Research Protocol for Exploratory Study of Entire-body PET Scans for Multiple Sclerosis (EPSMS)*

Carl Taswell

Abstract

Basic question: *Can an entire-body positron emission tomography (PET) scanner be exploited to improve evaluation, monitoring and measurement of both peripheral and central demyelination in multiple sclerosis (MS) patients?* We assume here that demyelination outside the brain may involve the spinal cord if not also possibly some of the larger peripheral nerves outside the spinal column in a manner that may be detected with the greater sensitivity and resolution of the most recent state-of-the-art PET scanners.

Initial approach: Adopt a cost-effective and reduced-risk approach initially for an exploratory study by using commercially available and already FDA-approved PET amyloid imaging radiopharmaceuticals that also bind to myelin to follow radiotracer uptake in white matter, thereby tracking demyelination versus remyelination for MS patients in comparison with normal healthy subjects. This initial approach with the greater sensitivity and resolution of modern entire-body PET scanners when used for amyloid/myelin imaging should hypothetically enable monitoring of increased versus decreased activity in both the peripheral nervous system (PNS) and the central nervous system (CNS), rather than only imaging the brain as performed in most conventional imaging evaluations for MS patients.

Future approach: Investigate other possible radiotracers (including those not yet FDA approved) that may be useful for monitoring demyelination, neuroinflammation and/or microglial activation in both the PNS and CNS of MS patients. PET myelin imaging by PET-CT scanners will be compared with analogous imaging by PET-MR scanners.

Significance: Improved molecular imaging with new entire-body PET scanners that provide improved detection sensitivity and spatial resolution for quantitative measurement of demyelination and remyelination will support better decision-making for patient care with more robust outcome measures for monitoring therapeutic drugs evaluated in clinical trials for the treatment of multiple sclerosis.

Keywords

Contents

Administrative Information

Trial Title: Research Protocol for Exploratory Study of Entire-body PET Scans for Multiple Sclerosis (EPSMS).

Trial Registration: ClinicalTrials.gov Identifer NCT04390009 registered 14 May 2020; Brain Health Alliance Research Protocol BHA-2020-11.

WHO Data Set: Table 1 presents the WHO Trial Registration Data Set (per Version 1.3.1) as summarized for the EPSMS clinical trial.

Protocol Version: BHA-2020-11 dated 14 May 2020.

Funding: Brain Health Alliance for monetary and management support; Avid Radiopharmaceuticals for material support providing use of the Amyvid radiopharmaceutical; collaborating medical imaging centers for equipment and personnel support providing use of PET-CT scanners. Avid Radiopharmaceuticals Inc., a wholly owned subsidiary of Eli Lilly and Company, has supported this study by providing Amyvid doses free of charge. Avid Radiopharmaceuticals has not otherwise participated in the design, development, conduct, analysis, or funding of the study.

Principal Investigator: Carl Taswell, MD, PhD; Director at Brain Health Alliance, Ladera Ranch, CA; Professor at University California San Diego, La Jolla, CA.

Roles and Responsibilities: Brain Health Alliance serves as the trial sponsor. Brain Health Alliance operates as a US 501-c-3 not-for-profit organization for research and education in brain health sciences, engineering, and medicine. The Principal Investigator, Dr. Carl Taswell, has developed and written this research protocol. Dr. Taswell may be contacted by phone 1-949-481-3121 and USPS mail at 8 Gilly Flower St, Ladera Ranch, CA 92694 USA.

Introduction

Background and Rationale

Basic question: *Can an entire-body positron emission tomography (PET) scanner be exploited to improve evaluation, monitoring and measurement of both peripheral and central demyelination in multiple sclerosis (MS) patients?* We assume here that demyelination outside the brain may involve at least the spinal cord if not also possibly some of the larger peripheral nerves outside the spinal column in a manner that may be detected with the greater sensitivity and resolution of the most recent state-of-the-art PET-CT scanners such as the United Imaging uEXPLORER and the Siemens Biograph Vision PET scanners (see also Cherry *et al.* [1], Badawi *et al.* [2], and Sluis *et al.* [3]). This report describes the clinical research protocol for an initial exploratory study as an international multi-site imaging trial with collaborating partners at medical research centers with operational installations of entire-body PET-CT scanners, or of entire-body PET-MR scanners, to measure both peripheral and central demyelination in MS patients compared to normal healthy subjects.

Literature review: Demyelination in both the peripheral and central nervous systems plays a key role in the neuronal and axonal degeneration that occurs in the pathophysiology of MS (Lucchinetti *et al.* [4], Zephir *et al.* [5], Friese *et al.* [6]). To evaluate patients for the presence and severity of demyelination, magnetic resonance imaging (MRI) has been well established as the imaging modality most used in routine clinical practice (Losseff *et al.* [7], Thorpe *et al.* [8], Barkhof [9], Lycklama *et al.* [10], Bakshi *et al.* [11]). However, in recent years, molecular imaging with PET scanners has been considered as an alternative imaging modality for MS (Niccolini *et al.* [12], Moccia *et al.* [13], [14]). PET metabolic and amyloid imaging has been demonstrated to be useful and safe for monitoring neurodegenerative disorders other than MS (Anand *et al.* [15], Taswell *et al.* [16], [17]). However, the three radiopharmaceuticals currently approved by the US FDA for amyloid imaging (Amyvid F18-florbetapir, NeuraCeq F18-florbetaben, Vizamyl F18-flutemetamol) have not yet been validated as a myelin imaging probe for the routine clinical evaluation of MS patients.

Most PET amyloid imaging research studies with MS patients have used Pittsburgh compound B with C11 as the radiotracer (abbreviated as [11C]-PiB PET; see work by Stankoff [18], Glodzik *et al.* [19], Veronese *et al.* [20], Matias-Guiu *et al.* [21], Bodini *et al.* [22], Zeydan *et al.* [23]), and have successfully demonstrated the utility of this PET amyloid imaging agent for monitoring demyelination. As examples, Bodini *et al.* [24] reported that "this technique is able to quantify myelin content in multiple sclerosis (MS) lesions and to capture dynamic demyelination and remyelination over time" and Bodini *et al.* [25] concluded that "[11C]-PiB PET allows quantification of myelin dynamics in MS and enables stratification of patients depending on their individual remyelination potential, which significantly correlates with clinical disability. This technique should be considered to assess novel promyelinating drugs." In addition, some research studies with MS patients have demonstrated encouraging results with the use of F18-florbetaben (Matias-Guiu *et al.* [26]–[28]) and F18-florbetapir (Pietroboni *et al.* [29]) as the radiopharmaceuticals used for PET amyloid imaging. The images in Figure 1 with both an axial slice and a sequence of sagital slices, provided courtesy of Dr. C. Rowe (at the University of Melbourne, Australia), demonstrate the high myelin binding of the off-target white matter uptake of F18-flutemetamol in a PET brain scan negative for gray matter uptake of the amyloid radiotracer.

Moreover, in a recent editorial entitled "A new frontier for amyloid PET imaging: multiple sclerosis", Morbelli *et al.* [30] commented that

> "the development and clinical testing of remyelinating drugs is currently hindered by the lack of quantitative measures able to quantify remyelination reproducibly across the spectrum of MS... amyloid PET (AMY-PET) has also been suggested as a potential marker of WM damage in MS. In fact, all AMY-PET tracers bind to the WM, regardless of the presence or absence of beta-amyloid deposition in the adjacent GM... From a clinical trial perspective,

Table 1: WHO Trial Registration Data Set for EPSMS Clinical Trial

| Data category	Information
Primary Registry Trial Identifier	ClinicalTrials.gov Identifier NCT04390009.
Primary Registry Registration Date	14 May 2020.
Secondary Identifying Numbers	Brain Health Alliance Research Protocol BHA-2020-11.
Sources of Monetary or Material Support	Brain Health Alliance for monetary and management support; Avid Radiopharmaceuticals for material support providing use of the Amyvid radiopharmaceutical; collaborating medical imaging centers for equipment and personnel support providing use of PET-CT scanners.
Primary Sponsor	Brain Health Alliance, a US 501-c-3 not-for-profit organization for research and education in brain health sciences, engineering, and medicine.
Secondary Sponsor	None.
Contact for Public Queries	Dr. Julie Neidich, 1-949-973-7714, jneidich at BrainHealthAlliance.org, Brain Health Alliance, 8 Gilly Flower St, Ladera Ranch, CA 92694 USA.
Contact for Scientific Queries	Dr. Carl Taswell, 1-949-481-3121, ctaswell at BrainHealthAlliance.org, Brain Health Alliance, 8 Gilly Flower St, Ladera Ranch, CA 92694 USA.
Public Title	Entire-body PET Scans for Multiple Sclerosis (EPSMS).
Scientific Title	Research Protocol for Exploratory Study of Entire-body PET Scans for Multiple Sclerosis (EPSMS).
Countries of Recruitment	North America, Europe, Australia.
Health Condition Studied	Multiple sclerosis.
Interventions	Entire-body PET-CT scans with Amyvid radiopharmaceutical with study arms by different PET-CT scanners such as United Imaging uEXPLORER, Siemens Biograph Vision, and other new state-of-the-art scanners. Disclosure of imaging results from the scans.
Key Inclusion Criteria	Include for: (a) Men and women between ages 25 and 55 inclusive. (b) MS patients with advanced state of the disease as evidenced by severe disability scores (EDSS > 5) with impaired motor control of extremities. (c) Normal healthy subjects. (d) Willing and able to lie motionless on the PET-CT scanner bed for at least 10 minutes and up to 20 minutes for the duration of the PET-CT medical imaging scan.
Key Exclusion Criteria	Exclude for: (a) Any additional complicating medical illness other than MS including any other neuropsychiatric illness unrelated to MS diagnosed prior to the onset of initial symptoms of MS. (b) Pregnancy or breast feeding. (c) Diabetes or other metabolic-endocrine disorders. (d) Any known concomitant acute infection. (e) History of metastatic or locally invasive cancer. (f) Recent surgery, chemotherapy or radiation therapy.
Study Type	Non-randomized prospective longitudinal study with intervention of Amyvid radiopharmaceutical imaging with entire-body PET-CT scanners and parallel study arms corresponding to different makes and models of PET-CT scanners.
Date of First Enrollment	Anticipated after 1 January 2021.
Sample Size	None enrolled yet; planned enrollment of 20 participants.
Recruitment Status	Pending.
Primary Outcome	Amyvid radiotracer activity levels in the myelinated, demyelinated, or remyelinated white matter of MS patients compared to normal healthy subjects.
Secondary Outcome	Psychometric surveys of psychological health of participants before and after disclosure of imaging results from the PET-CT scans.
Ethics Review	Research protocol BHA-2020-11 was approved on 16 April 2020 by the Institutional Review Board of Brain Health Alliance chaired by Dr. Julie Neidich (see above Contact for Public Queries).
Completion Date	Anticipated 1 March 2022.
IPD Sharing Statement	All appropriately anonymized and de-identified individual participant data will be shared with collaborating investigators at the partnering medical imaging sites prior to publication of the trial results, and with other investigators after publication of the trial results.
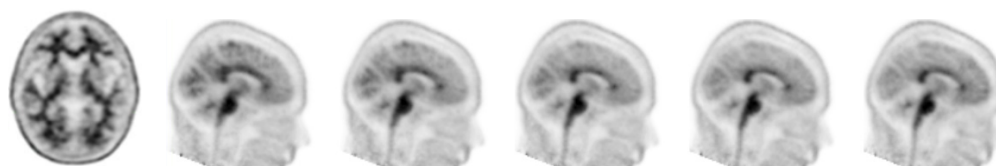
Figure 1: Myelin binding of F18-flutemetamol.

the availability of fluorinated AMY-PET tracers (with their longer halflife) already used in dementia diagnosis, may make the use of AMY-PET in tissue repair studies a realistic possibility... AMY-PET imaging in patients with MS might be a suitable tool to objectively evaluate outcome measures in proof-of-concept clinical trials as well as to validate MRI metrics of remyelination."

Finally, it should be noted that none of the literature searches completed for this pilot study project description have yet found any published study on the use of PET molecular imaging agents with MS patients for both the peripheral nervous system (PNS) and central nervous system (CNS), ie, where the entire body with peripheral nerves, spinal cord and brain were all imaged simultaneously.

Initial approach: This exploratory study proposes to adopt initially a cost-effective and reduced-risk approach by using commercially available and already FDA-approved amyloid PET tracers that also bind to myelin to measure radiotracer activity in white matter, thereby observing for demyelination versus remyelination in MS patients compared to normal healthy subjects. Patients with advanced MS as indicated by high disability scores and impaired motor control of extremities will be selected for the comparison with normal healthy subjects to increase the likelihood of detecting an appreciable difference in the spinal column and peripheral nerves between MS patients and normals. Of the three FDA-approved amyloid tracers, Vizamyl (F18-flutemetamol) has the highest binding to myelin and uptake in white matter. However, Amyvid (F18-florbetapir) is more widely and readily available. This initial approach with PET Amyvid imaging for myelin with the most recent entire-body PET-CT scanners, exploiting their dramatically improved and much greater sensitivity and resolution (Cherry et al. [1], Badawi et al. [2], Sluis et al. [3]), should hypothetically enable monitoring and measurement of increased versus decreased activity in both PNS and CNS. Institutional review board (IRB) approval has already been obtained from the IRB at Brain Health Alliance, and will also be obtained from the IRB of any collaborating institution that joins the study as an imaging site.

Next approach: At other collaborating sites with PET-MR scanners (instead of PET-CT scanners), recently published multi-modal spatial resolution enhancement methods (Grecchi et al [31]) with the wavelet transform and statistical modeling will be applied to the image processing for the brain scans as recommended by Morbelli et al. [30]. Actual PET scanning protocols for administration of the Amyvid imaging scans, whether with the PET-CT scanners or the PET-MR scanners, will be harmonized as best possible by consensus between the cooperating collaborators at the imaging sites.

Future approach: If successful with the imaging results from the initial exploratory study, the clinical trial will be extended and continued with grant applications submitted to major funding agencies for a multi-year multi-site entire-body PET imaging trial to increase the sample size and evaluate multiple serial scans for each patient instead of just a single scan per research subject. The research investigation could also be expanded to include the study of other possible radiotracers (including those not yet FDA approved) that may be useful for monitoring demyelination, neuroinflammation and/or microglial activation in both the PNS and CNS of MS patients (Matthews et al. [32] and Werry et al. [33]).

Significance: Improved molecular imaging with new entire-body PET scanners that provide improved detection sensitivity and spatial resolution for quantitative measurement of demyelination and re-

myelination will support better decision-making for patient care with more robust outcome measures for monitoring therapeutic drugs evaluated in clinical trials for the treatment of multiple sclerosis.

Objectives

To collect exploratory data using the most recent PET-CT scanners with their increased detection sensitivity and spatial resolution for the evaluation of F18-florbetapir radiopharmaceutical uptake in the nervous system of the entire body with special attention to correlation of radiotracer activity levels in the myelinated, demyelinated, or remyelinated white matter of multiple sclerosis (MS) patients compared to normal healthy subjects. The pilot study will be conducted on 20 participants as a clinical research trial of PET amyloid and myelin imaging with the *primary objective* of identifying possible differences in F18-florbetapir radiotracer activity for MS patients compared to normal healthy subjects, and the *secondary objective* of monitoring psychological health of those participants who elect to be informed of imaging results and who complete a panel of psychometric scales before and after imaging results disclosure.

Trial Design

The clinical trial study design will be established as a non-randomized prospective longitudinal cohort study following a protocol similar to that described by Taswell et al. [17] with an approximate ratio of 3:1 for MS patients to normal healthy subjects, ie, with a sample size of about 15 MS patients and 5 normal subjects. The protocol for both study groups, MS patients and normal healthy subjects, will be the same. The protocol for different study arms will be distinguished only by the make and model of the PET-CT scanner. Participants will be assigned to the collaborating partner medical imaging site closest to their residence, and will be imaged with the scanner available at that imaging site.

Methods: Participants Interventions Outcomes

Study Setting

This exploratory study has been designed as a multi-site international clinical trial with collaborations anticipated for the initial, and if extended subsequent, clinical research trials at partner imaging sites associated with the University of Melbourne, Washington University St Louis, Case Western Reserve University, Mayo Clinic, Cleveland Clinic, University California San Diego, University California Davis, University of Pennsylvania, and Thomas Jefferson University. Brain Health Alliance serves as the sponsor and management site for the EPSMS clinical trial led by Principal Investigator Dr. Carl Taswell. Brain Health Alliance will remain responsible for the design, development, conduct, analysis and funding of the research study. Collaborating partner imaging sites and their research staff may join the clinical trial as either co-investigators or service providers according to the nature and extent of their contributions to the clinical trial in a manner consistent with ethical research standards for international multi-site imaging studies.

Eligibility Criteria

Inclusion Criteria

- Adult men and women between the ages of 25 and 55 inclusive will be selected for both groups of MS patients and normal healthy subjects.

- MS patients diagnosed with an advanced state of the disease will be selected as evidenced by severe disability scores (EDSS ≥ 5.5, Kurtzke [34]) with impaired motor control of extremities.

- Participants must be able to designate a study partner (family member, relative or friend) to assist and accompany them throughout their participation in the clinical trial.

- Both the participant and study partner should reside sufficiently close to the designated imaging center for their PET scan, or otherwise must be comfortably willing and able to tolerate and to fund their own travel to the imaging site.

- Willing and able to lie motionless in a supine position on the PET-CT scanner bed for at least 10 and up to 20 minutes.

- Willing and able to give informed consent, personal contact information (phone number, email and postal address), their health care insurance information, and the contact information for their primary care or specialty care physician.

Exclusion Criteria

- MS patients with additional complicating medical illness other than MS such as major gastro-intestinal, pulmonary or cardiovascular disease, and any other neuropsychiatric illness unrelated to MS diagnosed prior to the onset of initial symptoms of MS.

- Participants who are unwilling or unable to identify a study partner to assist and accompany them.

- No direct care provider, who should be either a primary care physician or a specialty care physician such as a neurologist.

- No health insurance.

- Body weight more than 200 kilograms (440 pounds).

- Claustrophobia.

- Creatinine levels > 1.5 mg/dL or estimated glomerular filtration rate (eGFR) < 60 ml/minute.

- Recent (within 90 days) contrast enhanced CT scan.

- Any known concomitant acute infection including upper respiratory infections, genitourinary infections, etc.

- History of metastatic or newly (last 5 years) diagnosed locally invasive cancer.

- Chemotherapy in the last 5 years.

- Radiation therapy in the last 3 years.

- Major surgery within the last 6 months.

- Pregnancy or breast-feeding.

- Diabetes or other metabolic-endocrine disorders.

- Inmates from jails or prisons, and involuntary patients committed to psychiatric hospitals.

- Standard MRI contraindications will be applied which include: (a) having a pacemaker or other implanted electronic device, (b) metal foreign bodies, aneurysm clips, heart valve prosthesis, vascular stents, cochlear implants, embolization coils, gunshot wounds with retained bullet fragments, certain types of penile implants, and certain types of intrauterine devices.

The MRI contraindications will be applied to the initial exploratory study (even though it is PET-CT only) to enable those early participants in this pilot study to transition later to the extended clinical trial, presumed to involve both PET-CT and PET-MR scanners in a future multi-year study with serial scans.

Interventions

Study Groups and Study Arms

In addition to psychometrics for psychological health (Taswell *et al.* [17]) on an opt-in or opt-out basis, both MS patients and normal healthy participants will be followed with a clinician-observed disability scale (Kurtzke [34]) and a patient-reported disability scale (Collins *et al.* [35]). MS patients will be sub-grouped as walkers or non-walkers, and may also be followed with other assessments including the Multiple Sclerosis Functional Composite (MSFC) [36] and the Brief International Cognitive Assessment for MS (BICAMS) [37]. All study participants will be (a) required to sign informed consent, (b) provided counseling by a neuropsychiatrist before and after the PET imaging, (c) required to participate in the psychological health monitoring with completion of psychometrics before and after disclosure of the PET imaging results if electing to be informed of the imaging results, (d) given the opportunity to decline participation in the imaging results disclosure process in which case they will not be informed of the Amyvid imaging results involving the nervous system that do not otherwise require emergent medical response and intervention, (e) if opting into the imaging results disclosure process, given the opportunity to be informed about findings related to nervous system grey matter, nervous system white matter, or both grey and white matter, and (f) given the opportunity to continue in a longer term study in the event that the pilot study with a single scan per subject is extended to a multi-year study with serial scans over time for the MS patients. Thus, the protocol for both study groups, MS patients and normal healthy subjects, will be the same. However, the protocol for different study arms will be distinguished only by the make and model of the PET-CT scanner, for example, the United Imaging uEXPLORER or Siemens Biograph Vision. Participants will be assigned to the collaborating partner imaging site closest to their residence, and will be imaged with the scanner available at that imaging site.

Special Circumstances

Multiple sclerosis patients with advanced disease are often treated with immunosuppressants, and remain at much greater risk of infection during a global viral pandemic. Start of this clinical trial for multiple sclerosis patients will be delayed and deferred until after progress

has been made by government authorities with more clarity about the public health management of the Covid-19 pandemic, and greater safety can be better assured for multiple sclerosis patients to participate in this exploratory study. Assuming the dangers of the Covid-19 pandemic lessen by 2021 with the arrival of safe and effective vaccines and/or anti-viral therapies, then the EPSMS clinical trial may begin sometime next year in 2021.

PET-CT Imaging Scans

Radiopharmaceutical: Amyvid (F18-florbetapir) was approved by the US FDA in 2012 (see Alzforum [38]), and has been used in both research trials and clinical practice extensively for almost a decade now without concerns for any major adverse events. The most common adverse reaction has been headache affecting less than 2% of individuals who undergo PET scans with the radiopharmaceutical as reported in the FDA-approved package insert for the prescribing information (Eli Lilly and Company [39]) which also details other uncommon side effects such as nausea, dizziness, anxiety, insomnia, *etc.*. As noted by Trembath *et al.* [40], "amyloid PET radiopharmaceuticals, used as directed in the product labeling, result in an effective whole-body dose of radiation that is similar to that from an F18-FDG PET scan (7 mSv for 370 MBq [10 mCi] of F18-FDG)."

PET-CT scanner: All PET scans will be performed on state-of-the-art PET-CT scanners such as the United Imaging uEXPLORER, the Siemens Biograph Vision, the GE Discovery MI, the Phillips Vereos, the Canon Cartesion Prime, similar models from the same manufacturers, and/or other comparable PET-CT scanners if and when they become available at collaborating partner imaging sites.

Imaging protocol: PET scans with a radiotracer for amyloid imaging (Rowe *et al.* [41]), hypothesized also to be useful for myelin imaging, will be performed according to a standardized protocol described by Trembath *et al.* [40] to facilitate comparison with other amyloid imaging studies such as the IDEAS study by Rabinovici *et al.* [42]. As discussed by Trembath *et al.* [40], "the recommended dose of F18-florbetapir is 370 MBq (10 mCi) in a maximum volume of 10 mL administered via intravenous bolus, followed by a saline flush" with PET images acquired for 10 minutes beginning 50 minutes after intravenous injection. Radiopharmaceutical doses used will be no greater than those described by Trembath *et al.* [40], but may be lower if possible as permitted by the greater sensitivity and resolution of the new PET scanners ([1]–[3]). PET scans performed at the imaging sites will be supervised and monitored by board certified nuclear medicine physicians who will manage and treat any allergic reaction to the Amyvid radiopharmaceutical that may be experienced by a research participant if and when such a rare adverse event occurs.

There are no special preparations required for participants prior to arriving at the scanner site on the day of their PET imaging visit. A nuclear medicine technologist will screen the participants to evaluate their readiness for the PET-CT scan with the required form approved by the local imaging center. A urine pregnancy test will be administered at no charge to all women of child-bearing potential. An intravenous (IV) line will be placed in the forearm by the study PET-CT technologist or nuclear medicine physician and the participant will be positioned supine on the scanner bed. Approximately 10 ± 2 mCi of F18-florbetapir (Amyvid from Avid Radiopharmaceuticals) will be hand injected through the IV and at the 50 minute timepoint post-injection, a 10-minute PET acquisition scan will begin on the PET-CT scanner. For those subjects who can tolerate a longer scan without significant discomfort, and who elect to do so via an opt-in process, the 10-minute scan (from 50 - 60 minute timepoints post-injection) will be continued and extended to a 20-minute scan (from 50 - 70 minute timepoints post-injection). This PET scan will be followed by an ultra low-dose (estimated at 1-2 mSv) CT scan. The IV line will be removed after completion of the PET and CT scans.

Image Reconstruction and Analysis: Data from the PET-CT scanner will be acquired in listmode. Data from the CT scan will be used for attenuation correction when processing the data from the PET scan. Data will be reconstructed using the PET-CT scanner manufacturer's recommendations.

Risk summary: With each participant imaged by only a single PET-CT scan in this initial exploratory study, participants' exposure to radiation from the CT component of the PET-CT scanner and radioactivity from the Amyvid radiopharmaceutical will be no greater in amount, with no greater risk of adverse events, than that experienced already in the past by the many individuals who have safely tolerated PET-CT scans with Amyvid over the past decade.

Outcomes

Psychometrics, MS disability scores, and PET imaging results for the participant groups will be analyzed with statistical methods similar to those described by Taswell *et al.* [16], [17]. PET scan images will be examined for relative increases and/or decreases in local radiotracer activity in target regions compared to reference regions, both qualitatively and quantitatively in an exploratory manner to discover any potential differences between MS patients and normal healthy subjects. Quantitative analysis for PET amyloid imaging SUV ratios (see methods used in recent study by Chiao *et al.* [43]), and analogously for myelin imaging SUV ratios, will examine different reference regions in the brain and spinal cord for comparison of relative increases or decreases of activity in the target regions of the brain and spinal cord. Identified lesions for each subject will be located, counted and measured in the brain, spinal cord and peripheral nerve roots.

Timelines

Subject participation: All subjects in both study groups, ie, in the MS patient group and the normal healthy subject group, will participate in the same study protocol involving one imaging visit of a half day, and possibly two educational counseling visits of a quarter day each before and after the imaging visit if the participant elects to be informed of the imaging results.

Enrollment duration: We anticipate completing enrollment within 6 months after start of the study.

Data analysis duration: We anticipate completing initial data analysis within 12 months after start of the study.

Study initiation: Start of the study will be deferred until after concerns subside about COVID-19 and the current global viral pandemic. MS patients will not be invited to participate in the study until after public health authorities stabilize and normalize the situation with regard to public health precautions that include physical distancing to prevent the spread of the virus.

Sample Size

Discussions on sample size for pilot studies have been published by Lancaster *et al.* [44], Moore *et al.* [45], and Whitehead *et al.* [46]. Because the EPSMS clinical trial will begin as an exploratory pilot study limited to an initial small number of participants for a novel approach to use of PET-CT scanners and F18-florbetapir for monitoring demyelination and remyelination in multiple sclerosis, no formal statistical power analysis has been presented for this pilot study . Instead, exploratory data analysis will be conducted to examine the distribution of the data which will be obtained from the small sample size of only 20 subjects expected to participate in the study.

Participant Recruitment

The initial pilot study will recruit 20 participants with an approximate ratio of 3:1 for MS patients to normal healthy subjects. This ratio has been chosen in order to allocate more of the Amyvid doses to scans for MS patients than to scans for normal subjects in this pilot study. Allocating more of the doses to the MS patients will improve the chances of observing differences between the MS patients as well as observing topographic differences of activity throughout CNS and PNS for any individual MS patient. These MS patients will be recruited via publicity at the web sites of Brain Health Alliance, the various multiple sclerosis organizations including the National Multiple Sclerosis Society, and clinical neurology departments including potential collaborations with those at the University of Melbourne, Mayo Clinic, Washington University St Louis, University California San Diego, University California Davis, Case Western Reserve University, University of Pennsylvania, and Thomas Jefferson University. Normal healthy subjects may be recruited with the assistance of successfully recruited MS patients so that each pair of healthy subject and MS patient can serve as mutual study partners for each other.

At the time of the consenting and screening visit, a study-specific inclusion and exclusion criteria form will be used to determinate eligibility for this study after obtaining informed consent. The consenting and screening visit with the subject will occur via televideo conferencing or at the subject's referring doctor's office not earlier than 4 weeks before the imaging visit at the scanner site. Study participants will be screened for eligibility at the time of the consenting and screening visit after signing the consent form. All subjects must submit their medical records from their primary care physician including recent laboratory results. The study doctor will review the results (in the subjects to whom any of these tests apply) and will report on the screening form the results and will state eligibility of the subject for the study.

Methods: Data Collection Management Analysis

Data Collection

At the time of PET-CT scan data acquisition, subject identifiable information will be entered in the research database, nuclear medicine department's medical imaging system (MIS), Radimetrics dose reporting system and electronic medical record (EMR) used by the local imaging center. Electronic image files, radiation dose reports and pertinent medical information will be stored on dedicated encrypted password-protected hard disks and workstations at the local imaging center, then also submitted to and shared with the research study

management site at Brain Health Alliance, which research staff may access. For use with staff who must interact directly with research participants, electronic files will contain the requisite patient identifiers to assure that data is recorded correctly and consistently. However, when this data is transferred for analysis by other staff on other computers or devices, it will be appropriately de-identified and anonymized. Research participants will be assigned a unique code number used to identify them in a separate database maintained independently of the database used for tracking de-identified participants. Only members of the research study team will have access to the data.

Data Management

All imaging data will be banked indefinitely for future use. Data will be stored on the computers at the local imaging center scanner site, also transmitted to and stored on the computers at the Brain Health Alliance study management site, on dedicated encrypted password-protected hard disks and workstations with access limited to authorized personnel. Electronic image files, radiation dose reports and pertinent medical information will be stored on the nuclear medicine department MIS and EMR systems at the local imaging center. A radiation dose report will be generated. This radiation dose report will be part of the banked data and will contain Protected Health Information. It will be sent to the Radimetrics system, which is a mandated tracking system for lifetime radiation dose. Future use of banked data may include improved image analysis, use as a normal atlas comparator, and use for other research purposes. Anonymous data may be shared with other entities if appropriate data use agreements are in place. The names and locations of these entities will be added to this protocol prior to sharing data via IRB-approved modifications.

Statistical Methods

Psychometrics, MS disability scores, and PET imaging results for the participant groups will be analyzed with statistical methods similar to those described by Taswell *et al.* [16], [17]. Image quality, quantitative comparisons and preliminary biodistribution data collection will be performed by means of regions of interest (ROIs) drawn in different organs and tissue types where pixel intensity and coefficient of variation within ROIs will be computed and recorded. Graphical methods including box-plots and histograms will be employed to examine the distributions of the measures. For all continuous variables, robust descriptive statistics, including medians, interquartile ranges, and percentiles will be computed. For categorical data, frequency, proportions, and percentages will be calculated. For calculation of effect sizes for differences, robust statistical estimators recently developed by Taswell and Taswell [47] will be used.

Withdrawal of Subjects

Subjects will be withdrawn from the study without their consent if: (a) They do not follow the study rules or they no longer meet the requirements to participate in the study. (b) The study is stopped by the sponsor or researcher investigators. (c) The study doctors and/or research staff feel it is in the participant's best interest to discontinue participation. Such circumstances may include adverse events such as unanticipated discomfort from lying on the scanner bed, or feelings of claustrophobia from being inside the scanner bore.

Methods: Monitoring

Data Safety Monitoring

Throughout the research study, members of the research team will consult with the Radiation Safety Officer and Institutional Review Board (IRB) at each collaborating local imaging center regarding the monitoring and reporting of adverse events and follow their recommendations. Any protocol changes involving the radiation dose will require and receive approvals from the local Radiation Use Committee prior to submitting a modification request to the local IRB at the imaging site. Protocol changes will not be implemented prior to local IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects. If any incidental findings or adverse events occur, they will be managed as described below.

Incidental Findings and Adverse Events

PET-CT images obtained in this study are intended for research. They are not meant to evaluate the subject's health as they would if obtained as part of a clinical (non-research) visit to an imaging clinic or medical center. These research scans will not receive routine clinical review by radiologists specially trained to interpret PET-CT scans. As a consequence, not all abnormalities or incidental findings, especially those unrelated to the nervous system, may be noticed by the research investigators examining the PET-CT scans. However, if during the research management of these PET-CT images, the PET-CT technicians performing the research scan does notice a possible concern, they will notify the study doctor, who will obtain consultation with a subspecialized radiologist on the questions. When the clinical radiologist examines the images, the subject's name will not be revealed in order to protect the subject's identity.

The study doctor will discuss these possible concerns with the subject within 4 weeks if not critical, or else immediately upon recognition of any critical finding that requires urgent intervention as required by the critical findings policy of the local imaging center where the PET-CT scan was acquired. The study doctor will assist the subject to obtain a more complete review of his/her PET-CT scan by a trained subspecialized physician who can determine if any clinical health condition may be present. If the specialist remains concerned about the presence of an active clinical problem, then the subject will be given a copy of the PET-CT scan to take to the physician of his/her choice. If the subject prefers, the PET-CT scans can be sent electronically. However, such digital transfers do incur a small risk that another person could view the files sent electronically via the internet.

A letter will be sent to the subject's chosen doctor stating that (i) the subject agreed to enroll in this research study, (ii) the images were collected and incidental findings that may be related to a medical condition were observed by the research study doctor and/or a specialist physician at the imaging center; (iii) the subject was provided with images that can be taken to the subject's doctor; (iv) the images did not receive any dedicated routine clinical review and all abnormalities may not necessarily have been noticed; (v) the PET-CT images were obtained for research and were not meant to evaluate the patient's health as they would be if they were part of a clinical (non-research) visit to an imaging clinic, doctor or hospital; (vi) the subject's personal physician may contact the research study doctor at any time regarding any concerns about the research study or the subject's PET-CT imaging results.

If there are any incidental findings or adverse events that cause the subject to fail the inclusion/exclusion criteria (e.g. marked claustrophobia or allergic reaction with an incomplete scan, incidental finding of metastatic cancer, etc.), these occurrences will be reported and the subject will be excluded from the study. Another participant will be added to the study to meet the recruitment target number of subjects.

Auditing and Breach of Confidentiality

Quality control will include regular data verification and protocol compliance checks by the management site PI and by the local imaging site coordinator or co-investigator. Confidentiality will be protected through periodic assessment, as new study materials and communication methods among research staff develop. Breaches of confidentiality at any local imaging center will be reported both to the local IRB and to the PI at the BHA management site using the forms required by both the local IRB and the BHA management site.

Ethics and Dissemination

Potential Benefits to Subjects

The benefit to subjects from joining the research study will be, contingent on their agreement to participate in the disclosure of imaging results to their treating physician, that their direct care provider may receive the imaging results from their PET scan and may use that information in supporting their future care. Additionally, subjects may benefit from increased knowledge about the PET scan's influence on clinical decision making and medical outcomes when the research study results become available. In the future, knowledge learned during this study could help guide the appropriate use of PET scan imaging in patients whose conditions are difficult to diagnose and monitor.

Potential Risks to Subjects

Risks to subjects may include adverse events, radiation risks, and unknown possible consequences related to incidental finding from the PET-CT scan:

- Discomfort and/or fatigue from lying on the scanner bed.

- Claustrophobic symptoms while lying inside the scanner bore.

- Bruising and/or infection at the IV site used for administering the Amyvid radiopharmaceutical.

- Adverse events in response to the Amyvid radiopharmaceutical including the possibility of an allergic reaction.

- Radiation risks: This study involves a radiation exposure that is typical of other diagnostic tests using ionizing radiation. The amount of radiation exposure received in this study remains limited to levels lower than those believed to result in any significant risk of harmful effects.

- Incidental findings: The PET-CT scan may detect possible incidental findings and/or false positive findings that may require clinical follow-up (ie, non-research imaging, medical or surgical

health care) associated with all the risks that accompany these subsequent medical or surgical procedures if pursued. Such risks range from minor to major including permanent disabilities and death. If any incidental findings are detected by the PET scan, then these results will be managed as described above.

Economic Burden to Subjects

Subjects will not be charged for their participation in this research study. In case of abnormal, uncertain and/or incidental findings, the subject may decide in agreement with his/her referring specialist doctor or primary care doctor to further investigate and the cost of this health care will be borne by the subject and/or his/her insurance.

Community-Based Participatory Research

This research study does not involve community-based participatory research.

Investigational Drugs or Devices

There are *not* any investigational drugs or devices involved in this research study.

Review Requirements

There are *not* any contractual obligations or other considerations that require IRB review of this research, or review at intervals other than those required by the US FDA or Common Rule.

Research Ethics Approval

This Brain Health Alliance research protocol BHA-2020-11 has been approved by the BHA Institutional Review Board chaired by Dr. Julie Neidich of Washington University St Louis. This protocol has also been approved by the UC Davis Health Radiation Use Committee.

Protocol Amendments

The PI and members of the research team will consult with the Radiation Safety Officer and Institutional Review Board (IRB) at each collaborating local imaging center prior to making any changes in the study protocol. If any changes are made to the study protocol, then all relevant parties will be notified promptly.

Informed Consent

Informed consent for all study participants will be obtained by the PI and research team at Brain Health Alliance. Additional informed consent may also be obtained by collaborating investigators or service providers at each local imaging site where the PET-CT scans are performed.

Provisions to Protect the Privacy Interests of Subjects

The investigator obtaining consent from the research participant will meet with the candidate in a private setting and will dedicate sufficient time to explain the study procedures and answer any questions. It will be explained that participation is strictly voluntary and declining to participate will not affect them in any way. A HIPAA disclosure form will be signed by research participants residing in USA to allow access to their medical records. Research participants who reside in other countries will be asked to sign any corresponding disclosure form if their jurisdiction of residence requires it.

Sharing of Results with Subjects

PET scan results for each subject will be shared with that subject and their direct care physician on an opt-in or opt-out basis with respect to the findings regarding either nervous system grey matter, nervous system white matter, both or neither as described above. Moreover, if any incidental findings unrelated to the nervous system may be detected by the PET scan, these imaging results will be managed as described above.

Compensation for Research-Related Injury

If a research subject is injured as a result of participating in this imaging study, the medical center associated with the local imaging site will provide the necessary medical treatment. Depending on the circumstances, the costs of this medical treatment may be covered by the local medical center or may be billed to the participant's health insurance company in a manner similar to that for other health care costs. However, the local imaging site and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, the subject may contact the local imaging site and medical center where the research participant obtains the PET-CT scan.

Dissemination Policy

All appropriately anonymized and de-identified individual participant data will be shared with collaborating investigators at the partnering medical imaging sites prior to publication of the trial results, and with other investigators after publication of the trial results.

Acknowledgments

Appendix

Biological Specimens: Biological specimens (urine and blood samples) are used only for screening purposes. After the results are

recorded the biological specimens will be discarded.

Informed Consent: Publicly available as the document "Participant Informed Consent for Exploratory Study of Entire-body PET Scans for Multiple Sclerosis (EPSMS)".

Citation

References

[1] S. R. Cherry, T. Jones, J. S. Karp, *et al.*, "Total-body PET: Maximizing sensitivity to create new opportunities for clinical research and patient care," *Journal of Nuclear Medicine*, vol. 59, no. 1, pp. 3–12, Jan. 2018. DOI: 10.2967/jnumed.116.184028.

[2] R. D. Badawi, H. Shi, P. Hu, *et al.*, "First human imaging studies with the EXPLORER total-body PET scanner," *Journal of Nuclear Medicine*, vol. 60, no. 3, pp. 299–303, Feb. 2019. DOI: 10.2967/jnumed.119.226498.

[3] J. van Sluis, J. de Jong, J. Schaar, *et al.*, "Performance characteristics of the digital biograph vision PET/CT system," *Journal of Nuclear Medicine*, vol. 60, no. 7, pp. 1031–1036, Jan. 2019. DOI: 10.2967/jnumed.118.215418.

[4] C. Lucchinetti, W. Brück, J. Parisi, *et al.*, "Heterogeneity of multiple sclerosis lesions: Implications for the pathogenesis of demyelination," *Annals of Neurology*, vol. 47, pp. 707–717, 2000.

[5] H. Zephir, T. Stojkovic, P. Latour, *et al.*, "Relapsing demyelinating disease affecting both the central and peripheral nervous systems," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 79, no. 9, pp. 1032–1039, Feb. 2008. DOI: 10.1136/jnnp.2006.108290.

[6] M. A. Friese, B. Schattling, and L. Fugger, "Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis," *Nature Reviews Neurology*, vol. 10, no. 4, pp. 225–238, Mar. 2014. DOI: 10.1038/nrneurol.2014.37.

[7] N. A. Losseff, S. L. Webb, J. I. O'Riordan, *et al.*, "Spinal cord atrophy and disability in multiple sclerosis," *Brain*, vol. 119, no. 3, pp. 701–708, 1996. DOI: 10.1093/brain/119.3.701.

[8] J. W. Thorpe, D. Kidd, I. F. Moseley, *et al.*, "Spinal MRI in patients with suspected multiple sclerosis and negative brain MRI," *Brain*, vol. 119, no. 3, pp. 709–714, 1996. DOI: 10.1093/brain/119.3.709.

[9] F. Barkhof, "MRI in multiple sclerosis: Correlation with expanded disability status scale (EDSS)," *Multiple Sclerosis Journal*, vol. 5, no. 4, pp. 283–286, Aug. 1999. DOI: 10.1177/135245859900500415.

[10] G. Lycklama, A. Thompson, M. Filippi, *et al.*, "Spinal-cord MRI in multiple sclerosis," *The Lancet Neurology*, vol. 2, no. 9, pp. 555–562, Sep. 2003. DOI: 10.1016/S1474-4422(03)00504-0.

[11] R. Bakshi, A. J. Thompson, M. A. Rocca, *et al.*, "MRI in multiple sclerosis: Current status and future prospects," *The Lancet Neurology*, vol. 7, no. 7, pp. 615–625, Jul. 2008. DOI: 10.1016/S1474-4422(08)70137-6.

[12] F. Niccolini, P. Su, and M. Politis, "PET in multiple sclerosis," *Clinical Nuclear Medicine*, vol. 40, no. 1, e46–e52, Jan. 2015. DOI: 10.1097/RLU.0000000000000359.

[13] M. Moccia and O. Ciccarelli, "Molecular and metabolic imaging in multiple sclerosis," *Neuroimaging Clinics of North America*, vol. 27, no. 2, pp. 343–356, May 2017. DOI: 10.1016/j.nic.2016.12.005.

[14] M. Moccia, N. de Stefano, and F. Barkhof, "Imaging outcome measures for progressive multiple sclerosis trials," *Multiple Sclerosis Journal*, vol. 23, no. 12, pp. 1614–1626, Oct. 2017. DOI: 10.1177/1352458517729456.

[15] K. Anand and M. Sabbagh, "Amyloid imaging: Poised for integration into medical practice," *Neurotherapeutics*, vol. 14, no. 1, pp. 54–61, Aug. 2017. DOI: 10.1007/s13311-016-0474-y.

[16] C. Taswell, V. L. Villemagne, P. Yates, *et al.*, "18F-FDG PET improves diagnosis in patients with focal-onset dementias," *Journal of Nuclear Medicine*, vol. 56, no. 10, pp. 1547–1553, 10 Oct. 2015, published online 6 Aug 2015, ISSN: 1535-5667. DOI: 10.2967/JNUMED.115.161067.

[17] C. Taswell, C. Donohue, M. T. Mastwyk, *et al.*, "Safety of disclosing amyloid imaging results to MCI and AD patients," *Mental Health in Family Medicine*, vol. 14, pp. 748–756, 2 2018. url: http://mhfmjournal.com/pdf/MHFM-120.pdf.

[18] Stankoff, "Imaging central nervous system myelin by PET in MS using C11-PiB," *Ann Neurol*, vol. 69, no. 4, pp. 673–680, Feb. 2011. DOI: 10.1002/ana.22320.

[19] L. Glodzik, H. Rusinek, J. Li, *et al.*, "Reduced retention of Pittsburgh compound B in white matter lesions," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 42, no. 1, pp. 97–102, Oct. 2014. DOI: 10.1007/s00259-014-2897-1.

[20] M. Veronese, B. Bodini, D. García-Lorenzo, *et al.*, "Quantification of [11C]-PIB PET for imaging myelin in the human brain: A test-retest reproducibility study in high-resolution research tomography," *Journal of Cerebral Blood Flow & Metabolism*, vol. 35, no. 11, pp. 1771–1782, Jun. 2015. DOI: 10.1038/jcbfm.2015.120.

[21] J. A. Matías-Guiu, M. N. Cabrera-Martín, C. Oreja-Guevara, *et al.*, "Pittsburgh compound B and other amyloid positron emission tomography tracers for the study of white matter and multiple sclerosis," *Annals of Neurology*, vol. 80, no. 1, pp. 166–166, May 2016. DOI: 10.1002/ana.24666.

[22] B. Bodini, M. Veronese, F. Turkheimer, *et al.*, "Benzothiazole and stilbene derivatives as promising positron emission tomography myelin radiotracers for multiple sclerosis," *Annals of Neurology*, vol. 80, no. 1, pp. 166–167, May 2016. DOI: 10.1002/ana.24667.

[23] B. Zeydan, V. J. Lowe, C. G. Schwarz, *et al.*, "Pittsburgh compound-B PET white matter imaging and cognitive function in late multiple sclerosis," *Multiple Sclerosis Journal*, vol. 24, no. 6, pp. 739–749, May 2017. DOI: 10.1177/1352458517707346.

[24] B. Bodini and B. Stankoff, "Imaging central nervous system demyelination and remyelination by positron-emission tomography," *Brain Plasticity*, vol. 2, no. 1, pp. 93–98, Dec. 2016, ISSN: 2213-6304. DOI: 10.3233/BPL-160042.

[25] B. Bodini, M. Veronese, D. García-Lorenzo, *et al.*, "Dynamic imaging of individual remyelination profiles in multiple sclerosis," *Annals of Neurology*, vol. 79, no. 5, pp. 726–738, May 2016. DOI: 10.1002/ana.24620.

[26] J. A. Matías-Guiu, M. N. Cabrera-Martín, J. Matías-Guiu, *et al.*, "Amyloid PET imaging in multiple sclerosis: An 18F-florbetaben study," *BMC Neurology*, vol. 15, no. 1, Nov. 2015. DOI: 10.1186/s12883-015-0502-2.

[27] J. A. Matías-Guiu, C. Oreja-Guevara, M. N. Cabrera-Martín, *et al.*, "Amyloid proteins and their role in multiple sclerosis: Considerations in the use of amyloid-PET imaging," *Frontiers in Neurology*, vol. 7, Mar. 2016. DOI: 10.3389/fneur.2016.00053.

[28] J. A. Matías-Guiu, M. N. Cabrera-Martín, A. Cortés-Martínez, *et al.*, "Amyloid PET in pseudotumoral multiple sclerosis," *Multiple Sclerosis and Related Disorders*, vol. 15, pp. 15–17, Jul. 2017. DOI: 10.1016/j.msard.2017.05.002.

[29] A. M. Pietroboni, T. Carandini, A. Colombi, *et al.*, "Amyloid PET as a marker of normal-appearing white matter early damage in multiple sclerosis: Correlation with CSF □-amyloid levels and brain volumes," *European Journal of Nuclear Medicine and Molecular Imaging*, Oct. 2018. DOI: 10.1007/s00259-018-4182-1.

[30] S. Morbelli, M. Bauckneht, S. Capitanio, *et al.*, "A new frontier for amyloid PET imaging: Multiple sclerosis," *European Journal of Nuclear Medicine and Molecular Imaging*, Dec. 2018. DOI: 10.1007/s00259-018-4232-8.

[31] E. Grecchi, M. Veronese, B. Bodini, *et al.*, "Multimodal partial volume correction: Application to [11c]PIB PET/MRI myelin imaging in multiple sclerosis," *Journal of Cerebral Blood Flow & Metabolism*, vol. 37, no. 12, pp. 3803–3817, Jun. 2017. DOI: 10.1177/0271678X17712183.

[32] P. M. Matthews and G. Datta, "Positron-emission tomography molecular imaging of glia and myelin in drug discovery for multiple sclerosis," *Expert Opinion on Drug Discovery*, vol. 10, no. 5, pp. 557–570, Apr. 2015. DOI: 10.1517/17460441.2015.1032240.

[33] E. L. Werry, F. M. Bright, O. Piguet, *et al.*, "Recent developments in TSPO PET imaging as a biomarker of neuroinflammation in neurodegenerative disorders," *International Journal of Molecular Sciences*, vol. 20, no. 13, p. 3161, Jun. 2019. DOI: 10.3390/ijms20133161.

[34] J. F. Kurtzke, "Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)," *Neurology*, vol. 33, no. 11, pp. 1444–1444, Nov. 1983. DOI: 10.1212/wnl.33.11.1444.

[35] C. D. Collins, B. Ivry, J. D. Bowen, *et al.*, "A comparative analysis of patient-reported expanded disability status scale tools," *Multiple Sclerosis Journal*, vol. 22, no. 10, pp. 1349–1358, Jul. 2016. DOI: 10.1177/1352458515616205.

[36] G. R. Cutter, "Development of a multiple sclerosis functional composite as a clinical trial outcome measure," *Brain*, vol. 122, no. 5, pp. 871–882, May 1999. DOI: 10.1093/brain/122.5.871.

[37] R. H. Benedict, M. P. Amato, J. Boringa, *et al.*, "Brief international cognitive assessment for MS (BICAMS): International standards for validation," *BMC Neurology*, vol. 12, no. 1, Jul. 2012. DOI: 10.1186/1471-2377-12-55.

[38] Alzforum, Ed. (Apr. 9, 2012). "FDA approves Amyvid for clinical use," url: https://www.alzforum.org/news/research-news/fda-approves-amyvid-clinical-use.

[39] Eli Lilly and Company, Ed. (Dec. 2, 2013). "Amyvid (florbetapir f 18 injection) for intravenous use: Highlights of prescribing information (revised)," url: https://pi.lilly.com/us/amyvid-uspi.pdf.

[40] L. Trembath, M. Newell, and M. D. Devous, "Technical considerations in brain amyloid PET imaging with 18f-florbetapir," *Journal of Nuclear Medicine Technology*, vol. 43, no. 3, pp. 175–184, Aug. 2015. DOI: 10.2967/jnmt.115.156679.

[41] C. C. Rowe and V. L. Villemagne, "Brain amyloid imaging," *Journal of Nuclear Medicine Technology*, vol. 41, no. 1, pp. 11–18, Feb. 2013. DOI: 10.2967/jnumed.110.076315.

[42] G. D. Rabinovici, C. Gatsonis, C. Apgar, *et al.*, "Association of amyloid positron emission tomography with subsequent change in clinical management among medicare beneficiaries with mild cognitive impairment or dementia," *JAMA*, vol. 321, no. 13, p. 1286, Apr. 2019. DOI: 10.1001/jama.2019.2000.

[43] P. Chiao, B. J. Bedell, B. Avants, *et al.*, "Impact of reference and target region selection on amyloid PET SUV ratios in the phase 1b PRIME study of aducanumab," *Journal of Nuclear Medicine*, vol. 60, no. 1, pp. 100–106, May 2018. DOI: 10.2967/jnumed.118.209130.

[44] G. A. Lancaster, S. Dodd, and P. R. Williamson, "Design and analysis of pilot studies: Recommendations for good practice," *Journal of Evaluation in Clinical Practice*, vol. 10, no. 2, pp. 307–312, May 2004. DOI: 10.1111/j..2002.384.doc.x.

[45] C. Moore, R. Carter, P. Nietert, *et al.*, "Recommendations for planning pilot studies in clinical and translational research," *Clinical and Translational Science*, vol. 4, no. 5, pp. 332–337, 2011. DOI: 10.1111/j.1752-8062.2011.00347.x.

[46] A. L. Whitehead, S. A. Julious, C. L. Cooper, *et al.*, "Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable," *Statistical Methods in Medical Research*, vol. 25, no. 3, pp. 1057–1073, Jun. 2015. DOI: 10.1177/0962280215588241.

[47] S. K. Taswell and C. Taswell, "Generalizing effect sizes for differences with an alternative to cohen's d coefficient," in *International Biometric Society XXXIst Conference of the Austro-Swiss Region (ROeS)*, (Sep. 9, 2019), Lausanne, Switzerland, 2019. url: brainhealthalliance.org/pub/docs/ROES2019RGES0828.pdf.