PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol of The Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research (CHARIOT): Prospective Readiness cOhort (PRO) SubStudy
AUTHORS	Udeh-Momoh, Chinedu; Watermeyer, Tamlyn; Price, Geraint; de-Jaegar Loots, Celeste; Reglinska-Matveyev, Natalia; Ropacki, Michael; Ketter, Nzeera; Fogle, Michael; Raghavan, Nandini; Arrighi, Michael; Brashear, Robert; Di, Jianing; Baker, Susan; Giannakopoulou, Parthenia; Robb, Catherine; Bassil, Darina; Cohn, Martin; McLellan-Young, Heather; Crispin, Jennifer; Lakey, Kristina; Lisa, Curry; Chowdary Seemulamoodi, Yellappa; Kafetsouli, Dimitra; Perera, Dinithi; Car, Josip; Majeed, Azeem; Ward, Heather; Ritchie, Karen; Perneczky, Robert; Kivipelto, Miia; Scott, David; Bracoud, Luc; Saad, Ziad; Novak, Gerald; Ritchie, Craig; Middleton, Lefkos

VERSION 1 – REVIEW

REVIEWER	Zaman, Shahid University of Cambridge, Psychiatry
REVIEW RETURNED	11-Jan-2021

GENERAL COMMENTS	Review of: Protocol of The Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research (CHARIOT): Prospective Readiness cOhort (PRO) SubStudy. The sub-sections are clearly written. They highlight some of the limitations of a study like this-that a very large number of volunteers is needed to capture those who will develop AD and to be able to discover a pre-diagnostic signature (using markers of disease and cognitive test) that would predict AD well in advance. Regarding the cognitive tests, conceptually one could argue that they are not necessarily going to be so sensitive in predicting AD as they are tests that focus on modalities accepted as part of AD diagnostic criteria. In my opinion, it would be better to use more “dynamic tests” that stress cognitive function or tests which would indicate or measure that the brain is working harder to maintain normal cognition. It’s a shame that this is only a 3.5 year follow up as amyloid accumulation, even with the large numbers being recruited, is only going to occur in small numbers as large or significant changes or changes that manifest clinically. Perhaps plan to continue with follow-up if funds can be found.

	Why not use centiloids to measure and compare amyloid accumulation? Other assessments that would be useful (but may be too late or expensive to add): hearing and gait. Also, for the physical to include dental health. Why not add potentially promising biomarkers as Neurofilament Light? This will become apparent at the analysis if data stage, but due regard will obviously be given to sex, age and ApoE status. I would include a COVID-19 infection questionnaire as this is likely to impact brain function. P31, line 25 to 26 needs checking.

REVIEWER	Gilsanz, Paola Kaiser Permanente Division of Research
REVIEW RETURNED	16-Feb-2021

GENERAL COMMENTS	This is an interesting study that is well described in this manuscript. Below are a few comments suggesting edits that may be helpful for readers. • Please include the start date in the abstract. • Authors mentioned participants are between ages of 60-85. Was 85 the upper age limit as part of the eligibility criteria? • It would be helpful if the authors could speak to the diversity of the cohort. • Word count permitting it would be helpful for the authors to provide a sentence or two about safety protocol so that readers don't have to look up the referenced article. • The second half the following sentence might be incomplete: Any clinically significant findings were passed on for follow-up to the participant's GP, and participants who were determined to have an active unstable illness as defined by the inclusion/exclusion criteria. • Do all follow-up visits occur in a clinic? • Please include a discussion of study limitation in the discussion section.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Shahid Zaman, University of Cambridge

Comments to the Author:
Review of: Protocol of The Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research (CHARIOT): Prospective Readiness cOhort (PRO) SubStudy.

The sub-sections are clearly written. They highlight some of the limitations of a study like this-that a very large number of volunteers is needed to capture those who will develop AD and to be able to

discover a pre-diagnostic signature (using markers of disease and cognitive test) that would predict AD well in advance.

Regarding the cognitive tests, conceptually one could argue that they are not necessarily going to be so sensitive in predicting AD as they are tests that focus on modalities accepted as part of AD diagnostic criteria. In my opinion, it would be better to use more “dynamic tests” that stress cognitive function or tests which would indicate or measure that the brain is working harder to maintain normal cognition.

Thank you for this comment. We have considered this point in the Discussion section, on page 19 under limitations. However, our analyses will include explorations of “process errors”, such as perseveration or intrusion errors in word list or verbal fluency tasks as well as speed-accuracy trade-offsthat may serve this purpose. These metrics have been found to be potentially useful in identifying those at risk for cognitive decline prior to the emergence of overt mild cognitive decline and dementia (see Thomas, Kelsey R et al. “Using Neuropsychological Process Scores to Identify Subtle Cognitive Decline and Predict Progression to Mild Cognitive Impairment.” Journal of Alzheimer's disease: JAD vol. 64,1 (2018): 195-204. doi:10.3233/JAD-180229). Furthermore, as our Manuscript indicate we also make use of computerised cognitive assessment (CDRAS, Cogstate and Cognito) which automatically capture reaction time data and are not typical tests used in routine AD assessment. These measures arguably are more “stressing” to elderly population given their electronic presentation format.

It’s a shame that this is only a 3.5 year follow up as amyloid accumulation, even with the large numbers being recruited, is only going to occur in small numbers as large or significant changes or changes that manifest clinically. Perhaps plan to continue with follow-up if funds can be found.

We are pleased to report that as 15th February 2021, a Protocol Amendment was implemented which involves an additional year extension to the follow-up period. As such, the study is now funded up to 4.5 years by a consortium of funders that include Gates Foundation, Merck and Takeda, alongside the original sponsors, Janssen.

Why not use centiloids to measure and compare amyloid accumulation?

Centiloid validation did not exist for all three tracers when this study began. Tracer-specific SUVR cutoffs were used instead. Moving forward, we agree a universal CL cutoff should be employed.

Other assessments that would be useful (but may be too late or expensive to add): hearing and gait. Also, for the physical to include dental health.

We have added this as a limitation in the Discussion section on page 19. As described in our Methods section, we do collect extensive medical history information that would include any clinical abnormalities in such body functions (e.g. development of mobility issues, hearing impairment).

Why not add potentially promising biomarkers as Neurofilament Light?

As per our Methods section on page 14 and 15, we collect biofluids such as blood to process plasma and serum for evaluation of promising peripheral biomarkers e.g. NFL, pTau 181, 217 etc. We have included a statement on page 14 within the Methods section to better clarify our intentions, at this stage. As we also have CSF we will correlate with central protein levels. This is part of the participant consent for provision of bio-samples to be bio-banked for future AD-related biomarker work. This will

become apparent at the analysis of data stage, but due regard will obviously be given to sex, age and ApoE status.

I would include a COVID-19 infection questionnaire as this is likely to impact brain function.

During the Covid-19 pandemic, the CPROSubstudy was transitioned to virtual visits to allow continued longitudinal assessments, and we have provided our strategy for operationalising this activity:
'Udeh-Momoh CT, de Jager-Loots CA, Price G, Middleton LT. Transition from physical to virtual visit format for a longitudinal brain aging study, in response to the Covid-19 pandemic. Operationalizing adaptive methods and challenges. Alzheimers Dement (N Y). 2020 Aug 27;6(1):e12055. doi: 10.1002/trc2.12055. PMID: 32885022; PMCID: PMC7453144.'

As part of the general visits, we collect detailed information on all medical, especially Covid-related incidents including more recently information on Covid-19 vaccinations. These data are designated Covid-related within our database for easy identification of such cases.

P31, line 25 to 26 needs checking.

Thank you, this was a formatting error created by the reference manager. This has been resolved.

Reviewer: 2
Dr. Paola Gilsanz, Kaiser Permanente Division of Research

Comments to the Author:
This is an interesting study that is well described in this manuscript. Below are a few comments suggesting edits that may be helpful for readers.

- Please include the start date in the abstract.

Thank you, this has been updated as the 3rd July 2015. This has been added to the Abstract.

- Authors mentioned participants are between ages of 60-85. Was 85 the upper age limit as part of the eligibility criteria?

Yes this is correct. Participants were aged 60-85 years at study entry. This age range reflects that which has been used in several recent clinical trials in preclinical AD, e.g. the Janssen EARLY trial of atabecestat [NCT02569398; clinicaltrials.gov] and the Lilly A4 study of solanezumab [NCT02008357; clinicaltrials.gov].

- It would be helpful if the authors could speak to the diversity of the cohort.

We are preparing a comprehensive paper describing the baseline demographic information of our cohort where the diversity of the cohort will be considered in detail. We would prefer for this to be addressed in the baseline paper.

- Word count permitting it would be helpful for the authors to provide a sentence or two about safety protocol so that readers don't have to look up the referenced article.

We have now included this information on page 16 under the Safety Reporting section.

- The second half the following sentence might be incomplete: Any clinically significant findings were passed on for follow-up to the participant's GP, and participants who were determined to have an active unstable illness as defined by the inclusion/exclusion criteria.

Thank you. We have amended this sentence as follows: "Any clinically significant findings were passed on for follow-up to the participant's GP. Participants who were determined to have an active unstable illness, as defined by the inclusion/exclusion criteria, were excluded."

- Do all follow-up visits occur in a clinic?

Follow-up visits do occur in clinic; however, over during the COVID pandemic, at the Imperial site these have been adapted for the online environment. We have emphasised this in the Methods section on page 12.

- Please include a discussion of study limitation in the discussion section.

Please find further discussion surrounding study limitations, in our Discussion section on page 19:

Although an ambitious project, some limitations of this work are worth mentioning. The amyloid positivity rate is low and due to a need for equal number of participants in each group (amyloid positive; amyloid negative), a high number of participants (78.6%) were excluded from the longitudinal follow-up phase. As a mitigating measure, enrichment criteria were introduced, with requirement of first-degree family history in volunteers aged 60-65 years old. The conduct of the study at only two sites is not typical of multi-site international trials; on the other hand, this minimizes several sources of variability that are independent of aging and incipient Alzheimer's disease (e.g., inter-rater variability and differences in psychometric equivalence among different translations). It could be argued that the cognitive battery set may not be sensitive in predicting AD in healthy older adults, since these mostly tax modalities associated with AD dementia diagnostic criteria. Nonetheless, the high frequency (quarterly) follow-up of participants will facilitate determination of those assessments most sensitive for identifying the earliest signs and symptoms of AD and offers an opportunity to assess other performance parameters (e.g. qualitative errors, lack of practice effect) that may indicate changes in cognitive and/or cerebral integrity in the lead up to AD dementia. Similarly, other assessments of physical health pertinent to AD risk, such as gait, hearing, or dental health are not included in our study. However, we do collect extensive medical history information at baseline and follow-ups that includes clinical abnormalities (e.g. mobility issues; hearing impairment) that may be useful in our analyses.

VERSION 2 – REVIEW

REVIEWER	Zaman, Shahid University of Cambridge, Psychiatry
REVIEW RETURNED	08-Apr-2021

GENERAL COMMENTS	The authors have adequately commented on issues raised in the review.

REVIEWER	Gilsanz, Paola Kaiser Permanente Division of Research
REVIEW RETURNED	24-Apr-2021

GENERAL COMMENTS	I appreciate the author's effort in addressing prior comments. I have a couple minor additional comments that I believe the authors can easily address: • I am happy to hear the authors are in the process of preparing a manuscript with detailed information regarding baseline demographics of the cohort. I think it would be valuable for readers of this manuscript/article if there was a sentence or two regarding any recruitment goals or criteria related to the distribution of the sample by race/ethnicity or sex. • The references are missing information related to date, volume number, and page numbers.

VERSION 2 – AUTHOR RESPONSE

Reviewer #2 stated that it would be valuable for readers of this manuscript/article if there was a sentence or two regarding any recruitment goals or criteria related to the distribution of the sample by race/ethnicity or sex. We have added the following at the end of the paragraph on participant recruitment on page 10: "Recruitment efforts resulted in 1,914 individuals screened at ICL to enrol 409 participants, and 537 screened at Edinburgh to enrol 110. Screened participants were not selected based on race/ethnicity or gender, resulting in a predominance of participants of European ancestry (> 95%) and a slight majority of women." In addition, we deleted the numbers of recruited individuals in parentheses in the methods section of the abstract, as we did not consider this detail as useful as knowing the number that actually entered screening; the "recruited" numbers included encounters with individuals by a variety of means, and not all of them actually made an appointment to be screened.

In addition to providing the correct year/volume/pages in the references, we also added some references accidentally deleted that appeared in Table 2.