

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	CALGARY NORMATIVE STUDY: STUDY DESIGN OF A PROSPECTIVE LONGITUDINAL STUDY TO CHARACTERIZE POTENTIAL QUANTITATIVE MR BIOMARKERS OF NEURODEGENERATION OVER THE ADULT LIFESPAN
<b>AUTHORS</b>	McCreary, Cheryl; Salluzzi, Marina; Andersen, Linda; Gobbi, David; Lauzon, Louis; Saad, Feryal; Smith, Eric E.; Frayne, Richard

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Keith Thulborn University of Illinois USA
<b>REVIEW RETURNED</b>	02-Apr-2020

<b>GENERAL COMMENTS</b>	well written manuscript of a project that serves the purpose of documenting the imaging evolution of normal aging. There are no details about the nature of the statistical analysis of reproducibility and repeatability within examination or across time although these data are being acquired. These statistical methods will determine the success of this commendable data acquisition
-------------------------	---

<b>REVIEWER</b>	Christian Habeck Columbia University USA
<b>REVIEW RETURNED</b>	17-May-2020

<b>GENERAL COMMENTS</b>	<p>I think the authors have a done a good job with clear descriptions. I would like to see more elaboration on several aspects:</p> <ul style="list-style-type: none"><li>- Data sharing: the past report about internal data sharing and the process of registration with a standard form seems fine. I was somewhat confused how much editorial control was exercised by the study investigator when speak about the "intended purpose" of the proposed analysis. Is any purpose legitimate, and the authors just want the compliance with the purpose without straying to unplanned analyses? Or are the study investigators exercising more control?</li><li>- Standard scanner maintenance, software upgrades etc.: The authors hint at this inevitable necessities in a frank discussion of repeatability. I wonder to what extent documentation will be provided in the data sharing process.</li><li>- The protocol mentions "repeatability" which I think is important, particularly in contrast to "replication". While it might be outside the</li></ul>
-------------------------	---

	<p>brief of this protocol review, but is "repeatability" operationalized as a quantifiable measure, allowing difference in degree? Or is it a dichotomous 1/0 judgment? Could the authors briefly elaborate?</p> <p>- I appreciate the STROBE checklist. I take that items that are left blank, rather than marked with N/A, for instance: item 13 c ("consider flow diagram"), are not done? Is this correct? Could the authors be more explicit and state "was not included"?</p>
--	---

## VERSION 1 – AUTHOR RESPONSE

### Reviewer: 1

Reviewer Name: Keith Thulborn

Institution and Country: University of Illinois, USA

Please state any competing interests or state 'None declared': none

*Well written manuscript of a project that serves the purpose of documenting the imaging evolution of normal aging. There are no details about the nature of the statistical analysis of reproducibility and repeatability within examination or across time although these data are being acquired. These statistical methods will determine the success of this commendable data acquisition*

**Response:** A Statistical Analyses section has been added on page 15 that provides a brief statement of the planned statistical approach to be used for future publications.

### Reviewer: 2

Reviewer Name: Christian Habeck

Institution and Country: Columbia University, USA

Please state any competing interests or state 'None declared': None declared

*I think the authors have done a good job with clear descriptions. I would like to see more elaboration on several aspects:*

*- Data sharing: the past report about internal data sharing and the process of registration with a standard form seems fine. I was somewhat confused how much editorial control was exercised by the study investigator when speak about the "intended purpose" of the proposed analysis. Is any purpose legitimate, and the authors just want the compliance with the purpose without straying to unplanned analyses? Or are the study investigators exercising more control?*

**Response:** The section on data sharing has been revised to hopefully clarify the statement of “intended purpose”. The investigators wish only to prevent unplanned or additional analyses outside those outlined in the data sharing application and not exercise more control. Inclusion of this statement is to avoid the remote possibility of duplication of analyses between multiple groups. The sentence now reads:

“Groups requesting data are asked to limit use and analysis of the data to those outlined in their data sharing agreement, not sharing with other groups or using the data for other unplanned analyses, and to acknowledge the CNS and the CNS funding agencies in presentations or publications. Further or previously unplanned analyses of requested data would require a simple amendment to the data sharing agreement ”

*- Standard scanner maintenance, software upgrades etc.: The authors hint at this inevitable necessities in a frank discussion of repeatability. I wonder to what extent documentation will be provided in the data sharing process.*

**Response:** The robustness of each measure to system change may vary between be each quantitative metric. Where possible, data may be selected with specified acquisition dates between major system changes to mitigate their potential impact. These considerations will be discussed with the investigator as part of the data sharing request. Available documentation and repeatability data and/or appropriate references may be provided if requested. A statement to this effect is now included in the manuscript on page 15.

“Information regarding MR system upgrades, protocol changes, and repeatability data may be provided upon request.”

- The protocol mentions "repeatability" which I think is important, particularly in contrast to "replication". While it might be outside the brief of this protocol review, but is "repeatability" operationalized as a quantifiable measure, allowing difference sin degree? Or is it a dichotomous 1/0 judgment? Could the authors briefly elaborate?

**Response:** Repeatability will be defined quantitatively for each metric and will be the topic of future manuscripts. We have clarified this point at the end of the Repeatability and Measurement Validation section by adding the following sentence:

“The variance and minimum detectable difference, including the possible impact of MR system changes on these measures for individual quantitative metrics are topics for future publications.”

- I appreciate the STROBE checklist. I take that items that are left blank, rather than marked with N/A, for instance: item 13 c ("consider flow diagram"), are not done? Is this correct? Could the authors be more explicit and state "was not included"?

**Response:** The STROBE checklist generally applies to completed observational studies. As this is an ongoing study, the manuscript was submitted as a protocol paper. Unfortunately, this caused us some confusion as to how to respond and a few items in the checklist were left blank. We have revised the checklist, adding responses that were previously missing, and included footnotes for clarification.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Christian Habeck USA Columbia University
<b>REVIEW RETURNED</b>	22-Jun-2020
<b>GENERAL COMMENTS</b>	I am satisfied with the response to my comments.