PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Acute Exacerbation and Respiratory InfectionS in COPD (AERIS): protocol for a prospective, observational cohort study
AUTHORS	Bourne, Simon; Cohet, Catherine; Kim, Viktoriya; Barton, Anna; Tuck, Andy; Aris, Emmanuel; Mesa Vela, Sonia; Devaster, Jeanne-Marie; Ballou, Ripley; Clarke, Stuart; Wilkinson, Tom

VERSION 1 - REVIEW

REVIEWER	Gavin Donaldson University College London
REVIEW RETURNED	23-Jan-2014

GENERAL COMMENTS	With apologies to Tom Wilkinson and his colleagues, there is very little new in this protocol. The methodology for this type of study in COPD has been described before. The aims are not unique and have been studied by many groups and consortia. Electronic tracking of patient symptoms have been carried out in clinical trials sponsored by Cheisi and Novartis. I feel that the authors need to make it very clear what they are going to do which is (a) novel and (b) derived from their own ideas. It is not enough to combine protocols and methodology described by others and publish it. It also has to be made clear why publishing this protocol is necessary given that much of it will be described in the methods or on-line supplements of papers or already publicly available at ClinicalTrials.gov. There are a few other issues I would raise. It is unlikely that exacerbations will be seen with 3 days of the onset of symptoms although they might be seen within 3 days of the onset of an exacerbation. Aaron and colleagues showed that some exacerbation can have a few days of symptoms insufficient to reaching the threshold for diagnosis of exacerbation. There should be explicit exclusion of patients on long term oral corticosteroids or antibiotics. These medications can be prescribed for non-COPD reasons but affect inflammatory markers. This is an enriched cohort of patients with only those patients experiencing one or more exacerbations in the previous year included. This limits the generalizability of the population as a significant number of patients do not experience exacerbations (over 40% in year1 of the Eclipse study). Furthermore, enriching a cohort on one or more exacerbations in the previous year does not increase the mean annual exacerbation rate in the subsequent year much (about 0.5 per year) compared to recruiting all-comers as a number of clinical trials has found (eg., Forward by Cheisi) and at a cost of making recruitment more difficult.

REVIEWER	De Soyza, Anthony Newcastle University

REVIEW RETURNED	27-Jan-2014

GENERAL COMMENTS	This is an important study but the manuscript needs I feel some work Respiratory viruses commonly associated with AECOPD ARE DIVERSE AND INCLUDE include human rhinoviruses, influenza and parainfluenza viruses, respiratory syncytial virus, coronavirus and adenovirus Table 1 typo Theproportion Exclusion criteria include other known respiratory conditions, such as asthma, as the only cause of the respiratory obstructive disorder, α-1 antitrypsin deficiency, cystic fibrosis, tuberculosis, lung cancer, previous history of lung surgery and other conditions imposing pneumonia risk. HAVE THE AUTHORS SPECIFICALLY INCLUDED OR EXCLUDED COPD WITH ASSOCIATED BRONCHIECTASIS? THIS HAS BEEN REPORTED VARIABLY IN COPD OPBSERVATIONAL COHORTS Subjects on long-term antibiotic therapy at the time of enrolment and those who have received antibiotics and/or steroids in the month prior to the enrolment are also excluded. WERE RECENT EXACERBATORS RE-SCREENED AND ENTERED AFTER RECOIVERY OR PERMANANETLY EXCLUDED? COULD THE AUTHORS PROVIDE THEIR RULES FOR INCLUSION/ EXCLUSION WITH REGARSD THE PATIENTS PULMONARY REHABILITATION STATUS? WAS IT RECORDED AT ALL WHY DID THE AUTHORS ACCEPT Current or prior history of ≥10 pack years of cigarette smokinga,b” This is a low smoking exposure history and less than studies of 20-30pack years Table 3 THERE IS AN EXTENSIVE SET OF QUESTIONNAIRES THAT THE AUTHORS HAVE TRIED TO MINIMISE BY REDUCING TO QUARTERLY- IN MANY INSTANCES- THIS IS PRAGMATIC AND REASONABLE IF SUCH ATTEMPTS WERE MADE WAS THERE A REASON NOT TO INCLUDE ANXIETY/DEPRESSION SCORING?? UNDER CLINICAL ASSESSMENTS- There are several potential tense changes “are assessed” and “will be”; one should be chosen- this maps to the acknowledgements which thank the patients for participation..

	PLEASE REWORD: “degree of bronchiectasis and emphysema resulting from COPD “ degree of bronchiectasis and emphysema NOTED- causality for bronchiectasis is unclear and in some cases may be separate diagnoses… Please reword “Questionnaires” TI “Questionnaires and other indices” BODE INDEX IS NOT A QUESTIONNAIRE Various outcomes are assessed quarterly and at exacerbation using a series of questionnaires and patient-reported outcomes instruments such as the COPD Assessment Test (CAT),31 the Nottingham Extended Daily Activities Scale (NEADL),32 the Council on Nutrition Appetite Questionnaire (CNAQ),33 and the EQ-5D.34 The BODE index (Body-Mass Index, Degree of Airflow Obstruction, Level of Functional Dyspnea, Exercise Capacity)35 will also be calculated. WILL THE AUTHORS CONSIDER THE ADO INDEX TOO??? NEW PARAGRAPH Healthcare use is recorded at all visits, including medication, vaccination, oxygen therapy, use of mechanical ventilation, pulmonary rehabilitation treatment, surgical intervention, outpatient visits (including GP visits and telephone contacts to COPD team), emergency room visits, hospitalisations, and productivity loss (time missed from work or usual activities due to worsening of COPD symptoms). Potential changes in disease management following an exacerbation (e.g. change in medication use) are also recorded. UNDER STATS ANALYSIS As this is a cohort intensively studied and potentially to be replicated: “We will construct a CONSORT diagram and capture where possible reasons for screen failure, drop outs and loss to follow up”. Reporting will be in accordance with STROBE guidance.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Gavin Donaldson
Institution and Country: University College London
Please state any competing interests or state ‘None declared’: None

With apologies to Tom Wilkinson and his colleagues, there is very little new in this protocol. The methodology for this type of study in COPD has been described before. The aims are not unique and have been studied by many groups and consortia. Electronic tracking of patient symptoms have been carried out in clinical trials sponsored by Cheisi and Novartis.

I feel that the authors need to make it very clear what they are going to do which is (a) novel and (b) derived from their own ideas. It is not enough to combine protocols and methodology described by others and publish it. It also has to be made clear why publishing this protocol is necessary given that much of it will be described in the methods or on-line supplements of papers or already publicly available at ClinicalTrials.gov.

Response: We are grateful to Dr. Donaldson for his comments and apologies are not required as they allow us to emphasise the novelty and importance of the AERIS study.

Acute exacerbations of COPD remain a tremendously important clinical issue and, despite many decades of study, significant advances in therapy are still required. COPD is both a heterogeneous and multi-systemic disorder and, to take forward this field, studies are required which include in-depth analysis of all aspects of the disease in a standardised manner in the same patient population. Furthermore, in the era of molecular microbiology and advanced cellular immunology, there has not been a well-designed study to prospectively determine host–pathogen interactions and the interplay with important co-morbidities such as nutritional status. Here, AERIS is both novel and important; the clinical cohort model may appear familiar to Dr. Donaldson, but the in-depth nature and complexity of the approaches taken is not. It will enable new statements about the microbiological definition of exacerbations to be made, dynamics of airway microbiome to be mapped prospectively using molecular typing and interactions with nutritional and adaptive immune status studied for the first time. We have made changes to the manuscript to highlight these key discriminating features.

- Abstract Introduction.
- Abstract discussion
- Introduction page 7 para 3
- Discussion p19-20

The publication of the research protocol paper is clearly required as from this reviewer's comments it is apparent that new approaches to studying these common phenomenon are required and that discriminating clearly the approaches taken will inform the research community and indeed patients in appropriate detail about current thinking and imminent outputs in this area.

The reviewer is correct in highlighting the use of electronic diaries in industry-sponsored clinical trials. However, the use of these tools to capture real-time reported symptoms has not been utilised to help determine the microbiological aetiology of exacerbations and the relationships between timing of symptom onset and changes in the airway microbiome. This point is highlighted in the discussion.

Reviewer 1:
There are a few other issues I would raise. It is unlikely that exacerbations will be seen with 3 days of the onset of symptoms although they might be seen within 3 days of the onset of an exacerbation. Aaron and colleagues showed that some exacerbation can have a few days of symptoms insufficient to reaching the threshold for diagnosis of exacerbation.

Response:
The reviewer's own comment on the use of electronic diaries highlights that in fact understanding of the timing of onset of exacerbation symptoms and the relationship with infectious pathogens is not understood (even by experts). By tracking symptoms prospectively and sampling events early on in their natural history we will be able for the first time to study the onset of these events and not the aftermath as in previous studies.

Reviewer 1:
There should be explicit exclusion of patients on long term oral corticosteroids or antibiotics. These medications can be prescribed for non-COPD reasons but affect inflammatory markers.

Response: This is in fact mentioned as exclusion criterion in the text, but not in Table 2. We have added this information to Table 2 (page 10).

Reviewer 1:
This is an enriched cohort of patients with only those patients experiencing one or more exacerbations in the previous year included. This limits the generalizability of the population as a significant number of patients do not experience exacerbations (over 40% in year1 of the Eclipse

study). Furthermore, enriching a cohort on one or more exacerbations in the previous year does not increase the mean annual exacerbation rate in the subsequent year much (about 0.5 per year) compared to recruiting all-comers as a number of clinical trials has found (eg., Forward by Cheisi) and at a cost of making recruitment more difficult.

Response:
The approach taken to include subjects with at least one documented exacerbation in the previous year considered the literature alluded to by the reviewer, in addition to a broader range of experiences from a number of clinical trials.

We agree that a significant number of patients with COPD do not exacerbate and therefore, as the main outcome of this study is to inform on the nature of the exacerbation event, with a limited population of subjects as with many other studies enrichment was used. As highlighted, we also agree that the use of a single event does not dramatically skew the observed exacerbation rate. Whilst any enrichment can limit the available pool of suitable patients, we are fortunate in Southampton to have developed very robust recruitment processes and this is not a concern.

An edit has been made in the discussion to highlight this issue (page 21).
Reviewer Name de soyza
Institution and Country: Newcastle University
Please state any competing interests or state 'None declared': No competing interests with this study

This is an important study but the manuscript needs I feel some work

P7: "Respiratory viruses commonly associated with AECOPD ARE DIVERSE AND INCLUDE include human rhinoviruses, influenza and parainfluenza viruses, respiratory syncytial virus, coronavirus and adenovirus."

Response:
This sentence has been edited as requested.

Table 1 typo: Theproportion

Response:
Table 1 has been checked for typos.

P9: "Exclusion criteria include other known respiratory conditions, such as asthma, as the only cause of the respiratory obstructive disorder, α-1 antitrypsin deficiency, cystic fibrosis, tuberculosis, lung cancer, previous history of lung surgery and other conditions imposing pneumonia risk."

HAVE THE AUTHORS SPECIFICALLY INCLUDED OR EXCLUDED COPD WITH ASSOCIATED BRONCHIECTASIS? THIS HAS BEEN REPORTED VARIABLY IN COPD OPBSERVATIONAL COHORTS

Response:
As stated in the paper, all patients with a dominant respiratory diagnosis other than COPD were excluded. However, as many patients may have subclinical bronchiectasis, a CT scan is performed at enrolment to describe the degree of bronchiectasis present in all patients as described in paragraph 1, page 14. Patients with bronchiectasis are not excluded, provided they do not have other respiratory exclusion criteria.

P9: "Subjects on long-term antibiotic therapy at the time of enrolment and those who have received

antibiotics and/or steroids in the month prior to the enrolment are also excluded."

WERE RECENT EXACERBATORS RE-SCREENED AND ENTERED AFTER RECOVERY OR PERMANANETLY EXCLUDED? COULD THE AUTHORS PROVIDE THEIR RULES FOR INCLUSION/ EXCLUSION WITH REGARDS THE PATIENTS PULMONARY REHABILITATION STATUS? WAS IT RECORDED AT ALL.

Response:
As mentioned in the footnote of Table 2: "Subjects with recent COPD exacerbations, in stable condition, and having stopped antibiotics, can be enrolled one month post-exacerbation. " This has now also been stated in the main manuscript (page 9). As clearly stated in the Methods, once enrolled, subjects are followed monthly for 2 years, and seen in the clinic within 72 hours of onset of symptoms of AECOPD.

Pulmonary rehabilitation involvement was not an inclusion or exclusion criterion, but was recorded in the healthcare record.). Measures of functional status (e.g. 6 minute walk test and grip strength) were performed to enable analysis of function in comparison to other clinical and laboratory variables in the study.

P9: WHY DID THE AUTHORS ACCEPT "Current or prior history of ³10 pack years of cigarette smokinga,b" This is a low smoking exposure history and less than studies of 20-30 pack years

Response:
As the study aimed to recruit patients with AECOPD across the spectrum of disease, use of a higher smoking threshold was not considered appropriate. A smoking history of 10 pack years has been used as a minimum smoking threshold in other studies of COPD.

Table 3
THERE IS AN EXTENSIVE SET OF QUESTIONNAIRES THAT THE AUTHORS HAVE TRIED TO MINIMISE BY REDUCING TO QUARTERLY- IN MANY INSTANCES- THIS IS PRAGMATIC AND REASONABLE IF SUCH ATTEMPTS WERE MADE WAS THERE A REASON NOT TO INCLUDE ANXIETY/DEPRESSION SCORING??

Response:
It was necessary to select questionnaires and patient-reported outcome instruments considered most appropriate to use in order to assess the impact of AECOPD on health-related quality-of-life and healthcare resource utilisation. We were unable to include all potentially suitable measures due to the potential burden on patients and so prioritisation was required. No questionnaire was specifically administered to assess anxiety and depression; however, the EQ-5D does include anxiety/depression as one of the 5 component items. A sentence has been added to paper to highlight this (page 15).

UNDER CLINICAL ASSESSMENTS-
There are several potential tense changes "are assessed" and "will be"; one should be chosen- this maps to the acknowledgements which thank the patients for participation.

Response:
The tense of this paragraph and the statement in the Acknowledgements has been amended as requested.

PLEASE REWORD:
"degree of bronchiectasis and emphysema resulting from COPD "

degree of bronchiectasis and emphysema NOTED- causality for bronchiectasis is unclear and in some cases may be separate diagnoses…

Response:
This sentence has been amended as requested (page 14).

Please reword

P15: “Questionnaires” TO “Questionnaires and other indices” BODE INDEX IS NOT A QUESTIONNAIRE

Response:
This subtitle has been amended to read “Questionnaires and other patient-reported outcome instruments” (page 15). Table 3 (page 12) has also been amended accordingly.

P15: Various outcomes are assessed quarterly and at exacerbation using a series of questionnaires and patient-reported outcomes instruments such as the COPD Assessment Test (CAT),31 the Nottingham Extended Daily Activities Scale (NEADL),32 the Council on Nutrition Appetite Questionnaire (CNAQ),33 and the EQ-5D.34 The BODE index (Body-Mass Index, Degree of Airflow Obstruction, Level of Functional Dyspnea, Exercise Capacity)35 will also be calculated. WILL THE AUTHORS CONSIDER THE ADO INDEX TOO???

Response:
As previously stated, it was necessary to select questionnaires and patient-reported outcome instruments considered most appropriate to use in order to assess the impact of AECOPD on health-related quality-of-life and healthcare resource utilisation. Composite scores which can be derived from the clinical indices recorded such as BODE and ADO will be assessed.

P15: NEW PARAGRAPH Healthcare use is recorded at all visits, including medication, vaccination, oxygen therapy, use of mechanical ventilation, pulmonary rehabilitation treatment, surgical intervention, outpatient visits (including GP visits and telephone contacts to COPD team), emergency room visits, hospitalisations, and productivity loss (time missed from work or usual activities due to worsening of COPD symptoms). Potential changes in disease management following an exacerbation (e.g. change in medication use) are also recorded.

Response:
This information is now shown in a separate paragraph as requested (page 15).

UNDER STATS ANALYSIS
As this is a cohort intensively studied and potentially to be replicated: “We will construct a CONSORT diagram and capture where possible reasons for screen failure, drop outs and loss to follow up”. Reporting will be in accordance with STROBE guidance.

Response:
The requested statements have been added to the paper (pages 17 and 19).