about the study, including study requirements, and study risks and benefits.

The consent process will take place while the prospective participant is attending their audiology evaluation in the audiology clinic. The consent discussion will occur prior to routine tympanometry. Participation privacy will be maintained, and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process.

This consent form must be signed by the participant or parent/guardian and the person obtaining the consent. An e-consent form will be presented to the participants/parent/guardian for review, which may be electronically signed. The participant/parent/guardian will receive an electronic copy of the signed consent form execution, and if requested, a hard copy will be provided. The informed consent process will be documented in the electronic medical record. We will obtain informed consent for adults 18 years and older. In case of eligible children, informed consent will be obtained from parent/guardian and an assent will be sought from children 7 years and above in accordance with **UAMS IRB Policy 17.1 Special Populations: Children in Research** and parental consent will be obtained.

Compensation

Adult participants and families of child participants will receive a $20 electronic gift (e-gift) card after completing the study. Participants will complete a gift card form in REDCap that will be separate from study data. The e-gift card will be provided through UAMS approved e-gift card system and sent to the participant's (or caregiver's) email address. If the participant prefers not disclosing their email address in REDCap, a research email account will be used to process the e-gift card and a printout of the e-gift card will be provided to the participant.

Data Storage and Sharing

Data from the study will be stored in electronic medical records, paper forms, a secure REDCap database and/or UAMS Box. Any deidentified data from the study necessary for refinement of the device will be shared with our biomedical engineer collaborators at Duke University. This pilot validation study will support a larger NIH-funded R33 grant application, with University of Pretoria, our commercial collaborator hearX, and Duke University as partners. Data from the validation study will be shared with our partners as needed to prepare the R33 grant application, which involves a larger clinical validation study. Duke University, University of Pretoria, and hearX will have access to deidentified data that will be shared via a secure REDCap database. Deidentified raw data and aggregate findings of the study will be shared with these collaborators for the continued co-development of the mHealth tympanometer.

Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant. The study will be listed on ClinicalTrials.gov, and information will be updated in a timely manner in accordance with FDA and institutional requirements.

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