STATISTICAL ANALYSIS PLAN: ACHIEVE HIFU

PROTOCOL: Randomized Trial of Telehealth versus Conventional Hearing Care Delivery in the ACHIEVE Study

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LIST OF ABBREVIATIONS

ACHIEVE	Aging and Cognitive Health Evaluation in Elders Randomized Trial
ARIC	Atherosclerosis Risk in Communities
COSI	Client-Oriented Scale of Improvement
CSCC	Collaborative Studies Coordinating Center
dB	decibels
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
NIDCD	National Institute on Deafness and Other Communication Disorders
HHC	Hearing health care
HHIE-S	Hearing Handicap Inventory for the Elderly Screening Version
HIFU	Hearing Intervention Follow-Up Study
IOI-CHI	International Outcome Inventory – Comprehensive Hearing Intervention
ITT	Intention-to-treat
SAP	Statistical analysis plan

1. Introduction

The Aging & Cognitive Health Evaluation in Elders (ACHIEVE) Hearing Intervention Follow-Up (HIFU) study is a randomized controlled trial nested within the ACHIEVE trial. Approximately 340 of the 490 participants in the hearing intervention group from the parent ACHIEVE study will be randomized to one of two conditions—telehealth Hearing Health Care (HHC) or conventional HHC. ACHIEVE-HIFU participants will be community-dwelling adults that were assigned to the hearing intervention arm of ACHIEVE, completed their final ACHIEVE Year 3 visit, and are willing and able to participate in two additional years of follow-up.

2. Background

Age-related hearing loss in older adults is a chronic health condition, according to the World Health Organization [1] [2] [3]. Current rates of hearing aid use among older adults with hearing loss in the U.S. are <20%, and rates of discontinuation of hearing aid use among older adults are estimated to be >30% [4] [5] [6] [7]. The clinic-based HHC model may be a contributor to low hearing aid utilization rates [8] [9] [10] [11]. Telehealth delivery of HHC is a form of remote service delivery that allows patients to access health care services from home via smartphones, tablets, and computers. Telehealth can be used to deliver services to adults with hearing loss including ongoing self-management support [12].

3. Objectives

The primary aim of ACHIEVE-HIFU is to compare the effect of telehealth HHC vs conventional HHC on hours of hearing aid use at one-year post-randomization. A secondary aim is to examine the effects of telehealth HHC vs conventional HHC on patient-centered hearing and communication outcomes. Exploratory analyses include (1) subgroup analyses of the primary and secondary outcomes, (2) differences in the utilization of hearing services, (3) quantifying the dose-response relationship between utilization of hearing services and hours of hearing aid use, and (4) assessing trends over time from randomization to the two-year follow-up.

4. Study Design

ACHIEVE-HIFU is a randomized trial with two treatment arms: telehealth HHC and conventional HHC. Both treatment arms will receive the same clinic-based hearing intervention provided in the parent ACHIEVE study. However, participants assigned to the telehealth HHC treatment arm will be granted immediate access to HHC services via telehealth. Participants assigned to the conventional HHC treatment arm will be given access to the same telehealth services one year after randomization.

To be eligible for ACHIEV-HIFU, participants must (1) have been eligible for and participated in the hearing intervention arm of ACHIEVE, (2) complied with ACHIEVE protocols, (3) be willing to be randomized to the telehealth HHC or conventional HHC treatment arm, and (4) be willing and able to complete two years of follow-up. The inclusion criteria for ACHIEVE were (1) 70 to 84 years old, (2) adult-onset bilateral hearing loss with a better-ear 4-frequency (0.5 to 4 kHz) pure tone average ≥30 and <70 dB, (3) free of substantial cognitive impairment (Mini-Mental State Exam ≥23 for high school degree or less; ≥25 for some college or more), (4) word recognition score in quiet ≥60% correct in the better-hearing ear, community-dwelling, and (5) being a fluent English speaker. The exclusion criteria for ACHIEVE were (1) self-reported disability in ≥2 activities of daily living, (2) vision impairment worse than 20/63 on the MNREAD acuity chart (Precision Vision, Woodstock, IL) while using glasses or other reading aids typically used at home (corresponding to inability to comfortably read 14-point font), (3) self-reported hearing aid use in the past year, (4) permanent conductive hearing loss, (5) medical contraindication to hearing aid use, or (6) unwillingness to wear hearing aids on a regular basis.

Randomization for ACHIEVE-HIFU occurred up to 9 months after the participant's ACHIEVE Year 3 visit except at the University of Minnesota where delayed Institutional Review Board approval caused some participants to be randomized after more than 9 months. Spouse pairs were randomized to the same treatment arm. Participants will be followed for two years, with ACHIEVE Year 3 visit serving as the baseline.

5. Power

ACHIEVE-HIFU is predicated on a finite sample of participants recruited from the treatment arm of the parent ACHIEVE study. An estimated 340 participants will be randomized to telehealth HHC or conventional HHC. Assuming conservatively that 5% of participants are lost to follow-up or death each year, we would have a sample of N=322 participants one-year post-randomization. With 80% power and a 5% Type 1 error rate, this sample would have the ability to detect an average treatment effect of 1.5 hours of hearing aid use between the telehealth HHC and conventional HHC arms.

6. Analysis Populations

Analyses will follow the intention-to-treat (ITT) principle in which participants will be analyzed in the condition to which they were randomized, regardless of whether they received the assigned intervention. Primary analyses will be based on the ITT population, which includes all randomized participants.

7. Statistical Analysis

7.1 General Considerations

Study data will be monitored on an ongoing basis by the Data Coordinating Center (DCC). The DCC will send data clarification requests to the clinical sites for resolution while the study is ongoing. Final cleaning and editing of the study database will be carried out after the final participant completes their one-year follow-up assessment. The process will be repeated after the final participant completes their two-year follow-up assessment. Unblinding of treatment assignments will not be performed until the study data are cleaned, queries resolved, and database lock achieved. A permanent archive of the database will be maintained by the DCC. Randomization will be implemented within the Carolina Data Acquisition and Reporting Tool used by the DCC. Although the ACHIEVE hearing interventions are by nature unmasked, in order to minimize bias based on review of accumulating data by the project team, the ACHIEVE PIs, co-investigators, and key project staff (except one unblinded statistician) will remain blinded to accumulating data. In all cases, hours of hearing aid use (primary outcome), a completely objective data point, will be gathered directly from hearing aid data logging software, and source data will be verified as part of the quality assurance procedures. All other non-audiological secondary outcomes will be collected by trained technicians, rather than the site audiologist.

This statistical analysis plan (SAP) was developed prior to review of the study dataset and under the assumption that all data were collected in adherence to the protocol and in accordance with good clinical research practices. As the data are analyzed, some deviation is anticipated (e.g., missing data, small sample sizes, etc.). In instances where these deviations would make the proposed analyses inappropriate, modifications to the analysis plan will be made and noted in the final report.

All programs used in the statistical analysis of study data will be documented, tested, and archived. This includes the original written specifications for the analyses, any subsequent modifications, the computer program file, and the log, list and other output files produced by the program. All programming will be done by the DCC using SAS® version 9 or later.

7.2 Primary Outcome

The primary outcome is average daily hours of hearing aid use at one year, as measured through objective hearing aid data logging. If a participant wears a hearing aid in both ears, then the ear with the greatest number of hours logged will be selected.

7.3 Primary Analysis

We will use a weighted regression model with an identity link to compare average daily hours of hearing aid use at one-year post-randomization between participants assigned to the telehealth HHC or conventional HHC. To account for the non-normal distribution of the outcome, confidence intervals and p-values will be obtained using a bias corrected and accelerated bootstrap resampling procedure with 10,000 replicates. Consistent with best practices in clinical trials, we will assess the comparability of the randomized groups with respect to potential confounders [13], such as recruitment source, site, level of hearing impairment, Quick Speech in Noise score, self-reported acceptance of telehealth at baseline, self-reported and objectively measured baseline hours of hearing aid use, self-reported baseline hours of hearing assistive technologies use, the number of days hearing log data was measured prior to randomization, and the number of visits prior to randomization at which a participant provided hearing logging data. If there is an imbalance between randomized treatment assignment we may adjust for relevant confounders as well as explore the use of a prespecified inverse probability of treatment weight [14] or a precise, locally efficient, augmented, simple estimator [15]. A logistic regression model will be used to model the probability of attrition according to the confounders described above plus age, sex, and applicable interactions. Inverse probability of attrition weights will be calculated and either included in the model for the primary outcome directly or cross-multiplied with inverse probability of treatment weights.

7.4 Sensitivity Analyses of the Primary Outcome

Additional analyses of the primary outcome may include, but are not limited to:

1. A replication of the primary analysis with stratification by recruitment source (ARIC vs de novo). An interaction between treatment assignment and recruitment source will be tested relative to $p < 0.10$.
2. An analysis of subjective, self-reported hours of hearing aid use including differences between the use of hearing aids and hearing assistive technologies.
3. An analysis restricted to participants who wore the same type of hearing aid.
4. Exploration of the impact on the primary analysis by further adjustment for additional explanatory variables.

7.5 Secondary Outcomes

Secondary outcomes that will be examined include:

1. Treatment satisfaction, as assessed by a single item from the International Outcome Inventory – Comprehensive Hearing Intervention (IOI-CHI). The IOI-CHI is an interviewer-administered scale that consists of 6 items where participants self-report satisfaction with the hearing intervention using a 5-point Likert scale. A higher score indicates a more favorable outcome.
2. Ability to hear for the primary communication goal as assessed by a single item from the Client-Oriented Scale of Improvement (COSI) goals achievement questionnaire. COSI goals are rated using a 5-point Likert scale. A higher score indicates the participant is able to hear more of the time.
3. Hearing-specific quality of life, as assessed by the Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S) questionnaire. The HHIE-S is an interviewer administered questionnaire that consists of 10 items. Participants rate whether hearing loss affects them in

different situations (yes, sometimes, or no). The total score is the sum of all responses and ranges from 0 to 40, with higher scores indicating greater hearing issues.

For continuous secondary outcomes, groups will be compared for differences at the one-year follow-up using the same analytic approach specified for the primary outcome. For binary secondary outcomes, either logistic regression or Poisson regression with robust error variance will be employed depending on whether the outcome is rare or common. For categorical outcomes, either ordinal or multinomial logistic regression models will be utilized depending on the nature of the measure and empirical tests of the proportional odds assumption.

7.6 Exploratory Analyses

Exploratory analyses may include, but are not limited to:

1. The 5 remaining items from the IOI-CHI as well as a composite score created by computing the mean across all 6 items.
2. The 2 remaining items from the COSI as well as a composite score created by computing the mean across all 3 items.
3. Telehealth acceptance as assessed by an interviewer-administered scale that consists of 5 items in which participants rate the ease of use or utility of telehealth equipment using a 5-point Likert scale. A higher score indicates a more favorable rating. Each item will be examined separately before being analyzed collectively as part of a composite score created by computing the mean across all 5 items.
4. Subgroup analyses of the primary and secondary outcomes including but not limited to sex, race, and education. Interactions between treatment assignment and subgroups will be tested relative to $p < 0.10$.
5. The effect of treatment assignment on the total number of contacts between the provider and participant. The total number of provider-participant contacts is quantified by the study audiologists using forms completed at every encounter. In a supplemental analysis, the number of contacts will be examined across specific modalities including face-to-face contact in a clinic, face-to-face contact outside of a clinic (e.g. home visits), and remote contact (e.g. video calls, phone calls, etc.)
6. The effect of treatment assignment on the total time spent between provider and participant. The total number of minutes during which the provider and participant interacted is quantified by the study audiologists using forms completed at every encounter. In a supplemental analysis, the number of minutes will be examined across specific modalities including face-to-face contact in a clinic, face-to-face contact outside of a clinic, and remote contact.
7. Estimating the linear and potentially nonlinear dose-response relationship between utilization of hearing services and hours of hearing aid use at one-year post-randomization. This will include testing the total number of contacts between the provider and participant, the total amount of time the provider and the participant spend interacting, and differences by modalities such as face-to-face contact in a clinic, face-to-face contact outside of a clinic, and remote contact.
8. Using mixed effects models to examine trends over time from randomization to the two-year follow-up assessment. Time will be defined categorically or continuously with a time spline specified at 12 months. An interaction between treatment assignment and time will be included in the model to estimate the effect of participants in the conventional HHC treatment arm gaining access to telehealth services one-year post-randomization.

7.7 Adjustment for Multiple Comparisons

Statistical significance for the primary outcome will be defined as $p < 0.05$. Secondary outcomes will be evaluated for statistical significance with a Hochberg modification to the Bonferroni adjustment, in which the p-values of the five outcomes will be ordered. The largest p-value will be compared relative to $p < 0.05$,

and if met, all parameters will be considered significant. If not, then the second largest p-value will be assessed relative to $p < 0.05/2 = 0.025$, and if met then it and all other parameters will be considered significant, and so on for the third p-value at 0.05/3=0.017.

8. Software and Statistical Programming

Tabulations and statistical analyses will be performed using SAS® Version 9 (or later). All programming will be done by the ACHIEVE DCC which is housed in the Collaborative Studies Coordinating Center (CSCC) at the University of North Carolina at Chapel Hill. Standard CSCC statistical computing procedures will be followed. That is, research staff will submit a written statistical computing request to the statistical programming staff. A computing request number will be assigned to the request and information about the request entered into a database. A statistical programmer will then be assigned to undertake the request. Statisticians will review the programs and output. If necessary, changes will be requested in writing. After the programming has been completed to the satisfaction of the staff, all materials will be archived under the request number. Archived materials will include the original computing request, any subsequent changes, the SAS® code as well as any output, including log and list files and datasets created in the request.

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