PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of the Covid-19 pandemic on people in need of care or support: protocol for a SARS-CoV-2 registry
AUTHORS	Gensichen, Jochen; Zöllinger, Isabel; Gagyor, Ildiko; Hausen, Anita; Hölscher, Michael; Janke, Christian; Kühlein, Thomas; Nassehi, Armin; Teupser, Daniel; Arend, Florian M.; Eidenschink, Christine; Hindenburg, Dagmar; Kosub, Helena; Kurotschka, Peter Konstantin; Lindemann, Daniela; Mayr, Katharina; Müller, Susan; Rink, Laura; Rottenkolber, Marietta; Sanftenberg, Linda; Schwaiger, Rita; Sebastião, Maria; Wildgruber, Domenika; Dreischulte, Tobias; BaCoM Study Group, The

VERSION 1 – REVIEW

REVIEWER	Azzolino, Domenico University of Milan
REVIEW RETURNED	18-Jan-2023

GENERAL COMMENTS	In the present article, the authors present a protocol for a SARS-CoV-2 registry in frail older people. It is a good research idea given the lack of long-term data about the long-lasting consequences of SARS-CoV-2 infection on older people. I have some small comments to improve the present protocol. I suggest slight editing of English mainly related to the accordance of tenses. Please avoid the term “elderly” since it is pejorative and reductionist. It would be better “older people” or “older adults”. Inclusion criteria: Age≥18 years. Why not age ≥ 60 or 65 years? If the paper is focused on older people… What about the assessment of nutritional status? COVID-19 severely impacts the already weakened nutritional status of older persons. I read that only BMI was included in the assessment. However, BMI presents some limitations in older people since it includes both fat and fat-free mass. In some cases, BMI does not capture a reduction in muscle mass (if masked by an excess of fat mass). There are simple and easy-to-implement measures to capture modifications of nutritional status like unintentional weight loss (which is included in the Global Leadership Initiative on Malnutrition [GLIM] criteria as a phenotypic criterion) and/or calf circumference. https://doi.org/10.3390/nu13051616

REVIEWER	Price, Angeline Salford Royal NHS Trust, Ageing and Complex Medicine
REVIEW RETURNED	25-Jan-2023

GENERAL COMMENTS	This paper outlines a study protocol entitled Impact of covid-19 pandemic on frail elderly: a protocol for a SARS-COv2 registry.

	The proposed aim of the study is to develop a registry by collecting data from a large sample of adults and separating these between one study group and two smaller control groups. You wish to determine differences in both baseline characteristics and a variety of outcomes between those who require care and have tested positive for covid-19, vs those who do not require and have tested positive for covid-19. You will also compare with those who require care but have never tested positive for covid-19. Follow up in the study continues for a total of 3 years, with data capture points every 6 months. Data will also be collected 6 monthly from formal and informal care givers via questionnaires, and 60 one-off qualitative interviews will be undertaken to explore the interface between care providers. Data will be analysed descriptively and stratified by level of care, outpatient/domestic and inpatient care, gender and age groups. This is an ambitious project, and will no doubt highlight important issues pertaining to covid-19 and its holistic impact, particularly for those who are dependent on formal or informal caregivers. However, I feel there are some important considerations to note, and which require further clarity before the protocol can be published. These are listed below: Major issues: 1. The title and abstract of the study appear to be somewhat misleading. You propose to recruit patients > 18 years of age who either do/do not require care, therefore the study is not strictly focussing on frailty and older people. Although clinical frailty score and some components of other frailty assessment tools are included as part of data collection, if the main outcome measure (that you mention in the data analysis section) is level of care dependence, should this not be in the title rather than frailty and the word elderly be removed? 2. Following on from point one, I am not able to find where you have defined care level (I-V) in the paper. Could you do so please, and also define inpatient vs outpatient setting? 3. Also following on from point one, Clinical Frailty Scale is not widely validated for use in younger populations. May it be possible that younger participants dependent upon care may live with a physical or intellectual disability, rather than with frailty? What is your position on this? A re-wording of the title and abstract might be helpful in avoiding this mislabelling 4. The exclusion criteria notes that anyone deemed to have a life expectancy < 6 months will be excluded from the study. This means that anyone with a CFS 8/9 should be automatically excluded, and the inclusion/exclusion criteria should reflect this 5. The inclusion criteria table is unclear for CG2: No existing need for care (care level I-V) or support (according to the clinical judgement of the recruiting doctor: current need for care or expected need in the near future (Clinical Frailty Scale ≥=5)) Does this mean they already have a CFS of ≥ 5?, in which case, they do already require care. If not, this table could be made clearer. 6. I have some concerns regarding the inclusion of adults with severe cognitive impairment and would be interested in your thoughts on this. The data collection and follow up schedule are lengthy and fairly involved for someone who is unable to decide for themselves whether to give consent. The blood tests and spirometry testing in particular may be problematic (either not tolerated, or unnecessarily distressing) or even clinically inappropriate if a person is receiving palliative focussed treatment.

	What will you do to mitigate against this? I feel that the consent section should be expanded to reflect these nuances 7. Additionally, could you be more specific about the protocol for a person who initially gives consent but then subsequently loses capacity at one or more of the data collection time points? This could be included in the consent section 8. Have you considered the impact of the above on the social isolation and psychosocial assessments and subsequent analysis? There will be a lot of missing data, as a next of kin would not be able to provide this information. How will this impact the findings? 9. The sample size calculation and stratification section is not easy to read. You mention that 30% of the study participants, across all levels of care, will still be alive. Where is this estimate taken from? A reference would be helpful Minor issues: 1. You mention convenience sampling, but given the eligibility criteria and control groups would it not be more accurate to say that this is purposive sampling? 2. 'older people living with frailty' would be preferential to 'frail elderly' if this description is to remain in the title and throughout the text 3. It would be helpful to include detail on who is trained to undertake the assessments required in data collection, for example the CFS, time up and go etc. Is there a way of ensuring interrater reliability for these assessments? 4. How can you be sure that covid-19 has not gone untested/undiagnosed in the CG2?. If antibody test comes back positive for someone in CG1, what happens to them – are they re-allocated? 5. You could add further detail to the qualitative data analysis section. Who has experience with this and what exactly will they be doing/how will the results be presented alongside the quantitative findings? 6. With regards to data management, who inputs into the electronic record? Where are the paper copies stored? This information could be included for clarity 7. In the sub-study description, you use the term constellations of actors. I understand what you mean, but this is not a commonly used and recognised term. Stakeholders may be more appropriate 8. My apologies, I am not able to comment on the quality of references or make any suggestions to the bibliography as I am not able to read those that are written in German

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment # 1. I suggest slight editing of English mainly related to the accordance of tenses. Please avoid the term "elderly" since it is pejorative and reductionist. It would be better "older people" or "older adults".

→ **Our response**: We have carefully reviewed the manuscript to ensure the accordance of tenses. We agree that the term "older people" is more appropriate and adopt it in the study protocol.

Comment # 2. Inclusion criteria: Age≥18 years. Why not age ≥ 60 or 65 years? If the paper is focused on older people…

→ **Our response:** Thank you for this comment. Our target group are patients in need of care or support, which predominantly includes older people but not necessarily. We have therefore not included an age threshold (apart from the exclusion of children) and revised the manuscript to reflect that our target group is not restricted to older people.

Comment # 3. What about the assessment of nutritional status? COVID-19 severely impacts the already weakened nutritional status of older persons. I read that only BMI was included in the assessment. However, BMI presents some limitations in older people since it includes both fat and fat-free mass. In some cases, BMI does not capture a reduction in muscle mass (if masked by an excess of fat mass). There are simple and easy-to-implement measures to capture modifications of nutritional status like unintentional weight loss (which is included in the Global Leadership Initiative on Malnutrition [GLIM] criteria as a phenotypic criterion) and/or calf circumference. https://doi.org/10.3390/nu13051616

→ **Our response:** Thank you for this interesting thought and we agree with you that in older people BMI does not optimally reflect malnutrition. On the other hand, in addition to BMI and weight, we also collect other factors that are associated with malnutrition as described in the paper you mentioned. These include, for example, a reduced muscle mass and consequently lower mobility, which are recorded in BACOM by e.g. the Timed up & go Test or the Barthel Index (Activities of Daily living). BACOM also records hospitalisations and Covid-19 symptoms such as nausea, diarrhea, vomiting, anosmia (loss of smell) and ageusia (loss of taste), which are also associated with malnutrition. Since we are at an advanced stage of the study, we ask for your understanding that we cannot include any new parameters at this point.

Reviewer 2

Major issues:

Comment #1: The title and abstract of the study appear to be somewhat misleading.
You propose to recruit patients > 18 years of age who either do/do not require care, therefore the study is not strictly focussing on frailty and older people. Although clinical frailty score and some components of other frailty assessment tools are included as part of data collection, if the main outcome measure (that you mention in the data analysis section) is level of care dependence, should this not be in the title rather than frailty and the word elderly be removed?

→ **Our response:** Please, see our response to reviewer 1/comment #2

Comment #2: Following on from point one, I am not able to find where you have defined care level (I-V) in the paper. Could you do so please, and also define inpatient vs outpatient setting?

→ **Our response:** Thank you for spotting this.
There is a short definition of the care level in the abstract level of care I-V (I=minor/V=most severe impairment of independence), but we additionally integrated a more precise definition of the care level in the paper below Table 1 p.6:

The degree of independence of the person in need of care is decisive for classification into the care grades. The levels of care are:
Care level 1: minor impairment of independence
Care level 2: significant impairment of independence
Care level 3: severe impairment of independence
Care level 4: most severe impairment of independence
Care level 5: most severe impairment of independence with special requirements for nursing care.

We also integrated a definition of inpatient vs outpatient setting in the Participant recruitment section on page 7:
Inpatient setting is defined if the person is cared for in a long-term/inpatient care facility.
Outpatient setting is defined as home care provided by a informal caregivers and/or outpatient care services.

Comment #3: Also following on from point one, Clinical Frailty Scale is not widely validated for use in younger populations. May it be possible that younger participants dependent upon care may live with a physical or intellectual disability, rather than with frailty? What is your position on this? A re-wording of the title and abstract might be helpful in avoiding this mislabelling
→ **Our response:** We also thank you for this suggestion and would like to also refer to our response to our response to reviewer 1/comment #2. It is indeed the case that younger persons can have a need for care due to e.g. a physical disability but are not frail.
The inclusion of the younger population groups in the study does therefore not take place via the application of the Frailty Score, but only via the criterion of an existing care level. The inclusion criterion using the Clinical Frailty Scale is used to include older people who need support in everyday life but do not have a formal care level (e.g. because they have not yet been formally assessed).

Comment #4: The exclusion criteria notes that anyone deemed to have a life expectancy < 6 months will be excluded from the study. This means that anyone with a CFS 8/9 should be automatically excluded, and the inclusion/exclusion criteria should reflect this

→ **Our response:** Thank you also for this interesting comment. A person can participate in the study group if he or she has a frailty score of >=5 and, according to a physician's clinical judgement, has at least 6 months of life expectancy left. This would mean that people with CFS =9 would automatically drop out. In order to make this more explicit, we have therefore corrected the inclusion criterion of SG and CG 1 to CFS >= 5 and CFS<9.

Comment #5: The inclusion criteria table is unclear for CG2: No existing need for care (care level I-V) or support (according to the clinical judgement of the recruiting doctor: current need for care or expected need in the near future (Clinical Frailty Scale ≥=5)) Does this mean they already

have a CFS of ≥ 5?, in which case, they do already require care. If not, this table could be made clearer.

→ **Our response:** Please excuse the unclear wording at this point. It is meant that persons in the control group 2 may NOT have a existing need for 1) care (care level I-V) or 2) support (Clinical Frailty Scale ≥=5). We have reworded the criteria of CG 2 and hope that they are now more understandable.

Comment #6: I have some concerns regarding the inclusion of adults with severe cognitive impairment and would be interested in your thoughts on this. The data collection and follow up schedule are lengthy and fairly involved for someone who is unable to decide for themselves whether to give consent. The blood tests and spirometry testing in particular may be problematic (either not tolerated, or unnecessarily distressing) or even clinically inappropriate if a person is receiving palliative focussed treatment. What will you do to mitigate against this? I feel that the consent section should be expanded to reflect these nuances

→ **Our response:** We understand the reviewer's concerns about the inclusion of adults with severe cognitive impairments. Patients treated for palliation or those with an expected life expectancy of <6 months are excluded from the study. In order to address the reviewer's request for expanding the consent section, we have added the following text to the manuscript: "We made a conscious decision in the study design not to exclude people with severe cognitive impairment, as these groups (such as people with dementia), may have suffered particularly from the effects of the pandemic (e.g. through isolation rules, etc.). In order to mitigate undue distress to this vulnerable group, the length of the survey is reduced because some questionnaires are not applicable (e.g. Health Literacy) or the information is collected through an external survey of relatives or carers where this has previously been shown to be possible (e.g. PHQ-9). Staff responsible for data collection are insructed to interrupt or end interviews with participants if they notice signs of distress. "

Comment #7: Additionally, could you be more specific about the protocol for a person who initially gives consent but then subsequently loses capacity at one or more of the data collection time points? This could be included in the consent section

→ **Our response:** Thank you also for this important question. In this case, we will only carry out further surveys if the consent to the study is then also signed by the existing legal guardian. We now specify in the protocol that "In case a person who initially gives consent subsequently loses capacity at one or more of the data collection time points, we only carry out further surveys if the consent to the study is also signed by the legal guardian"

Comment #8: Have you considered the impact of the above on the social isolation and psychosocial assessments and subsequent analysis? There will be a lot of missing data, as a next of kin would not be able to provide this information. How will this impact the findings?

→ **Our response**: We can record the effect of increasing cognitive impairment on social isolation because we also assess the cognitive status of the participants (Six-Item-Screener, MoCA-BLIND) with every survey in the BACOM study. If the "Six-Item-Screener" (0-6 points) is not successfully completed (< 4 points), the information collection of the self-reports will be ensured according to the substitution principle, that means that information collecion is to be ensured by relatives or caregivers that are asked instead. This is not possible for all questionnaires, but for a

majority it is. For example an external assessment is possible for the questionnaires like PHQ-9, GAD-7, IES-R, EQ-VAS, but not for others like e.g. Health Literacy (HLS-EU-Q16) or Self-Efficacy (SES6G).

Comment #9: The sample size calculation and stratification section is not easy to read. You mention that 30% of the study participants, across all levels of care, will still be alive. Where is this estimate taken from? A reference would be helpful

→ **Our response:**
We now explain in the manuscript that our estimate is conservative and is based on: *Jacobs, K., Kuhlmey, A., Greß, S., Klauber J., Schwinger A., Pflege-Report 2017: Die Versorgung der Pflegebedürftigen. Stuttgart: Schattauer 2017.*

Minor issues:

Comment #1: You mention convenience sampling, but given the eligibility criteria and control groups would it not be more accurate to say that this is purposive sampling?

→ **Our response:** Thank you for this thought. We agree with you, that the term "purposive sampling" is more appropriate here and adopt it in the study protocol.

Comment #2: 'older people living with frailty' would be preferential to 'frail elderly' if this description is to remain in the title and throughout the text

→ **Our response**: Please refer to our reply to the comment #1 of the major issues, in which we described the adaptation of the title and abstract

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Comment #3: It would be helpful to include detail on who is trained to undertake the assessments required in data collection, for example the CFS, time up and go etc. Is there a way of ensuring interrater reliability for these assessments?

→ **Our response:** Thank you for this question. The study staff who collect the data is specifically and extensively trained for the individual questionnaires and clinical tests (e.g. MoCA-Blind, Timed up & go), so that interrater reliability for these assessments can be ensured. We included this also in the protocol.

Comment #4: How can you be sure that covid-19 has not gone untested/undiagnosed in the CG2? If antibody test comes back positive for someone in CG1, what happens to them – are they re-allocated?

→ **Our response:** Thank you for this comment. We now specify that "Test results from antigen tests are interpreted in combination with any evidence of nucleocapsid antibodiesmeasured as part of the study protocol (see data collection below). The assessment of nucleocapsid antibodies serves as a further means to verify any previous infection with SARS-CoV-2, which is not influenced by exposure to vaccines (since vaccines only trigger antibodies against the spike protein). Patients, who have previously been allocated to CG1, but who subsequently test

positive for nucleocapsid antibodies are classified as group-switchers and are reallocated to the SG accordingly."

Comment #5: You could add further detail to the qualitative data analysis section. Who has experience with this and what exactly will they be doing/how will the results be presented alongside the quantitative findings?

→ **Our response:** We have revised the section to provide further details. We now specify that „All semi-structured interviews will be conducted by appropriately trained staff with a background in sociology (KM), who will also conduct or supervise all qualitative analyses."

Comment #6: With regards to data management, who inputs into the electronic record? Where are the paper copies stored? This information could be included for clarity

→ **Our response:** Thank you also for this question. Only trained and authorized members of the BACOM Study Group enter the data at the study centers to retrieve the eCRFs. The data connection between client computer and server is encrypted. Through the use of a hierarchical access concept, unauthorized access to the pseudonymised patient data in the database is impossible.
All paper-based records are stored in a secure, inaccessible place in the study center and will be treated confidentially. The identification list and the consents of the study participants are kept separately from the CRFs.

Comment #7: In the sub-study description, you use the term constellations of actors. I understand what you mean, but this is not a commonly used and recognised term. Stakeholders may be more appropriate

→ **Our response**: Thank you for this comment. „Constellation of actors" is a sociological term, which we agree may not be readily understood by the readership of BMJ Open. We have therefore taken the reviewer's advice and changed it to „stakeholders".

Comment #8: My apologies, I am not able to comment on the quality of references or make any suggestions to the bibliography as I am not able to read those that are written in German

→ **Our response:** Apologies. A lot of relevant literature in this field is in German.

VERSION 2 – REVIEW

REVIEWER	Azzolino, Domenico University of Milan
REVIEW RETURNED	28-Apr-2023

GENERAL COMMENTS	All my comments have been addressed

REVIEWER	Price, Angeline Salford Royal NHS Trust, Ageing and Complex Medicine
REVIEW RETURNED	20-Apr-2023

GENERAL COMMENTS	Thank you for you comprehensive response to comments. With the changes to the manuscript, this now reads much more clearly and describes the population of interest more accurately. As previously mentioned, this is an ambitious but important study and I look forward to reading the results