Protocol

MUSIC & MEMORY: A PRAGMATIC TRIAL FOR NURSING HOME RESIDENTS WITH ALZHEIMER'S DISEASE (METRICAL)

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PRÉCIS

Study Title

METRIcAL: Music & MEmory: A Pragmatic TRIal for Nursing Home Residents with ALzheimer's Disease

Objectives

To conduct a repeat parallel, pragmatic cluster randomized control trial (RCT) of personalized music for nursing home (NH) residents with moderate to severe dementia cared for in 81 NHs within four NH health care systems: PruittHealth, Good Samaritan Society, Vetter Senior Living, and CommuniCare (Terrapins Division).

Design and Outcomes

Aim 1 of this study is to use a train-the-trainer model to implement M&M in 27 facilities with ongoing monitoring of the program's adoption and acceptance by long-stay NH residents with Alzheimer's disease-related dementias (ADRD). Using the implementation guide developed during the R21, corporate leadership will provide step-by-step training and support to facilities in the intervention arm to include: setting achievable milestones, reviewing progress, and assisting with mid-course corrections. Implementation will be closely monitored by Brown through monthly conference calls with the corporations and the leadership at the participating NHs.

Aim 2 of this study is to estimate the impact of M&M on agitated and aggressive behaviors in NH residents with moderate to severe dementia. Agitated and/or aggressive behaviors are measured three ways: by interviewing staff about resident behaviors over time (primary outcome); through direct observation of residents when using and not using M&M (secondary outcome); and using available administrative data (secondary outcome). Other secondary outcomes include: other emotional states directly observed while the resident is using and not using M&M (anger, pleasure, alertness, sadness), antipsychotic use, antidepressant use, anxiolytic use, and depression. In this cluster RCT, the unit of random assignment is the facility, but the unit of analysis is the patient, clustered within the facility. The analytic approach we propose is based upon the cumulative likelihood of reductions in agitated and aggressive behaviors in a long-stay population with moderate to severe dementia, conditional upon survival to at least one post-intervention observation. Outcomes will be evaluated using a repeat parallel design, comparing wave 1 (intervention) and wave 2 (control) NHs (n=54) in the first study year, and wave 2 (intervention) and wave 3 (control) NHs (n=54) in the second study year. The repeat design allows for modification of the intervention delivery between waves to increase adherence. Since we do not expect the intervention to affect mortality, the comparison will be based on the last observed total agitation score among residents meeting eligibility criteria in the treated and control groups. All deaths among exposed and control populations will be routinely controlled and reported to the data safety and monitoring board for monitoring purposes. Facilities will be stratified by corporation, and balanced on baseline agitated and aggressive behaviors and number of eligible residents, prior randomization. Because we are interested in the effect of the intervention among those who use it, we will also conduct an as-treated analysis, using a technique described by multilevel-mixture analysis for analyzing cluster randomized data with non-compliance.

Aim 3 of this study is to examine factors associated with variation in providers' adherence to the implementation of M&M. We will adopt six distinct approaches to documenting implementation adherence: 1) research staff will survey NHs at baseline to assess the quality improvement infrastructure and performance improvement practices; 2) using a user-defined assessment, NH staff will document aspects of the process by which potentially-eligible residents are assessed for their ability to listen to the music, their music preferences, and the results of their initial trial of the music; 3) NH staff (with the help of research staff) will capture metadata about each song played, including a count of the replays, which will yield estimates of the degree of exposure to the intervention; 4) research staff will document NH staff participation and attendance at all training sessions; 5) research staff will conduct interviews with NH staff to identify barriers, facilitators, and best practices related to implementation; and 6) research staff will conduct an environmental scan while on-site to capture observable characteristics of implementation variation, such as storage and use of equipment and staff familiarity with intervention. Our analysis will quantitatively and qualitatively characterize facility variation in implementation measures based on the consolidated framework for implementation research (CFIR)

constructs.

Interventions and Duration

M&M is a personalized music program that uses portable music players to deliver individualized music to people with dementia. NH staff provide cognitively-impaired people with music playlists tailored to their personal history of music preferences. The program assumes that musical memories remain present and that personalized music can quell the anxiety and agitation stimulated by the confusion secondary to dementia. NHs randomized to the first wave will receive the intervention in the first study year and end participation in the study; NHs randomized to the second wave will serve as controls in the first study year and receive the intervention in the second study year; and NHs randomized to the third wave will serve as controls in the second study year and receive the intervention in the third study year. During the first and second study years, we will collect primary data (repeat parallel design). In the third study year, we will only rely upon secondary data to conduct outcome analyses.

Sample Size and Population

Eligible facilities will have at least 15 long-stay residents with moderate to severe dementia, defined as a diagnosis of dementia and either a Brief Interview for Mental Status score ≤12 or moderately or severely daily decision-making. Preliminary research and pilot data informs our estimates of the potential effect of M&M on any improvement in agitated and aggressive behaviors. Assuming an intra-class correlation (ICC) of 0.12 and 6 points reduction in the outcome variable of interest (staff reporting of resident agitated and/or aggressive behaviors), we need 24 NHs in each arm to be able to test our primary outcome with power of .8 with a two-tailed alpha of .05. Since we plan on recruiting 27 facilities per arm, we will have adequate power even if we encounter unforeseen circumstances.

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The study is being conducted at 81 NHs owned by PruittHealth, Good Samaritan Society, Vetter Senior Living, and CommuniCare corporations. Corporate leadership for each corporation are listed above.

1 STUDY OBJECTIVES

Over 80% of people with Alzheimer's disease-related dementias ADRD exhibit behavioral and psychological symptoms of dementia (BPSD)(1, 2) that can adversely affect their experiences and outcomes.(3) BPSD are a heterogeneous group of symptoms ranging from agitation and anxiety to apathy, depression, delusions, and sleep or appetite changes.(2) BPSD not only adversely affects people's experiences and outcomes,(3) but also contributes to burden and stress for family caregivers(4-7) and healthcare providers.(8, 9) Use of antipsychotic medications to mitigate BPSD in ADRD increases the risk of serious complications,(10, 11) including extrapyramidal symptoms,(12-14) serious cardiovascular events,(14, 15) and even death.(16-18)(19) For this reason, existing guidelines recommend exhausting non-pharmaceutical options for treating these symptoms before initiating medications.(20, 21) Indeed, decreasing the use of antipsychotics for NH residents with dementia is a Centers for Medicare & Medicaid Services (CMS) goal.(22)

Eliciting musical memories using familiar or preferred music may decrease feelings of isolation and anxiety,(23, 24) as musical memories are encoded in areas of the brain affected later in the ADRD process than areas of the brain involved in verbal memory and executive functioning.(25, 26)(27-29) Studies have demonstrated that individualized music can reduce anxiety,(30-32) decrease negative affect or depression,(30, 31) and mitigate physically-agitated behaviors(33, 34) in people with ADRD. One specific music intervention, MUSIC & MEMORY^{SM} (M&M), provides people with ADRD with iPods populated with music playlists tailored to their personal history of music preferences.(35) The purpose of METRIcAL is to test the impact of implementing M&M on NH residents' BPSD outcomes during a four-year R33, by undertaking a pragmatic trial in four multi-facility NH corporations caring for residents with ADRD. We will conduct two parallel, cluster randomized controlled trial (RCT) with 81 facilities. The Specific Aims of the R33 are to:

Aim 1. Use a train-the-trainer model to disseminate M&M to 81 NHs, with ongoing monitoring of the program's adoption and acceptance by long-stay NH residents with ADRD.

Aim 2. Estimate the impact of M&M on agitated and aggressive behaviors, observed emotional states, antipsychotic use, antidepressant use, anxiolytic use, and depression for long-stay NH residents with ADRD.

Aim 3. Examine factors associated with variation in NHs' implementation of the implementation of M&M.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

ADRD(36-38) is the sixth leading cause of death and the only one in the top 10 that cannot be prevented, cured, or slowed.(39) Its prevalence is increasing with population aging and is expected to reach 7.1 million people by 2025—a 40% increase.(39) The Aging, Demographics, and Memory Study, a nationally representative sample of older adults, estimates ADRD prevalence at 5% for adults aged 71-79 years of age, rising to 24% for adults aged 80-89 years, and 37% for adults aged ≥90 years.(40)

Because of its effect on memory and other cognitive functions, ADRD leads to a loss of independent function that profoundly impacts patients, caregivers, and the healthcare system as a whole.(40) A significant number of people with ADRD require long-term services and supports (LTSS): the Centers for Disease Control and Prevention estimates that ADRD patients comprise nearly one-third of people receiving adult day (32%) or home health services (30%) and half of those living in assisted living (40%), hospice (44%), or NHs (49%).(41) Analyses of Medicare data, made publicly available through Brown's Long-term Care Focus website [http://ltcfocus.org/] suggest that 60% of long-stay NH residents have ADRD. Moreover, almost all people with ADRD exhibit BPSD over the course of their illness.(2, 3) The prevalence of BPSD is nearly 2.5 times as high among those in NHs (80%-96%)(1, 2) vs. the community (33%).(42) BPSD are a heterogeneous group of symptoms ranging from agitation and anxiety to apathy, depression, delusions, and sleep or appetite changes.(2) The pathogenesis is not well understood, although likely due to multifactorial causes.(2) BPSD not only adversely affects people's experiences and outcomes,(3) but also contribute to burden and stress for family caregivers(4-7) and healthcare providers.(8, 9)

BPSD-related problems contribute to high use of antipsychotic medications among NHs. CMS data reveal that, on average, 20% of long-stay NH residents are prescribed antipsychotics for BPSD symptoms.(43) A

2011 Office of the Inspector General (OIG) report found that 83% of NH antipsychotic use was off-label, and 88% of off-label use targeted residents with ADRD.(44) While antipsychotic use in NHs has decreased since 2012, likely as a result of the OIG report,(44) national efforts,(45, 46) and quality improvement (QI) campaigns,(47) prevalence remains high in light of the well documented adverse effects. Indeed, a 2011 systematic review documented the fact that antipsychotics increase the risk of cerebrovascular adverse events and death in this population.(48)

2.2 Study Rationale

Using antipsychotic medications to control agitation and aggression among people with ADRD increases the risk of complications,(11) including extrapyramidal symptoms,(12, 14) serious cardiovascular events,(14, 15, 49-51) and even death.(16)(17, 18, 20) For this reason, existing guidelines recommend exhausting non-pharmacological options;(20, 21) indeed, decreasing the use of antipsychotics for NH residents with ADRD is a CMS goal.(22) Unfortunately, as ADRD progresses, behavioral symptoms, including agitation and aggression, worsen, perhaps due to an inability to modulate responses as a direct effect of damage to the brain as well as sensory deprivation that can induce fear, anxiety, and confusion.(52-55) Eliciting musical memories using familiar music may decrease feelings of isolation and anxiety(23, 24) since musical memories are encoded in areas of the brain affected later than are areas of the brain governing verbal memory and executive functioning.(25-29) Individualized music has been shown to reduce anxiety,(30-32) decrease negative affect or depression,(30, 31) and to control physically agitated behaviors(33, 34) in people with ADRD. Further supporting the neurological pathway of eliciting musical memory, individualized music selections are more effective at reducing agitation compared to playing “relaxing” or classical music.(56) Several systematic reviews highlight the potential for music therapy to reduce agitation,(57-60) aggression,(58) anxiety,(61) behavioral symptoms,(61, 62) and mood.(62)This proposed pragmatic trial will **not** test the neurological premise on which individualized music is based, which would require complex imaging studies along with detailed behavioral monitoring. Rather, its significant contribution is testing the effectiveness of individualized music as a non-pharmacological treatment for BPSD.

MUSIC & MEMORY (M&M) is a music program that builds upon an evidence-based protocol(63) by using easily-operated iPods to deliver individualized music to people with ADRD. The program was developed by a social worker, Dan Cohen, with experience leveraging technology to benefit those who would otherwise have no access. Caregivers (providers, family, or others) provide cognitively-impaired people with music playlists tailored to their personal history of music preferences.(35) The program assumes that musical memories remain present and that personalized music can quell the anxiety and agitation stimulated by the confusion secondary to brain disease. Its potential is illustrated powerfully in the 2014 documentary, Alive Inside, which shows people with severe dementia begin to move, sing, and even describe memories.(64) Thousands of provider sites across the world have become certified in M&M, including hundreds of NHs in the U.S. NH staff participate in MUSIC & MEMORY, Inc.-led certification and training webinars that offer suggestions for choosing residents to receive iPods, identifying music preferences, and sustaining the use of the iPods. The M&M website offers materials and ongoing support to participating facilities. Twelve states have M&M NH demonstration projects underway. However, to date demonstration evaluations have revealed wide variation in the level, approach and sustainability of implementation of M&M. For example, there has been variation in which residents receive an iPod, where the iPods are stored, and how often residents have access to them.(65) Rigorous evaluation of a uniformly-implemented intervention is necessary to definitively establish the program’s efficacy and to characterize factors associated with effective implementation.

3 STUDY DESIGN

We will conduct two parallel, cluster RCTs of M&M for people with ADRD in 81 NHs; the unit of random assignment will be the facility and the unit of analysis the resident, clustered within the facility (see Table 1, next page). The primary study outcome is agitated and aggressive behaviors, as measured by interviewing a staff member who knows the resident well. Secondary study outcomes include: agitated and aggressive behaviors measured through direct observation of the resident when s/he is using and not using the music, agitated and aggressive behaviors as reported in available administrative data, emotional states observed while the resident is using and not using the music, antipsychotic use, antidepressant use, anti-anxiolytic use, and depression. First, using MDS data obtained from each corporation’s EHR and centralized corporate knowledge about their facilities’ capabilities and constraints, we will identify eligible facilities and contact facility

leadership to ensure that they want to, and have the necessary staffing resources to participate. Second, stratifying by corporation and prevalence and balancing on other key study variables at baseline, we will randomize facilities within corporation to one of three intervention waves. Third, we will use the most recent MDS data to identify eligible residents within each facility from the pool of long-stay residents with ADRD. At the same time, we will use knowledge gained from the R21 pilot phase to develop train-the-trainer materials and make any needed revisions to the step-by-step protocol. Fourth, we will train corporate trainers and support them as they train staff in participating facilities and mentor sites during implementation. Finally, we will obtain primary and secondary data for evaluation, using Research Assistant (RA) obtained observation and data from NHs' EHRs, merged with MDS and Medicare enrollment records. Obtaining, merging, and cleaning these data will occur throughout implementation phase.

Table 1. Repeat Parallel Design

	Period 1 (June, 2019 - January, 2020)	Period 2 (April, 2020 - November, 2020)	Period 3 (February 2021 - September, 2021)
Sequence 1 (27 Nursing Homes)	Intervention*† (405 residents)	Coronavirus Pandemic†	Intervention† (405 residents)
Sequence 2 (27 Nursing Homes)	Control*† (405 residents)	Coronavirus Pandemic†	Intervention*† (405 residents)
Sequence 3 (27 Nursing Homes)	Control† (405 residents)	Coronavirus Pandemic†	Control*† (405 residents

*Primary data collection conducted in Sequence 1 and Sequence 2 nursing homes during Period 1, and Sequence 2 and Sequence 3 nursing homes during Period 3

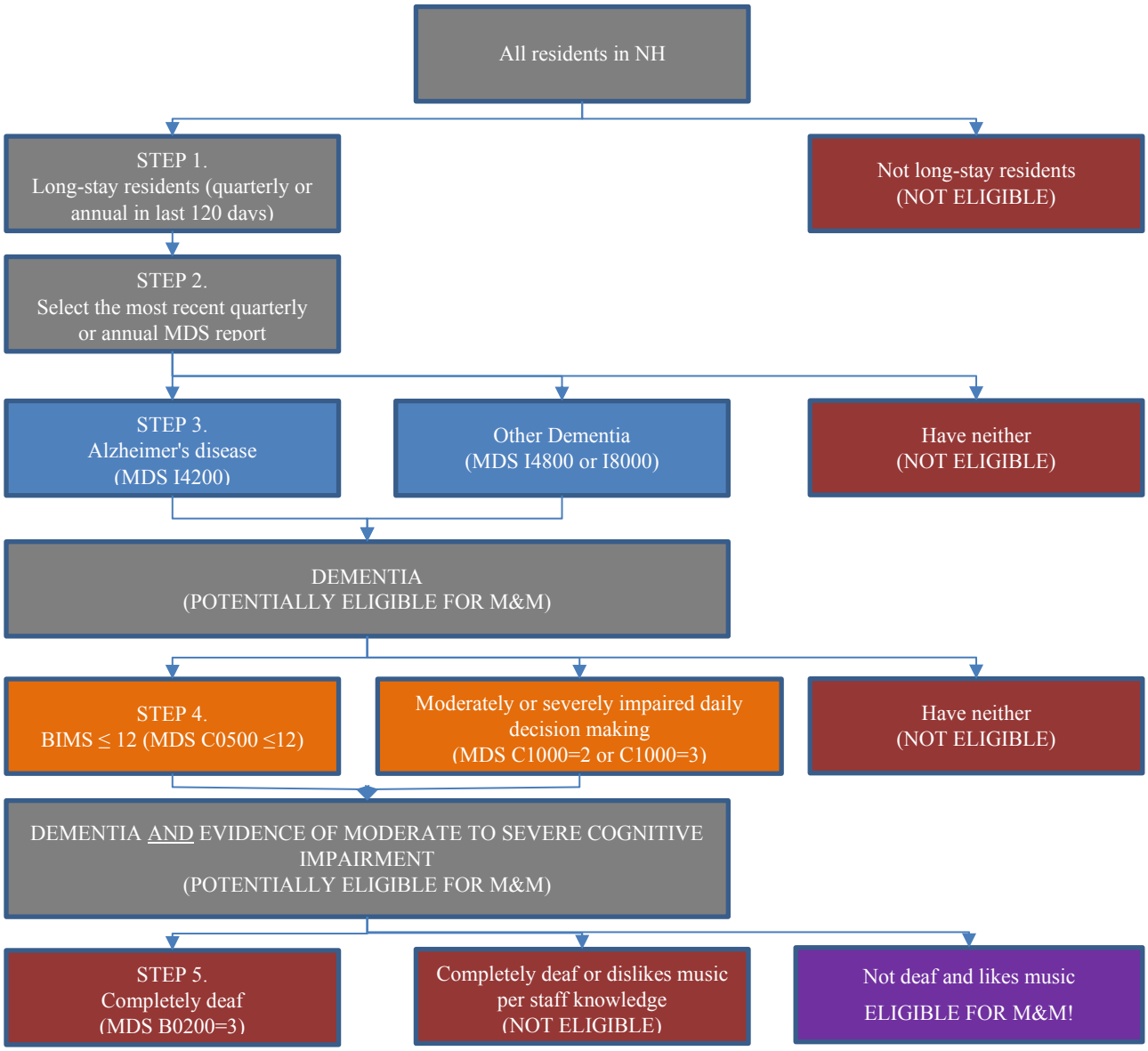
†Secondary data collection including Minimum Data Set (MDS) and medication order data collected in all periods for all sequences, even during the coronavirus.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Resident Inclusion & Exclusion Criteria

Eligible residents must be long-stay and have ADRD. Long-stay residents include anyone who had a quarter or annual assessment in the past four months. ADRD is defined by the presence of a dementia diagnosis and either a Brief Interview for Mental Status score ≤12 or moderately or severely daily decision-making. Resident exclusion criteria include being deaf or not liking music. Figure 2 describes the process for identifying eligible residents using Minimum Data Set (MDS) data.

Figure 2. Steps for Identifying Eligible Residents Using the Minimum Data Set



4.2 Facility Inclusion & Exclusion Criteria

Using the Minimum Data Set (MDS), Brown will identify facilities which have at least 15 eligible residents. Brown staff will provide a list of facilities who are likely to have enough residents meeting eligible criteria to corporate leadership. From the list of potentially eligible facilities, corporate leadership will eliminate any facing other significant threats to implementation (e.g., recent leadership changes, recent poor regulatory survey performance such as immediate jeopardy or monetary penalties). Corporate leadership will reach out to potentially eligible facilities to allow for an opt-out of participation and to verify that they are not currently using M&M.

4.3 Study Enrollment Procedures

4.3.1 Facility Recruitment Procedures:

Once eligible facilities are identified, they will be contacted by the Brown project leadership for a baseline telephone interview. The purpose of this call is to describe the study and provide a final opportunity for the facility to opt-out, without corporate leadership present. While senior corporate leaders strongly endorse the project, the final decision to participate in the intervention arm will be the individual facility's administrator.

Once the NHs are recruited, they will be randomly assigned (*see Section 4.3.3. for randomization procedures)* to one of three intervention waves by Brown statisticians.

4.3.2 Facility Recruitment Estimates:

Based upon our sample size calculations (*see Section 9.2*), we require 24 facilities per arm (72 facilities total). To account for the fact that some facilities may not successfully implement the intervention post-randomization, we increased our facility recruitment targets to 27 facilities in each study arm (81 facilities total) Table 2 provides the key characteristics of eligible facilities by corporation.

Table 2. Key Characteristics of Eligible Nursing Homes by Partnering Corporation

	Corporations			
	A	**B**	**C**	**D**
Eligible Nursing Homes (#)	69	12	25	76
Geographic Region	Mid-West	Mid-West	Mid-Atlantic	South
Black Residents (%)	1%	<1%	53%	42%
CMS Overall Quality Star Rating (Mean)	3.4	4.5	2.0	3.1
Ownership Type	Non-Profit	Non-Profit	For-Profit	For-Profit
Residents with any antipsychotic Use in Last 7 days (%)	23%	18%	25%	26%
Residents with any agitated or aggressive behaviors (%)	27%	14%	15%	17%

4.3.3 Facility Randomization and Stratification Procedures:

Facilities will be randomized within NH health care system strata. Within each health system, sites will be partitioned into triplets based on the Mahalanobis distance from the overall mean on the following key variables: percentage of eligible nursing home residents with any agitated or aggressive behavior (MDS Aggressive Behavior Scale > 0) on their most recent quarterly or annual assessment and number of eligible long-stay residents. The rationale for this additional balancing is that agitated and aggressive behaviors, a study outcome of interest, are known to vary considerably at the facility-level due to nursing home resident composition, staffing, and the degree of "ascertainment" and documentation of behaviors. It was also important to balance on the number of eligible residents in a nursing home, because nursing homes with more eligible residents can be more selective in who receives the program, possibly picking "better" candidates. Within balanced triplets, one facility will be randomly chosen for each of three periods (Table 1).

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The M&M personalized music program will be implemented for at least 8 months in each intervention facility. (Obviously, facilities are encouraged to continue to use the music devices with patients long after this 8-month period and the devices will remain at the facility for use among appropriate patients). The intervention consists of: 1) identifying the music a resident with ADRD preferred when she was between the ages of 18 and 24, either by consulting family members or through trial and error; 2) creating a personalized playlist for each resident; 3) loading this personalized playlist on the resident's music player (iPod); and 4) using the iPod with the resident twice a day for approximately 30 minutes to 1 hour per use, at times when residents with ADRD tend to experience BPSD. Recommended times are when the resident gets up in the morning (during daily personal care) and in the late afternoon, when sundowning is common. In addition to these set times, NH staff are encouraged to use the music at other times when an individual resident is likely to experience BPSDs. In the first parallel trial, NH staff will be responsible for completing all four steps. In the second parallel trial, research staff will create personalized playlists (step 2) and load music players (step 3). For the second parallel trial, staff will provide Brown with 15 eligible residents' "preferred" music genre and resident age. Brown research staff will preload iPods with popular music in the resident's preferred genre from when they were between the ages of 16 and 26 (current best practice recommendation). This process is similar to playlists generated by Spotify and other streaming services. Additionally, we will be using playlists from the first trial to culturally and regionally tailor music selections. This is particularly important for the current study as we have four regionally and racially diverse corporations: two NH corporations serving predominately white, rural

residents in the Midwest, one NH corporation serving mostly African American residents in the DC metro area; and one NH corporation serving southern African American and white residents. Based on our extensive population experience and large music database from the R21 and R33 phases we are able to observe differences in music preferences between a majority African American NH in rural Georgia and a majority African American NH in urban Maryland. Approximately 15% of all NH residents are African American; approximately 25% of the study sample is African American. This over-representation allows for cultural and regional tailoring of music playlists and has implications for the uptake of the Music & Memory program beyond the current study. By preloading devices with music, the program can be led by nursing staff from the beginning (step 4). We will compare the effects of these two processes on targeted use of the music to address clinical agitation.

In our preliminary work, funded by the Research and Retirement Foundation, Brown (in partnership with B&F Consulting) identified facilitators and barriers to implementing the M&M program in six, high-performing NHs in the northeast. Important findings from this preliminary work include the need to: align the intervention to priorities of individual facilities; pilot the intervention with a few residents before expanding to an entire unit or NH; and integrate M&M into routine care planning and quality improvement activities to sustain use. During the R21, Brown and B&F translated these lessons learned into a step-by-step Implementation Guide (Appendix A). The Implementation Guide addresses logistics and process steps, including:

- Identifying a computer to house an iTunes library,
- Charging and storing iPods,
- Researching resident playlist preferences,
- Downloading personalized playlists,
- Piloting the intervention with the first resident,
- Scaling the intervention across a unit / within a nursing home,
- Incorporating the intervention into care planning and data tracking, and
- Sustaining the program after the 8-month intervention period.

The Implementation Guide also provides checklists for tracking monthly progress towards successful implementation.

Each participating NH receives two types of intervention trainings. First, NH staff will participate in standard M&M training and certification. Standard M&M training and certification is offered as a two, 1.5-hour live webinars, covering the benefits of M&M and a basic introduction to the equipment. After completing these two webinars, NHs become certified in M&M and receive a certificate to display in their facility.

The second intervention training will be administered by the corporations for their participating facilities. This training will follow the steps outlined in the Implementation Guide. During the R33, B&F consulting will train and mentor corporate trainers in how to introduce and then disseminate M&M. This pragmatic approach mimics real-world diffusion and allows us to efficiently deliver the intervention to the 27 treatment NHs in each trial. In keeping with a pragmatic trial, implementation will be tailored to the needs of individual corporations and their facilities. However, at a minimum, corporate trainers will lead monthly coaching calls with the project team in the intervention facilities to track progress and set goals. Corporate trainers will help identify the “right” NH staff to participate in each NH’s M&M team and will mentor teams throughout the process, helping them to: set milestones, identify and track process data, review progress, and make mid-course corrections. The project team must include: the NH administrator, DON, activities staff, a nurse manager, and a certified nursing assistant. Other team members may be added, as appropriate. Corporate trainers will visit each NH at least twice during the intervention (launch and mid-implementation) to provide technical assistance and support.

The research team has established serval ways to monitor adherence to the intervention protocol which are described in *9.4.3 Process Measures for Implementation Analysis*.

5.2 Concomitant Interventions

Many eligible facilities are likely to have periodic, or even daily, music-based activities for residents. Facilities may also be testing other non-pharmaceutical options for addressing BPSD in ADRD while participating in the current study. However, facilities that are already systematically using personalized music, delivered through headphones or personal speakers, with multiple residents (whether M&M certified or not) will be excluded from the current study.

6 DATA SOURCES AND ELEMENTS

We seek to assess the effect of M&M on agitated and aggressive behaviors in NH residents with moderate to severe dementia. Agitated and/or aggressive behaviors are measured three ways: by interviewing staff about resident behaviors over time (primary outcome); through direct observation of residents when using and not using M&M (secondary outcome); and using available administrative data (secondary outcome). Other secondary outcomes include: other emotional states directly observed while the resident is using and not using M&M (anger, pleasure, alertness, sadness), antipsychotic use, antidepressant use, anxiolytic use, and depression. We would also like to understand best practices for integrating the Music and Memory program into existing care processes, facilitators and barriers of using the music, and how the intervention is implemented for each eligible patient (e.g. dose, reason for use, time of day) that might contribute or detract from its effectiveness.

6.1 Data Sources

Secondary Data

Electronic Health Records (EHRs): Three of our partners use PointClickCare (PCC); the other, has two vendors AmeriTec and Matrix Care. We are currently working with these EHR vendors on the PROVEN trial. Thus, we already have procedures in place to extract and link these EHR data with national Medicare repository data and ultimately to Medicare enrollment records. We will use the NHs' EHR to obtain "real-time," individual patient-level data for MDS assessments, user-defined assessments (UDAs), and medication order data.

Minimum Data Set (MDS): The MDS has nearly 400 data elements, including cognitive function, communication / hearing problems, physical functioning, behavioral problems, continence, mood state, diagnoses, health conditions, special treatments, and medication use. Staff complete assessments for *all* individuals admitted to Medicare and Medicaid-certified NHs, including enrollees in both traditional Medicare and Medicare Advantage. Staff are required to submit MDS data to CMS regularly(66-69) and complete assessments upon admission, quarterly, and with changes in status or transfer from the building. Repeated evaluations of the reliability of the MDS reveal adequate to good values on most data items and scales. Brown investigators found that missing data are scarce.(66-69) Research using MDS data has made major contributions to our understanding of how policy, fiscal, and clinical factors influence the quality of NH care,(68, 70-80) and much of this work has been conducted by Brown investigators participating in this proposed project.

Medicare Enrollment, Vital Status, and Chronic Condition Warehouse Data: Brown investigators have decades of experience working with Medicare files linked to MDS and provider-specific data. The Medicare enrollment file provides demographic information as well as Medicaid eligibility, HMO status, and mortality data. The Chronic Condition Warehouse data elements include a summary of the past presence of over 20 unique diagnoses present on any Medicare claim. Because we will obtain real-time MDS data from the facilities, we will also request the quarterly updates to the Vital Status and Chronic Condition Warehouse file from CMS; this will allow us earlier access to date of death than the enrollment file. These data allow us to track mortality even in the event that a resident is hospitalized and does not return to their original NH.

Certification and Survey Provider Enhanced Reporting (CASPER): CASPER are publicly-available data from the Medicare/Medicaid certification and inspection process that all NHs undergo. Brown investigators have assembled a three-decade data panel on all certified U.S. facilities including data on ownership, size, staffing, services, patient acuity, and quality inspection results.(81, 82)

Primary Data

Primary data collection tools can be found in Appendices B-H. These data will be collected by independent data collectors during three site visits (baseline, four, and eight months).

iPod Metadata: The iPod shuffle retains limited data about use. Information about the songs played (e.g., artist, album, track title, duration of track, genre) and the number of times a song is played are available and will be downloaded.

Staff Interviews: the RAs will interview the NH caregiver most familiar with the resident using the Cohen Mansfield Agitation Inventory (CMAI), a validated 29-item tool for measuring agitation in people with ADRD living in NHs.(83, 84) We will use the CMAI to assess the frequency and severity of eligible residents' behaviors over the previous week.

Resident Observation (Trial 1 Only): The Agitated Behaviors Mapping Instrument (ABMI) will be used to observe resident behaviors at the point of intervention. Using independent, trained observers, we will observe

the frequency of residents' agitated behaviors over short intervals, when they are using and not using the M&M intervention. We will also use the Lawton Observed Emotion Rating Scale (OERS),(85) which was designed to measure pleasure, anger, anxiety/fear, sadness, and general alertness. Reactions to music will be captured, when observations include the use of M&M.

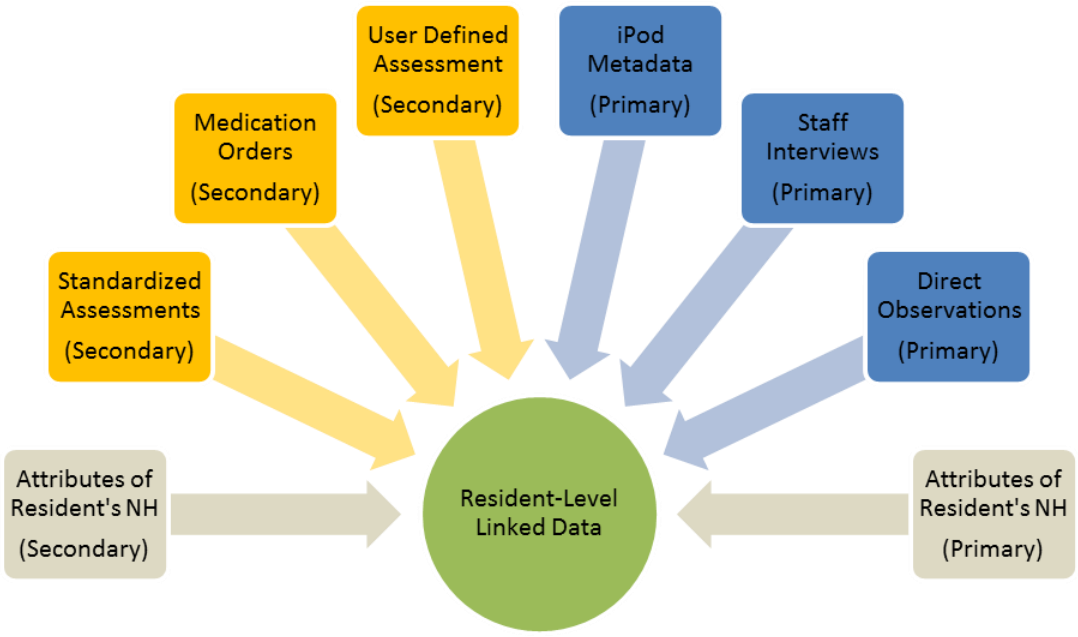
Implementation Observation Checklist: The Implementation Observation Checklist is completed by data collectors while on-site. It describes adherence to specific aspects of the study protocol (e.g., are the playlists individualized, are the iPods labeled, are frontline staff involved in delivering intervention to residents, etc).

Key Informant Interviews: Key informant interviews with the administrator and nursing lead in each intervention facility will be completed by Brown research team members at 4- and 8-months (mid- and full-implementation). These interviews will identify facilitators, barriers, and best-practices related to implementing the M&M program, and feedback on corporate trainings.

6.2 Data Linkages

During the R21, we developed and tested procedures for linking primary data, collected on-site at the nursing homes, to existing secondary data sources at the resident-level (Figure 2). Data linkage techniques are described in the paragraphs below.

Figure 3. Linking Primary and Secondary Data at the Resident-Level



As described in *Section 6.1 Data Sources*, there are four types of data that will be collected on-site: staff interview, resident observation, implementation observation, and iPod metadata. These data will be linked to secondary data obtained directly from NHs (MDS, UDA, and medication order data) and secondary data obtained directly from CMS (Medicare Enrollment, Vital Status, Chronic Condition Warehouse Data, and Certification and Survey Provider Enhanced Reporting). Data collected on-site will be entered using tablets through data entry systems developed in Qualtrics, the secure web-based survey tool supported by Brown's Computing & Information Services. Data will be uploaded to the Qualtrics central servers using a secure channel. When entering the study data in Qualtrics, the patient data will only be identified by a pre-assigned Brown study ID; no personally identifying information (PII) or existing IDs (e.g., medical record number, social security number) will be entered. In preparation for analyses, the primary data will be downloaded from Qualtrics and stored on a secure server at Brown. Using a secure crosswalk of Brown study IDs to real person identifiers, the primary data will be linked to the secondary data (the collection of which was already approved by the IRB) for analyses. All analytic files released by the Systems Manager to analysts will be stripped of PII and will include only the Brown study ID.

Brown University investigators and database management staff already receive national MDS, Medicare, and CASPER data semi-annually or quarterly under several CMS data use agreements (DUAs). There is a well-established database management structure for linking these files. Brown University also has experience

integrating EMR data from with CMS Medicare enrollment records and Medicare claims. Using algorithms based on standard patient identifiers including Heath Insurance Claim (HIC) numbers, date of birth, gender, and Social Security Numbers (SSNs), matching rates generally exceed 98%. The new activity for METRIcAL is linking primary data collected on-site to secondary data. In the R21 pilot study, secure data transfer and linkage of primary and secondary data for all four corporations were successfully accomplished.

7 SAFETY ASSESSMENTS

7.1. Minimal Risk Determination:

There are special informed consent considerations for individual residents in the study. The intervention is of relatively low risk, and it will be implemented facility-wide as part of the intervention facilities' standard operating procedures for addressing agitated and aggressive behaviors in dementia. Thus, we received a waiver of individual informed consent as set forth by the four criteria found in HHS 45 CFR 46:116 (Brown University IRB #1705001793):

1. The research involves no more than minimal risk;
2. The waiver will not adversely affect the rights and welfare of the subjects - we are merely asking the staff about resident behaviors and observing residents from afar with no direct contact;
3. The research could not practicably be carried out without the waiver this study involves evaluative measures of different types (observations, metadata from the music device, and MDS assessments) which need to be linked but are individually otherwise exempt or, due to their unobtrusive nature, readily waiver consent. These secure data linkages, necessary for the full evaluation, would not be possible without a waiver of individual consent; and
4. Whenever appropriate, subjects will be provided with additional pertinent information after participation

7.2. Serious Negative Reactions and Serious Adverse Events

Please refer to the Data Safety and Monitoring Plan and Data Safety Monitoring Board Charter for complete safety assessment information.

Adverse Events: An adverse event (AE) is any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. The potential AEs that could occur during this trial are: distress or strong negative emotional reactions in response to listening to the music delivered via the M&M intervention; and distress or strong negative emotional reactions in response to being observed (Trial 1 Only). Distress or strong negative emotional reactions to the music may include screaming / calling out, crying (not always a negative response), or attempting to remove headphones. Distress or strong negative emotional reactions to being observed may include screaming or becoming agitated / aggressive. Distress resulting from the music and the distress of being observed by a data collector would be classified as mild because the distress is easily tolerated and/or remediated, requires no medical evaluation, and has signs and symptoms that are transient. An immediate, negative reaction to the music would fit the study relatedness category "Definitely Related." A negative reaction to being observed would fit the study relatedness category "Possibly Related," as it will likely be difficult to precisely determine the origins of behaviors and reactions in residents with advanced dementia, and it is unclear the extent to which the resident might be aware that s/he is being observed. AEs resulting from negative reactions to the music are expected but likely rare. AEs resulting from negative reactions to the data collectors are not expected.

Serious Adverse Events: The potential serious adverse event (SAE) that could occur during this trial is a fall secondary to spontaneous ambulation (e.g., dancing) while listening to the music. Falls during spontaneous ambulation while listening to music could be classified as moderate or severe, depending on the presence of related injury and/or need for tertiary care. A fall during spontaneous ambulation while listening to the music is "Possibly Related" to the intervention, as this population of NH residents with moderate to severe dementia is prone to falls (independent of the intervention). This SAE is not expected, as falls are not consistent with available information about the intervention.

Unanticipated Problems: Unanticipated problems (UPs) are defined by DHHS 45 CFR part 46 as any incident, experience, or outcome that meets **all** of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the study population;
2. related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Deaths: This study involves NH residents with advanced dementia. Death is expected in this population. In one of our ongoing, large cluster-randomized trials, which enrolls a similar population of NH residents with advanced dementia, we are observing a 60% annual mortality rate. There is no anticipated relationship whatsoever between the intervention (personalized music) and death.

7.3. Followup for Serious Negative Reactions

Adverse Events, Serious Adverse Events, Unanticipated Problems, and Deaths have specific reporting procedures.

As part of NH staff training, instructions will be given as to what constitutes an AE / SAE / UP. NH staff will be instructed to stop the music if an event occurs in which resident distress seems to result from the music (AE). NH staff are already trained in fall response (SAE). The NH staff should report any AE / SAE / UP to his/her immediate supervisor as soon as possible, but not exceeding 4 hours after the event. If deemed by the supervisor to be a true AE / SAE / UP, the NH supervisor will complete a *Nursing Home Event Reporting Form*, which will be submitted to the research project director via email within 24 hours of the event. The project director will report the event to the PI via email or telephone immediately upon becoming aware of the event.

Similarly, as part of the observer training, data collectors will be given instructions as to what constitutes an AE / SAE / UP. Data collectors will be instructed to terminate an observation if an event occurs in which resident distress seems to result from being observed (AE). Data collectors will report events to the NH supervisor as soon as possible, but not exceeding 4 hours after the event. If deemed by the supervisor to be a true AE / SAE / UP, the NH supervisor will complete a *Nursing Home Event Reporting Form*, which will be submitted to the research project director via email within 24 hours of the event. The project director will report the event to the PI via email or telephone immediately upon becoming aware of the event.

Upon receipt of the *Nursing Home Event Reporting Form*, the project director and Dr. James Rudolph will contact the NH supervisor and complete the *Event Verification Form*. Dr. Rudolph is a co-investigator on the project and a board-certified geriatrician with NH medical experience. Specifically, the project director and Dr. Rudolph will review the details of the event with the NH supervisor, confirm that the event meets criteria for a true AE / SAE / UP, and classify the severity, expectedness, and relatedness of the event.

During verification, if it is determined that the event does not meet the criteria for a true AE/ SAE/ UP, the *Nursing Home Event Reporting Form* and the *Event Verification Form* will be retained by the study team, and no further action will be taken.

During verification, if it is determined that the event is a true AE (and not a SAE or UP), the *Nursing Home Event Reporting Form* and the *Event Verification Form* will be retained for quarterly reporting of AEs to the Data Safety Monitoring Board (DSMB), the NIA Program Officer, and the IRB. A summary of AEs will be included in the semi-annual DSMB report.

During verification, if it is determined that the event is a true SAE, the PI will notify the DSMB, the NIA Program Officer, and the IRB within 24 hours of the research team becoming aware of the event (within 48 hours of the event occurring). The *Event Verification Form* will also be used to capture the follow-up status of a resident who has experienced a SAE. The *Nursing Home Event Reporting Form* and the *Event Verification Form* will be retained and a summary of SAEs will be included in the semi-annual DSMB report.

During verification, if it is determined that the event is a true UP, the PI will notify the DSMB, the NIA Program Officer, the Office for Human Research Protections, and the IRB within 24 hours of the research team becoming aware of the event (within 48 hours of the event occurring). The *Event Verification Form* will also be used to capture the follow-up status of a resident who has experienced a UP. The *Nursing Home Event Reporting Form* and the *Event Verification Form* will be retained and a summary of UPs will be included in the semi-annual DSMB report.

We will receive information on deaths occurring within the nursing home monthly, based on administrative data sent from participating NH corporations to Brown University. Deaths among residents exposed to the intervention will be reported within 24 hours of study's knowledge of death. The report of death will be submitted via email to NIA Program Officer and to the DSMB Chair.

7.4. Protection Against Risks

Procedures to minimize against risks include: training NH staff on how to choose appropriate candidates to receive the intervention and how to deliver the intervention to minimize risk of negative reactions; training data collectors to conduct resident observations as unobtrusively as possible; and extensive data safety protocols.

Training NHs: There are several levels of ongoing training and monitoring. NH corporate leadership will receive a two-day initial training on how to help their participating NHs select residents who are likely to respond positively to the intervention. During this training, leadership will also be taught the best way to approach the residents with the music, in order to minimize negative reactions related to startling them. For example, the training details how to initially hold the headphones away from the resident's ears to allow the resident to hear and get used to the music before experiencing the sensory pressure of the headphones. Corporate leadership will then repeat this training with each of their participating NHs before the intervention begins. Once the intervention begins, monthly phone calls will be made to NH staff by corporate leadership and Brown University staff in order to reinforce these best practices for minimizing negative reactions and to monitor for any events that have not been otherwise reported. In addition, corporate leadership will visit each site twice during the study to make sure the intervention is being administered consistent with best practices.

Training Data Collectors: Data collectors will attend a three-day training at Brown University before the start of the intervention. During this training, data collectors will visit a NH to become familiar with the setting and to practice conducting observations unobtrusively. During the actual study, a maximum of four observations will be conducted for each resident during a data collector visit, with two data collector visits per resident over the course of the study. Each observation will be a maximum of five minutes in duration. The data collector will neither be left alone with the resident nor interact directly with the resident. Whenever possible, the observation will be done when the resident is in a common area, but this may not always be feasible. If the observation is done while the resident is in his or her room, the data collector will remain outside of the room and observe as discreetly as possible through an open door. The goal is for the data collector to be as inconspicuous as possible. This protocol has been approved by the Brown University IRB.

7.5. Safety Monitoring

A DSMB for METRIcAL will act in an advisory capacity to the National Institute on Aging (NIA) Director to monitor participant safety, data quality, and progress of the study. External DSMB members will be specified by the funding agency. Members of the METRIcAL team who will participate in the open sessions of the DSMB include the PI (Mor), the lead biostatistician (Gutman), and project director (McCreedy). The NIA project officer for METRIcAL, Partha Bhattacharyya, will attend DSMB meetings and serve as the liaison between the DSMB and NIA.

8 INTERVENTION DISCONTINUATION

The study may be discontinued at any time by the IRB, the NIA, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected. Individual facilities in the intervention may withdraw from study participation at any time at the discretion of their senior management or corporate supervisors. Individual residents or their proxies can refuse the intervention and/or the observation of the implementation of the intervention.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

We will conduct two parallel, cluster-randomized control trials (RCTs) of personalized music for nursing home (NH) residents with moderate to severe dementia cared for in 81 NHs within four NH health care systems: PruittHealth, Good Samaritan Society, Vetter Senior Living, and CommuniCare (Terrapins Division). Twenty-seven facilities will receive the intervention in each trial.

9.2 Sample Size and Randomization

The primary outcome for this study is agitated and aggressive behaviors, as measured by the Cohen-Mansfield Agitation Inventory (CMAI). We have three ways of measuring agitation and aggression – the Minimum Data Set (MDS), the Cohen-Mansfield Agitation Inventory (CMAI), and the direct observation of residents while using and not using the music. Prior research suggests that agitated behaviors are under-ascertained in the MDS, due to staff normalizing these behaviors when exhibited by the residents.(86) For this reason, we chose the CMAI as our primary study outcome. We based our sample size estimates and analytic plan on the CMAI (staff interview).

Sample size estimates are based on the primary trial outcome: total score on the CMAI among long-stay residents with dementia. Based on data from the first trial, We conducted a *post hoc* power calculation to estimate the required sample size for different effect sizes. We used the formula proposed by Teerenstra et al (2012) and imputed values from the trial data. For significance level α and power 1-β, the formula for the required number of residents is:

$$n_{res} = \frac{2\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \sigma^2}{\delta^2}(1 + (n-1)\rho)(1 - r^2),$$

where Z_x is the critical value from a normal distribution at x, σ^2 is the variance of the outcome CMAI, δ is the effect size, ρ is the intra-class correlation, n is the number of residents per cluster and r is the correlation between a cluster means at baseline and at follow-up. To obtain the number of clusters required per arm we would need n_{res}/n. In our parallel design experiment completed just before the pandemic, we found that $\sigma = 20$, $\rho = 0.12$ and $r = 0.5$. Assuming an alpha level of 0.05 and power of 80%, we need 24 NHs per study arm to detect a 6-point reduction in the total CMAI score. We recruited 27 NHs per study arm which will allow us to address possibly higher ICC values, non-participation and lower correlation between the baseline and outcome scores.

9.2.2. Treatment Assignment Procedures: Please refer to *section 4* for a detailed description of the treatment assignment procedures.

9.2.3. Blinding: Our partner health care systems will know which facilities are designated intervention facilities. Brown University statistician and data management staff will present aggregated post-random assignment comparisons of intervention and control facilities' baseline characteristics, but these preliminary analyses will be not generated at the individual facility level. Dr. Mor, the study PI, will be blinded to the identity of both the control and intervention facilities. Facility assignment will be unblinded to the DSMB members at their request.

9.3 Interim analyses and Stopping Rules

We do not include stopping rules in the METRIcAL trial protocol for two reasons. First, this is a minimal risk study for which serious negative reactions will be extremely rare *(see Section 7.1)*. Indeed, the Brown IRB has concurred with this interpretation, having allowed a waiver of consent specifically because they view the study as minimal risk. Second, a stopping rule would not be very feasible since the implementation period is only 8 months in each facility, meaning that interim data analyses will be difficult, if not impossible, to perform.

9.4 Outcomes

9.4.1 Primary outcome

The primary outcome for this study is the frequency of agitated and aggressive behaviors, as measured by the CMAI. The CMAI has 29 items organized under three domains: aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior.(83) For each item, a staff member familiar with the resident's behavior is asked how often each behavior occurred in the past week. Response choices are: never (1); less than once a week (2); once or twice a week (3); several times a week (4); once or twice a day (5) several times a day (6); or several times an hour (7). For NH residents with dementia the inter-observer reliability of the CMAI was: .62 for physically aggressive behaviors (reliable change index, RCI = 7.54), .73 for physically non-aggressive behaviors (RCI = 7.09), and .61 for verbally agitated behaviors (RCI = 5.80).(87)

Test-retest reliability was: .82 for physically aggressive behaviors (reliable change index, RCI = 2.59), .83 for physically non-aggressive behaviors (RCI = 5.44), and .86 for verbally agitated behaviors (RCI = 3.22).(87) During the R21 phase, the average total CMAI score for eligible residents at baseline was 60.98 (SD:15.37). Average total CMAI scores were similar across nursing home corporations (Table 3).

Table 3. Total CMAI Scores for Eligible Residents at Baseline During R21

	Obs	Mean	SD	Min	Max	Kurtosis
Overall	42	60.98	15.37	30	95	2.41
Good Sam	10	63.90	20.23	38	95	1.65
Vetter	12	59.58	13.79	38	89	3.10
Pruitt	10	58.20	10.35	42	77	2.39
CommuniCare	10	62.50	17.44	30	86	2.44

9.4.2. Secondary Outcomes:

Secondary outcomes are obtained from primary and secondary data sources.

Primary Data

Agitated and aggressive behaviors. The Agitated Behaviors Mapping Instrument (ABMI). The ABMI has 14 items which can be collapsed into total agitation, verbal agitation, and physical agitation.(90) Interrater reliability (IRR) for identification of behavior exceeds 90% in Cohen-Mansfield's publications (93%, 96%); reported intraclass correlations coefficient (ICC) .90.(90-92) Cohen-Mansfield also reports high ICCs between videotaped (blinded) coding of behaviors and direct observation of behaviors (not blinded): .94 for verbal agitation, .93 for physical nonaggressive agitation, and .94 for total agitation.(90) Pearson correlation coefficients for identical items on the ABMI and CMAI are: .317 for verbal agitation (requests for attention .372, screaming .432, cursing .168, and complaining .442); .389 for physical agitation (pacing .542, repetitions .555, and exit seeking .322); .203 for combined agitation; .411 for physical aggression and .400 for disruptiveness.(93)

Mood. Mood states are also observed using the Lawton Observed Emotion Rating Scale (OERS),(85) which was designed to measure pleasure, anger, anxiety/fear, sadness, and general alertness in nursing home residents with ADRD.

Secondary Data

Agitated and aggressive behaviors. In addition to the CMAI and the ABMI, we will also measure agitation and aggressive behavior using the MDS. The Aggressive Behavior Score (ABS) is derived from four items in MDS, Section E, which describe the frequency of: 1) physical behaviors (hitting kicking, pushing, etc.); 2) verbal behaviors (threatening, screaming, cursing, etc.); 3) other behaviors (scratching self, pacing, throwing, smearing food, etc.); and 4) rejection of care. Each behavior problem is rated in its frequency, ranging from 0 (never) to 3 (daily), and the ABS is constructed by summing these four items. It has an alpha reliability between 0.79 and 0.93.(95)

Receipt of antipsychotic medications and their substitutes. We have two data sources for receipt of antipsychotic, antidepressant, and anxiolytic medications: electronic medication orders and the MDS. The MDS assessment includes a count of the number of days in the last 7 in which an antipsychotic, antidepressant, and anxiolytic medication was received. We are also receiving standing medication orders from all four corporations. This data includes drug name and class, order date, ordering physician, and number of pills.

Mood. The MDS includes the Patient Health Questionnaire (PHQ-9) a validated measure of depressed mood asked of the residents or if unable to respond to the interview, rated by staff.(96)

9.4.3. Process Measures for Implementation Analysis:

We will adopt five distinct approaches to assessing implementation: 1) a user-defined assessment (UDA) by which potentially eligible residents are assessed for their ability to listen to music, their music preferences, and the results of the initial trial of the iPod; 2) iPod metadata about each song that is played, including a count of the times played (and therefore the sum of all plays per unit time); 3) documentation of NH staff participation and attendance in M&M training and monthly corporation calls; 4) key informant interviews of NH staff during and after implementation; and 5) implementation observation checklist, completed on-site by data collectors, to

describe adherence to specific aspects of the study protocol (e.g., are the playlists individualized, are the iPods labeled, etc). Table 4 describes the relationship between primary and secondary data sources and study outcomes.

Table 4. Relationship of Data Sources to Study Outcomes

	Agitation / Aggression	Mood	Antipsychotic Mediation	Anxiolytic Medications	Antidepressant Medications	Implementation
Secondary Data						
Minimum Data Set	X	X	X	X	X	
User Defined Assessment						X
Medication Order Records			X	X	X	
Primary data						
Staff Interview	X					
Resident Observation	X	X				
iPod Metadata						X
Key Informant Interview						X
Implementation observation						X

9.5 Data Analyses

The analytic approach in the second parallel trial is based on the minimum observed frequency of agitated and aggressive behaviors after intended exposure to the intervention (treatment) or after 8-months (control), conditional upon survival to at least one post-intervention observation (up to 4 months after baseline measurement). Our primary analysis is based upon an intent-to-treat principle, and we estimate complier average causal effect as a secondary analysis. The compliers analysis estimates the effects of the intervention for residents who received the music or would have received the music.

Our primary ITT analysis model is based on the model described by Murray & Blistein (2003) and Teerenstra et al (2012). Let Y_{ijk} be the staff interview for resident $i \in \{1, \dots, n\}$ from NH $j \in \{1, \dots, J\}$ at time $k \in \{baseline, post-exposure\}$, I_{ij} be an indicator that is equal to 1 if resident i in facility j is in the treatment group and T_{ij} is an indicator that is equal to 1 if this is the baseline score for resident i in facility j. We assume that $Y_{ijk} = \mu_{ijk} + \epsilon_{ijk}$, where $\epsilon_{ijk} \sim N(0, \sigma_\epsilon^2)$, and $\mu_{ijk} = \mu + \gamma T_{ij} I_{ij} + \tau(1 - T_{ij})(1 - I_{ij}) + \alpha(1 - T_{ij}) I_{ij} + u_j + (u\tau)_{j,k} + s_{ij}$. We define $u_j \sim N(0, \sigma_u^2)$ as the deviation of cluster j from the overall mean, $(u\tau)_{j,k} \sim N(0, \sigma_{u\tau}^2)$ represent the variation of each cluster at different time points, $s_{ij} \sim N(0, \sigma_s^2)$ is the variation of individuals, γ is the difference at baseline between the mean of the intervention and control clusters, τ is the change from baseline to follow-up of the control clusters means, and α is the conditional treatment effect. Individual level covariates comprise of baseline variables including baseline CMAI. The estimate of interest would be the difference in marginal means.

To estimate the effects among participants that would comply with the intervention we used a technique described by Jo et al. Let c_{ij} be an indicator that is equal to 1 if resident i in NH j would use the music if provided. We assume that residents who would not be offered the music will not attempt to obtain it on their own. Eligible residents who do not receive the intervention who and receive care in an intervention NH are referred to as "non-compliers." The effects of the intervention would be estimated using, $\mu_{ij} = \beta_0 + \beta_c c_{ij} + \alpha_c c_{ij} I_{ij} + \sum_{l=1}^{L} \gamma_{ijl} X_{ijl} + u_{nbj}(1 - c_{ij}) + u_{nwij}(1 - c_{ij}) + u_{cwij} c_{ij} + u_{cbj} c_{ij}$, where the macro-unit residuals u_{nbj} (non-compliers) and u_{cbj} (compliers) represent cluster-specific effects given I_{ijk} and X_{ijl}, which are assumed to be normally distributed with zero mean and the between-cluster variances σ^2_{nb} (noncompliers) and σ^2_{cb} (compliers), respectively. The micro-unit residuals u_{nwij} (non-compliers) and u_{cwij} (compliers) are assumed to be normally distributed with zero mean and the within-cluster variance σ^2_{nw} (non-compliers) and σ^2_{cw} (compliers), and are equal across clusters. The following model for compliance status was assumed:

$$P(C_{ij}=1)=\frac{exp\,(\sum_{l=1}^{L}\pi_{ijl}X_{ijl}+\tau_j)}{1+exp\,(\sum_{l=1}^{L}\pi_{ijl}X_{ijl}+\tau_j)}$$

Where π_{ijl} are unknown parameters and $\tau_j \sim N(0,\sigma_\tau^2)$ so that the proportion of compliers may vary across clusters. Compliance status is only known in the intervention arm. Thus, a mixture model for compliance status in the control arm would be applied. Using the full likelihood, parameter estimates of the effect among compliers are estimated

$$\hat{\delta}=(\hat{\delta}_1-\hat{\delta}_0)/\rho_c$$

where $\hat{\delta}_t$ are the average CMAI among compliers in treatment group t and where ρ_c is the proportion of compliers. $\hat{\delta}_t$ can be obtained from the above models across NHs. The variance of this estimate can be obtained via the delta method or using Markov chain Monte Carlo techniques.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Onsite Data Collection (Trial 1 Only)

Procedures for onsite data collection are detailed in the *Manual of Procedures*. Briefly, on-site data collection will be used to capture primary study outcomes of frequency of agitated and aggressive behaviors, as well as secondary quality of life and engagement outcomes. Data collectors will also capture responses to music, collect metadata from iPods, and conduct an environment scan for observable characteristics of implementation. Data collectors will be flown to Providence, RI for a three-day intensify training for on-site data collection. During data collection months (baseline, 4-, and 8-months), Brown staff will have weekly phone calls with data collectors and supervisors. Visits will occur at baseline (pre-implementation), four months (mid-implementation), and eight months (full implementation). Each visit will be two days in duration. There are several activities to be completed before, during, and after the on-site data collection visits. The following is an overview of these activities.

Before Arrival**:** Site visit dates should be arranged approximately one month in advance of the visit by the project manager. In addition to the dates for the visit (2 consecutive days), the site should be made generally aware of the staff needed for the interview portion of the data collection. Approximately one week in advance of the on-site visit, the project director should reach out again to remind the NH of the upcoming site visit and request the facilities do the following in preparation:

1. Prepare a list of the people who are currently using the program, or, in the case of baseline and 4-month visits, are likely to use the music during the intervention.
2. Schedule time with nursing staff who are able to directly speak to the behaviors of these residents. The interviews take approximately 15 minutes per resident. If possible, these interviews should be scheduled for the first day of the site visit.
3. Ensure the person most familiar with the technology (iTunes, iPods) will be available during the visit. In this email, the project director should also ask the preferred time for the data collector to arrive and the person s/he should ask for upon arrival. This information needs to be communicated to the evaluator.

On-Site (Day 1)**:** When the data collector arrives, she should first meet with the identified contact (often the administrator). The following tasks should be completed on the first day: 1) Obtain schedule for staff interview; 2) Interview staff at designated times; and 3) With assistance of staff, download metadata from personal music players.

The following information needs to be pre-populated in a secure tracking form to ensure the on-site data can be properly merged with the other administrative data used in this evaluation: resident last name, resident first name, birth month (MM), birth day (DD), birth year (YYYY), social security number (XXX-XX-XXXX), Point-Click-Care Enterprise ID (if available), and whether or not the resident has been exposed to the intervention (Y/N). The tracking form will have unique study identifiers. These unique identifiers cannot be traced to specific individuals without the tracking form, and will be used to link the staff interviews and direct observations to other administrative data integral to the study evaluation.

The data collector will interview NH staff members identified by the administration as being most familiar with the agitated and/or aggressive behaviors of the residents we will be observing during the second day of the visit. The purpose of interviewing the staff is to help us understand the frequency of behaviors. The staff member will be asked to approximate frequencies of specific resident behaviors over the past week and

estimate the amount of time staff spend attending to these behaviors. We will also ask staff to respond to items asking about the quality of life for this resident.

At the four- and eight-month site visits, the evaluator will assist staff in downloading the iPod metadata. iPod metadata refers to the information captured in iTunes when an iPod is synced via the designated M&M computer. Specifically, we are interested in capturing the following for each resident's playlist: song titles, song genres, song length, number of times a song has been played, and last time each song was played. By capturing the song length and the number of times a song has been played, we can better understand the amount of time the resident has received the intervention (approximate dose). By capturing last time the player was used, we can monitor attrition.

Off-Site (Day 1): All on-site data collection is completed assuming internet at NHs is not available or reliable. In the evening, between the first and second days, the data collector needs to: upload completed staff interviews in Qualtrics, and upload metadata to server.

On-Site (Day 2): The second day is dedicated to systematic observation of the residents, while using and not using the music. When the data collector returns the second day, she should notify the administrator or contact person that she is on-site and asked to be introduced to the nursing staff on the unit(s) where the observations will take place. Each of the residents will be observed at least 4 times during the day.

During the baseline visit none of the residents will have received the intervention. All observations will be of residents without the iPods. At the 8 month visit, all of the residents should have received the intervention and observations will be of residents while using and not using the iPods. At least four observations will be conducted for each resident: one in the morning; one mid-day; one in the late afternoon; and one with music (if music is being used for resident, else at a time chosen by data collector). At least one of the observations has to be during a meal. Residents will not be observed during any activities in which personal modesty is compromised (e.g., dressing or bathing). Whenever possible, residents will be observed in common areas, but may also be observed in their rooms with the door open or ajar. The evaluator should stand at an inconspicuous distance from the resident (minimum 5 feet from resident).

Off-Site (Day 2): All on-site data collection is completed assuming internet at NHs is not available or reliable. In the evening, after the second day, the data collector needs to: upload completed observations in Qualtrics and complete the implementation observation. The implementation observation captures direct observations of how the equipment is being stored and used by staff, and gestalt impressions of staff familiarity and buy-in. The implementation observation will be completed by the evaluator immediately after leaving the site on the second day.

All other data are derived from existing data. Please see *Section 6* which details these sources.

10.2 Data Confidentiality

Brown University's Center for Gerontology and Health Care Research will receive EMR patient-level data from partnering nursing home corporations. All four NH corporations have integrated sophisticated EMR systems in their facilities. The NH networks already have experience extracting MDS from their EMR systems for purposes of submitting mandatory, regular MDS reports to CMS. To protect patient confidentiality, the two corporations will place their data in a SSH secure server and will provide login information to Brown University. Data transfer to Brown University secure servers will be via SFTP protocol with password protection. Once the files have been uploaded to Brown University's servers they will be stored, unmodified, in a secure file location specific to these uploads. They will then be read into SAS datasets, one per file type. Brown University will then notify the facilities that the data was successfully downloaded and extracted, at which point the facilities will remove the data from their servers. All data files will be accompanied by a manifest detailing the number of distinct persons and records expected in them. Brown University will connect to the corporation servers on a monthly basis. Identifiers such as HICs and SSNs, will be included in order to be able to merge these person-level data to the data received from CMS. Brown University's information systems manager will be in charge of

the data transfer, and he will replace the HICs and SSNs fields with a Brown University-generated identification number (throughout our different data sources) to allow linkage of data for analytic purposes.

10.3 Data Management

Brown University's Center for Gerontology and Health Care Research will serve as the Data Management/Statistical Center for the METRIcAL trial. The Center will be responsible for: receiving all data from CMS (Medicare, MDS), receiving all EMR data from study facilities, linking all secondary data with primary data collected onsite, and creating an analytic file and conducting analyses. Brown University investigators and database management staff already receive national MDS, Medicare, and OSCAR data semi-annually or quarterly under several CMS DUAs. There is a well-established data base management structure to linking these files. Brown also has experience linking EMR data from facilities with CMS Medicare claims and the MDS. The integration will be easily achieved thanks to the availability of HIC and SSN personal identifiers in both the EMR data from facilities and in the CMS Medicare claims and MDS data.

10.4 Data Use Agreements

The Brown University Center for Gerontology has an extensive history of working with ResDac to obtain DUAs to use CMS MDS and Medicare data for NIH funded projects, which will be obtained for this project. Our team will ensure all DUAs are compliant with NIH requirements.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

The METRIcAL protocol was reviewed and approved by the Brown University Institutional Review Board (IRB).

Informed Consent Forms

The Brown IRB approved two waivers of individual consent. The Brown Institutional Review Board (IRB) approved a waiver of informed consent for secondary data under 45 CFR 46.116. This waiver covered the obtainment and linkages of EHR, MDS, Medicare Enrollment and Vital Status Data, and iPod metadata. The Brown IRB also approved a waiver of informed consent for the proposed primary data collection under 45 CFR 46.116. This made it possible to collect primary data for all eligible residents, and to link staff interview and direct observation data to the available secondary data.

11.2 Participant Confidentiality

The main risk to participant confidentiality is a breach of confidentiality with the use of identifiable data. All research staff involved in the study will receive training in the protection of human subjects. The procedures described here address our efforts to minimize the risk of breach of confidentiality. All data management and analyses will be conducted by the Brown Center for Long-Term Care Quality & Innovation (Q&I Center), which is administratively housed within the Center for Gerontology & Healthcare Research and which leverages Gerontology's administration and computing infrastructure. Researchers and staff have many years of experience working with identifiable data files on a large scale and have numerous security measures in place to ensure the integrity and confidentiality of the data. CMS data will be covered under the strict terms of a data use agreement (DUA). The CMS DUA will ultimately cover MDS, enrollment, and Vital Status File data. Though not required since HIPAA waivers cover the release of the resident data from the NH corporations to Brown University, if requested, we will also enter into DUAs with each of the NH corporations detailing the appropriate use of data. We will submit all executed DUAs to the IRB.

At the conclusion of this study, or by the date of retention identified in the DUA, a CMS "Certificate of Disposition" certifying the proper destruction of all data obtained from CMS will be sent to CMS. All non-CMS data will be handled in a similar restrictive manner. In addition, all output containing individual identifiable information is treated as confidential data. This information is never transferred electronically via email. Shredders are used on any printed material containing individual identifiers. We will ensure that systems are in place to minimize the risk of breach of confidentiality for all data in this trial. Brown maintains numerous confidential databases, including MDS and Medicare files, and has a high level of security built into its computing systems. We will work closely with NH corporate leadership to develop protocols to maintain a high

level of data confidentiality for extracting and merging data from their EHRs. As mentioned above, the Q&I Center leverages Gerontology's administration and computing infrastructure. Gerontology maintains numerous confidential databases and has a high level of security built into its computing system. All data received at the Center will be stripped of any HIPAA personal identifiers and assigned unique identifiers. Access to the crosswalk between personal identifiers and new unique identifiers is restricted to the systems manager, Mr. Hiris, and this information is maintained in very high-security data files. No analytic files will contain personal identifiers.

The procedures described here address our efforts to minimize the risk of breach of confidentiality. First, all staff involved in the study receive training in the protection of human subjects. Second, Brown University researchers and staff have many years of experience working with data files on a large scale and have numerous security measures in place to ensure the integrity and confidentiality of the data. We treat all output containing individual identifiable information as confidential data. This information is never transferred electronically via email or other protocols. Shredders are used on any printed material containing individual identifiers.

We maintain numerous confidential databases and have a high level of security built into our computing system. The computing infrastructure consists of a VMS cluster, which houses all substantial data, a group of Windows servers that provide computing services and infrastructure support for client systems, and client Windows PCs through which all users access our systems. Network security is provided by a combination of firewalls, local network access controls, and continuous auditing and monitoring for security breaches. All access from systems external to the LAN is limited to encrypted channels (e.g., SSL for VMS terminal sessions or VPN connections for LAN file sharing access). Unencrypted access is provided only for the CGHCR external Web site and general e-mail support functions. The VMS cluster acts as a file server for Windows clients, and file access controls are consistently applied whether access is from the VMS or Windows environment.

Security within the system is applied via Access Controlled Entries (ACEs) attached to all files on all systems. Security is applied uniformly to all files within a subtree of any file system, with the general rule that groups of users sharing a common task may read each other's files but, in most cases, not write to each other's files. VMS provides a highly-secure programming environment with ACEs applied to all objects and extremely controlled access to the larger system for individual users, as well as a versioning file system, secure batch queues and distributed processing, and efficient backup and recovery procedures. Windows clients are limited to a subset of these services (e.g., there is no way for file version information to be shown to Windows clients), but otherwise access is secured as for any other method of accessing data.

Personally- and partially-de-identified data are housed in files that are restricted to systems management or to programmers who have been identified as custodians. No data are ever moved to more "public" spaces without identification information being stripped or non-reversibly encoded. Encoding is generally done via fairly large Roman cyphers applied iteratively to the original character string. No reverse encoding is ever generated nor maintained. Any matching between personally-identified data sources is done within a secured area prior to any data being exported. Windows servers that house partially de-identified data have matching ACEs applied so that access restrictions are applied consistently with VMS-based data.

Since we use demographic covariates for many of our analyses, even the encoded data are best considered partially de-identified. ACEs restrict access to all data housed by CGHCR, such that access to any data elements on the servers is limited to those staff authorized to make such access. Authorizations are, in turn, granted by the core system's support staff upon request from a PI or other appropriate data owner. All users authorized to access CGHCR systems have access to some storage that is considered "general file sharing" but, by convention and policy, all individual or otherwise restricted data is prohibited from being stored on such space. Desktop systems are authorized to specific users, and it is assumed that they will store data they are authorized to work with on such local systems. The LAN is switched, yielding a reasonable amount of security between clients and servers within the LAN. Desktop systems are required to run current anti-virus software and are prohibited from running local file-sharing software. External analyses are run periodically to verify the security of systems within the LAN.

Similarly, the Windows servers which support the LAN are configured as a local, isolated, secure, collapsed AD forest local to our LAN. DNS, DHCP, and other critical services are secured within the context of the local forest and are not accessible externally (with the exception, of course, of VPN or RDP access from authorized client systems). Extensive monitoring is done from the VMS cluster to ensure the health and stability of the Windows forest structure, and the individual servers within it.

In summary, CGHCR's VMS computer system is highly secure and accessible only to authorized users. Within the group of authorized users, access to project data is restricted to individuals who are authorized to work on that specific research project. Access to identifiers is further restricted to the systems manager alone. Furthermore, CGHCR employees have signed an oath of confidentiality, and its violation is sufficient grounds for immediate termination.

12 ETHICAL CONSIDERATIONS

Ethical consideration for the METRIcAL trial will be in accordance with the Federal Policy for the Protection of Human Subjects (HHS Human Subjects Research 45 Code of Federal Regulations (CFR) 46).(99)

13 COMMITTEES

We have three standing committees: steering, intervention and training, and data and measurement. No adjudication is necessary since this is a pragmatic trial and the measured outcomes are not adjudicated.

The steering committee, consisting of the PI, the project director, and the project manager will have ultimate responsibility for all aspects of the study. Dr. Mor will serve as the primary liaison for the project to the NIH. The project's Steering Committee will oversee overall project direction, ensure timely submission of all requested project materials to the NIA, serve as the primary liaison between the project and the NH corporations, coordinate tasks among individual working groups, ensure project milestones are met, and review and approve all publications. The steering committee will also serve as the primary vehicle for decision-making and help resolve conflicts or divergent approaches amongst team members.

The intervention and training committee, consisting of the PI, project director, project manager, implementation lead, implementation consultants, and corporation representatives (as needed), are responsible for all aspects of implementation including: developing train-the-trainer materials; revising the Implementation Guide; training corporate staff; ensuring equipment delivery; monitoring and troubleshooting barriers to implementation; monitoring data collection activities; and conduct implementation evaluation. The implementation committee is largely responsible for the successful completion of the first and third study aims (see "Specific Aims"). The implementation team will meet twice a month or as needed.

The data and measurement committee, consisting of the PI, project director, project manager, measurement lead, statistical design and analysis lead, research team members, and intervention science lead, are responsible for: obtaining IRB approval for study; securing data use agreements and IRB approvals; identifying facilities which meet eligibility criteria; identifying and providing intervention facilities with lists of eligible residents; executing monthly transfers of EHR data; training research assistants for on-site data collection; collecting iPod, interview, and direct observation data while on-site; merging all data into a secure project database, and analyzing data. The data and measurement committee is largely responsible for the second study aim (see "Specific Aims") The data and measurement committee will meet twice and month, or as needed.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the NIA prior to submission.

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16 APPENDICES

Appendix A. Center Implementation Guide

Appendix B. Staff Interview - CMAI

Appendix C. Resident Observation - ABMI

Appendix D. Implementation Observation Tool

Appendix E. Key Informant Interview Guide - Administrator - Month 4

Appendix F. Key Informant Interview Guide - Administrator - Month 8

Appendix G. Key Informant Interview Guide - Director of Nursing - Month 4

Appendix H. Key Informant Interview Guide - Director of Nursing - Month 8

Appendix I. User-Defined Assessment