PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A study protocol for COPE study: COVID-19 in Older PEople – the influence of frailty and multimorbidity on survival. A multi-centre, European observational study
AUTHORS	Price, Angeline; Barlow-Pay, Fenella; Duffy, Siobhan; Pearce, Lyndsay; Vilches-Moraga, Arturo; Moug, Susan; Quinn, Terry; Stechman, Michael; Braude, Philip; Mitchell, Emma; Myint, Phyo Kyaw; Verduri, Alessia; McCarthy, Kathryn; Carter, Ben; Hewitt, Jonathan

VERSION 1 – REVIEW

REVIEWER	Simon Conroy University of Leicester Researcher in same/related field
REVIEW RETURNED	04-Jun-2020

GENERAL COMMENTS	Thank you for asking me to review this protocol, which purports to focus on the outcomes for older people with COVID-19. States that the most common form of COVID is bilateral pneumonia – is that true? There are increasing reports of frailty presentations such as delirium and the primary presenting feature? The section describing NSAIDs as possible risk factors perhaps needs updating now that they are being tested as therapeutic interventions? I am not sure why advertising of the collaborative and its future intentions appears in the introduction (it's a worthy initiative, but just not sure why this information included)? They have done well to assemble a large collaborative, but it is pushing things a bit to call it international with only one site outside of the UK Inclusion criteria start at age 18, yet frailty has not been validated in people aged under 65 so this is a worry. The inclusion of a clinical diagnosis of COVID-19 is problematic –even including PCR diagnosed patients has limitations given the variably reported sensitivity and specificity – how was the laboratory diagnosis standardised across different settings? Baseline data – why no measure of illness severity? Why not lymphocele count? Why no D-Dimer – what is the rationale for the included or excluded tests? Define short term mortality – 7 days, 30 days? The training video on using the CFS is good but it would be better to report inter-rater reliability following training as there is variability in completing CSF scores without substantial training Not sure how the sample size was arrived at given that they describe 30% mortality in older people yet are recruiting people of all ages? They mention frailty as a dichotomous variable in the sample size estimate, but haven't described the cut-offs they plan to use or indeed the rationale for any specific cut-off in the CFS

	Is the DMC separate and independent?

REVIEWER	Fulvio Lauretani University of Parma
REVIEW RETURNED	20-Jun-2020

GENERAL COMMENTS	Dear Authors the topic of the manuscript is actual and relevant. One suggestion is to try to standardize polypharmacotherapy and multimorbidity (see eg. Profiling the Hospital-Dependent Patient in a Large Academic Hospital: Observational Study. Eur J Intern Med 2019 Jun; 64:41-47)

REVIEWER	Anne Wissendorff Ekdahl Lund University Institution of Clinical Sciences, Helsingborg Sweden
REVIEW RETURNED	12-Jul-2020

GENERAL COMMENTS	A very interesting and well-done study protocol. Looking forward to take part of the results

VERSION 1 – AUTHOR RESPONSE

Editors/Reviewers Comment	COPE Study Response	Changes made to the manuscript (Inc Page and para)
Reviewer 1		
States that the most common form of COVID is bilateral pneumonia – is that true? There are increasing reports of frailty presentations such as delirium and the primary presenting feature?	We thank the reviewer for highlighting this point. At the time of manuscript development in March 2020, limited information was available on the clinical course and range of presentations common to COVID-19. The text has been updated to reflect what has been learned over the course of the pandemic.	Section 1 Introduction, pg 5 para 1: *Early on in the pandemic, the most commonly reported presentation in severe COVID-19 was bilateral pneumonia [2]. Emerging literature has identified delirium, gastrointestinal disturbance and falls as predominant clinical signs in older, frail patients (O'Hanlon & Inouye, 2020; Lithander et al, 2020)*
The section describing NSAIDs as possible risk factors perhaps needs updating now that they are being tested as therapeutic interventions?	We thank the reviewer for their comment. The section describes a speculative risk associated with NSAIDs, and the intention of their inclusion was to provide evidence to support or refute this worry. Whilst literature emerges to support the use of some anti-inflammatory agents in the treatment of severe COVID-19, the role of these is not yet fully understood and a level of uncertainty remains as to the influence across broader populations of hospitalised adults.	No changes made
I am not sure why advertising of the collaborative and its future intentions appears in the introduction (it's a worthy initiative, but just not sure why this information included)?	We thank the reviewer for this feedback, and have removed this information from the abstract and introduction. Our intention was merely to demonstrate the expertise of the group in frailty related research, its ability to access data rapidly from a pre-established network, and to provide assurance on the validity of data collection and interpretation. For this purpose a description of the collaborative remains within the text of the study design section, though has been compressed.	Section 2.2 study design and setting pg 8
They have done well to assemble a large collaborative, but it is pushing things a bit to call it international with only one site outside of the UK	We thank the reviewer for their comment. As a European Collaboration (www.OPSOC.eu) we have amended this to reflect our research team and previous European studies, as can be seen in the published study findings: (Hewitt et al. 2020) DOI: https://doi.org/10.1016/S2468-2667(20)30146-8	We have changed the study title to replace "International" to "European" and amended the description within the introduction section of the abstract

Inclusion criteria start at age 18, yet frailty has not been validated in people aged under 65 so this is a worry.	We thank the reviewer for highlighting this important point. As a collaborative we are typically primarily interested in older people, but for the purpose of this study we recruit all ages. The primary reason for this was in response to the NICE recommendations to assess CFS on COVID patients of all ages. A number of studies have previously reported the presence of frailty in the under 65's, using a variety of frailty assessment tools, and have reported worsening outcomes with increasing frailty: Richards et al, 2019 DOI: 10.1371/journal.pone.0219083 Hanlon et al, 2018 DOI:10.1016/S2468-2667(18)30091-4 Smart et al, 2017 DOI: 10.14283/jfa.2017.28 To our knowledge the CFS is not recommended in patients under 65 years. We hope to add to the evidence for validation in younger age groups. Within the main results paper (Hewitt et al, 2020), the distribution of cases and mortality between age and CFS can be found in Supplementary Table 1. It can be seen that increased frailty may be associated with mortality at all ages.	No changes made
The inclusion of a clinical diagnosis of COVID-19 is problematic –even including PCR diagnosed patients has limitations given the variably reported sensitivity and specificity – how was the laboratory diagnosis standardised across different settings?	We thank the reviewer for highlighting this point. In the earliest phase of the pandemic access to PCR testing and results were associated with some time delays. In order to ensure valuable data were captured, clinical diagnosis of COVID by other means – mostly CT chest but also patients describing clinical symptoms in keeping with COVID-19 - were included. The clinical diagnosis was made when the swab testing was negative but the clinical picture clearly suggested a diagnosis of COVID-19. Despite this, it can be seen within the study findings (Hewitt et al, 2020) that over 95% of patients were diagnosed by laboratory test, with the remaining small proportion clinically diagnosed. Statistical analysis demonstrated no clear difference between the groups that would lead to concern over reliability of the data. Whilst we acknowledge the limitations of PCR testing, guidance and Standard Operating Procedures have been in place across the UK and Europe wide, based upon World Health Organisation and European Centre for Disease Prevention and Control recommendation, giving reassurance that laboratory diagnoses were standardised across settings.	No changes made
Baseline data – why no measure of illness severity? Why not lymphocele count? Why no D-Dimer – what is the rationale for the included or excluded tests?	The COPE study was designed as an observational study, before we knew many features of COVID-19. As a readily accessible and utilised test, we included CRP as marker of illness severity at the time of ethics application. Although there has been increasing interest and emerging literature around the importance of other biochemical markers, some of these, including D-Dimer are not routinely collected. We accept that this article does not have the full depth we would have liked, but deliberately kept the exposures and confounders as per our health research authority approved protocol.	No changes made
Define short term mortality – 7 days, 30 days?	We thank the reviewer for highlighting this relevant point. A The protocol was revised to provide clarity. Short term mortality was defined as 7 days and All-cause time-to-mortality within the main results paper (Hewitt et al, 2020), and subsequent secondary analyses.	Section 2.4 Primary outcomes pg 9
The training video on using the CFS is good but it would be better to report inter-rater reliability following training as there is variability in completing CSF scores without substantial training	We thank the reviewer for highlighting this important point for consideration. For all sites, assessment of frailty using CFS was routinely collected data (as per NICE recommendations). In each site the assessment of CFS in COVID patients was undertaken by specialist COVID megateams – in the UK this comprised a team of consultant geriatricians, emergency physicians and intensive care consultants. The data for this study were collected by a group well experienced in frailty related research, so whilst it is not possible to retrospectively report inter-rater reliability, reassurance can be given that validation was performed by local teams and no concerns around CFS scoring were raised.	No changes made
Not sure how the sample size was arrived at given that they describe 30% mortality in older people yet are recruiting people of all ages?	We thank the reviewer for their comment. The COPE study was designed as an observational study, before we knew many features of COVID-19. The COPE study was formed by a geriatric led collaborative, so was initially focused on older people. However during March the population widened	No changes made

	consistent with the NHS guidance on reporting the CFS on all ages. We originally estimated that at least 500 patients would have been needed to estimate the impact of patients that were frail (CFS 5-9), versus not frail (CFS 1-4). We over recruited to increase the precision of our understanding of CFS as an exposure of frailty. With the achieved sample size we were able to estimate the exposure of CFS association with mortality with high degree of precision, and we were guided by our previous work in frailty, including younger adults, which found about 1000 patients provided adequate power to assess the association between CFS and mortality after adjustment for similar confounders. Rather than a post-hoc revision of the sample size, (which is not recommended) we have maintained a transparent version of events to how we determined the number of included participants.	
They mention frailty as a dichotomous variable in the sample size estimate, but haven't described the cut-offs they plan to use or indeed the rationale for any specific cut-off in the CFS	We thank the reviewer for their comment. We did not anticipate that there would be adequate number of events for each score so scores were grouped. The following text can be found in the following peer reviewed primary results paper *"The CFS (appendix p 6) was used to assess frailty. It bases the frailty assessment on how a patient was 2 weeks before hospital admission. The CFS is an ordinal hierarchical scale that numerically ranks frailty from 1 to 9, with a score of 1 being very fit, 2 well, 3 managing well, 4 vulnerable, 5 mildly frail, 6 moderately frail, 7 severely frail, 8 very severely frail, and 9 terminally ill. We did not anticipate that there would be adequate number of events for each score so scores were grouped 1–2 (fit), 3–4 (becoming vulnerable, but not frail), 5–6 (initial signs of frailty but with some degree of independence), and 7–9 (severe or very severe frailty) for the purposes of the analyses.* ***These groups were selected to fit with the clinical descriptions outlined in the CFS and we deemed them to be reasonable groupings of severity of frailty****"*	No changes needed
	The CFS is presented ungrouped in Table 1 of the paper, to allow for comparison of each CFS level. The purpose of the study was to establish the prevalence of frailty and its impact on death. Future studies may be able to look more closely at the prognostic value of the CFS.	
Is the DMC separate and independent?	No safety concerns were raised. However, we have amended the section to clarify how the safely aspects of the study were overseen.	Changes made to Section 2.7 Study Management Group pg 12 *This will be led by PKM (Aberdeen) and will involve reviewing safety data and, since the study collates observational data and there are minimal safety issues expected.*
Reviewer 2		
The topic of the manuscript is actual and relevant. One suggestion is to try to standardize polypharmacotherapy and multimorbidity (see eg. Profiling the Hospital-Dependent Patient in a Large Academic Hospital: Observational Study. Eur J Intern Med	We thank the reviewer for their feedback, and found the suggested literature of great interest and have added this to the reference list.	Reference added
Reviewer 3		
A very interesting and well-done study protocol. Looking forward to take part of the results	We thank the reviewer for their kind words and enthusiasm	

VERSION 2 – REVIEW

REVIEWER	Anne W Ekdahl Institution of Clinical Sciences Lund University Sweden
REVIEW RETURNED	04-Sep-2020

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.