PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Digital Acoustic Surveillance for Early Detection of Respiratory Disease Outbreaks in Spain: A protocol for an observational study
AUTHORS	Gabaldon-Figueira, Juan; Brew, Joe; Doré, Dominique; Umashankar, Nita; Chaccour, Juliane; Orrillo, Virginia; Tsang, Lai Yu; Blavia, Isabel; Fernández-Montero, Alejandro; Bartolomé, Javier; Grandjean Lapierre, Simon; Chaccour, C

VERSION 1 – REVIEW

REVIEWER	Turner, Richard Charing Cross Hospital, Department of Respiratory Medicine
REVIEW RETURNED	06-Apr-2021

GENERAL COMMENTS	A very interesting study protocol. My main request is that further details of the cough detection technology are given. Not necessarily how the automated acoustic algorithm works, but more detail from the study's preliminary results. How acceptable was the app to participants, and were most willing to have it running all night on a number of nights? Specifically, regarding the analytical performance of the app though, is the type of smartphone important, and does it need to be within a particular range of the subject to record accurately? And is a specificity of 96.5% sufficient to discriminate coughs from other explosive sounds (closing doors, snores, other vocalisations, etc)? The false positive rate for coughs could actually be very high in a noisy environment if the prevalence of cough is low. In a separate paper, the validation process for the cough detection algorithm should be described in detail, including how the human observers were trained to identify cough sounds. There are very few validated cough frequency detection systems currently in use in clinical research. This complexity of developing cough monitoring technology should be made more explicit in the introduction of the current manuscript. A recent review of cough monitoring technology, for example, is PMID: 33145097. As a further point, are there any data out there on the prevalence or range of cough frequencies in covid-19? If so, this should be referenced. Cough is common but, from personal experience of having the illness, and of looking after large numbers of people with covid-19, is by no means universal. Specific minor comments

	In the introduction, line 116-117, the statement "coughing increases person to person transmission (of covid-19)" needs to be either backed up by published evidence or be tempered with "probably" or "may". I would recommend avoiding mention of disease-specific cough sounds in covid-19 and other conditions (introduction, line 122-3). This is controversial, backed by little evidence in other conditions, and not of direct relevance to this study.

REVIEWER	Hossain , Forsad University of Massachusetts Amherst
REVIEW RETURNED	18-Apr-2021

GENERAL COMMENTS	Comments to the author: The study design doesn't mention the protocols for transferring and saving electronic data. For example, in the USA, to transmit and keep health-related information, you need to satisfy the "HIPAA" security protocol. As this study store data with metadata like a phone number, the data collected in the study can be used for identifying the participants. Please give us more information about the security protocol or measures are taken to make sure the stored data is safe and can only be accessed by researchers. Apart from that, I find the study design acceptable, and I wish good luck to the people involved in the study!

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Comment	Answer	Actions
1. My main request is that further details of the cough detection technology are given. Not necessarily how the automated acoustic algorithm works, but more detail from the study's preliminary results. How acceptable was the app to participants, and were most willing to have it running all night on a number of nights?	Thank you for taking the time to review the manuscript and provide your valuable feedback. The study's preliminary results are derived from a pilot roll-out in Cizur Menor, a small town south of Pamplona. Between November 9th 2020, and December 7th 2020 we recruited 57 participants, who were mostly contacted via an email list available to part of the research team, as part of a previous epidemiological study. The list included approximately 500 people, which indicates that little more than 11% of contacted individuals decided to participate. Enrolled patients generally accepted the app quite positively. While we initially asked participants to keep the app running for 24 hours during a period of one	Comments addressing this request have been incorporated to page 9 of the protocol.

	year, we started having numerous complaints regarding the increased battery consumption from smartphones. We therefore decided to instruct patients to limit its usage to night-time, and to record at least 6 hours every day. Similarly, we noticed that providing a clear, more realistic timeline to participants significantly increased their willingness to take part and use the app regularly, that's why we decided to establish 30 days of recording as our objective, with the possibility of keep using the app beyond that point for interested participants.	
2. Specifically, regarding the analytical performance of the app though, is the type of smartphone important, and does it need to be within a particular range of the subject to record accurately? And is a specificity of 96.5% sufficient to discriminate coughs from other explosive sounds (closing doors, snores, other vocalisations, etc)? The false positive rate for coughs could actually be very high in a noisy environment if the prevalence of cough is low.	These are all important questions, but we believe that the answers belong with the study results, not the protocol. Preliminarily we can comment that the type of smartphone is important. While the app runs both in Android and iOS systems, we have recently noticed a series of bugs in the iOS version that hinder user experience and make iOS users more hesitant to use the app regularly, prompting early withdrawal from the study. Even though user experience, and therefore participant retention, are better in Android systems, the quality of the smartphone's microphone is also important. The microphones of some low-cost Android models fail to accurately capture coughs. However, this limitation is addressed at the time of recruitment. To be included in the study, participants must complete a microphone calibration process, and participants who fail to pass this test are excluded from the study dataset and any further analysis. The reviewer is correct to point out that specificity measured at the unit of the explosive sound does not give a complete view of accuracy, since a very noisy sound environment (ie,	Eligibility criteria have been updated to reflect the cough calibration process. (page 8). A further comment on the limitations of the appraisal of accuracy based on sensitivity and specificity alone has been added to page 10.

	many explosive sounds) may result in a "high" specificity (a low percentage of false positives), but this does not translate, necessarily, to a low rate of false positives per *time* observed, nor does it take into account the "pre-test" probability of a sound being a cough (which is, of course, higher among someone ill with respiratory disease relative to someone who is entirely healthy). Similarly, sensitivity measured at the unit of the explosive sound does not, by definition, include sounds not captured (since they were not explosive), of which a non-zero number may have been cough. We thank the reviewer for these constructive critiques	
3. In a separate paper, the validation process for the cough detection algorithm should be described in detail, including how the human observers were trained to identify cough sounds. There are very few validated cough frequency detection systems currently in use in clinical research. This complexity of developing cough monitoring technology should be made more explicit in the introduction of the current manuscript. A recent review of cough monitoring technology, for example, is PMID: 33145097	Indeed, a more detailed discussion of the application's validation process will be included in a paper currently in preparation. This separate piece describes three potential use-cases identified in this study.	Further details on the complexities of developing an automated cough detection tool have been included in the discussion, using information from the reference you provided (pages 5-6).
4. As a further point, are there any data out there on the prevalence or range of cough frequencies in covid-19? If so, this should be referenced. Cough is common but, from personal experience of having the illness, and of looking after large numbers of people with covid-19, is by no means universal.	Certainly, cough is not a universal symptom of covid-19.	We have included a section in the introduction with a reference to a meta-analysis published in PLOS One (PMID:32574165) describing an overall prevalence of cough in patients with COVID-19 of 57%, with a confidence interval between 54 and 60%.
5. Specific minor comments	Accepted	We have rephrased line 116 of the introduction,

In the introduction, line 116-117, the statement "coughing increases person to person transmission (of covid-19)" needs to be either backed up by published evidence or be tempered with "probably" or "may".		which now reads "Additionally, cough is a key event in the transmission of COVID-19 and other respiratory pathogens." We have also included the following reference: PMID: 33746492.
6. I would recommend avoiding mention of disease-specific cough sounds in covid-19 and other conditions (introduction, line 122-3). This is controversial, backed by little evidence in other conditions, and not of direct relevance to this study.	Accepted	The reference to the use of cough sounds for the etiologic diagnosis of respiratory diseases has been removed from the introduction. This is a concept that we would like to furtherly explore in other projects, but we agree it is not relevant to this specific study.

Reviewer #2

Comment	Answer	Actions
1. The study design doesn't mention the protocols for transferring and saving electronic data. For example, in the USA, to transmit and keep health-related information, you need to satisfy the "HIPAA" security protocol. As this study store data with metadata like a phone number, the data collected in the study can be used for identifying the participants. Please give us more information about the security protocol or measures are taken to	Thank you for contributing to the peer review process of our manuscript and your good wishes. All study procedures have been approved by the ethics committee of Navarra. All acoustic data is stored on encrypted servers physically located in the United States. Data storage and access protocols are compliant with GDPR. Metadata collected by Hyfe does not contain any personally identifiable data and can only be joined to identifiable information via an anonymous ID	These comments have now been included in page 14.

make sure the stored data is safe and can only be accessed by researchers.	number. Only the sponsor (Clinical Universidad de Navarra) has access to the personal, identifiable data of participants, which is stored in physical locations under lock, and password-protected files in PCs at the University of Navarra. Only anonymized data will be shared with researchers outside the sponsor institutions.	

VERSION 2 – REVIEW

REVIEWER	Turner, Richard Charing Cross Hospital, Department of Respiratory Medicine
REVIEW RETURNED	10-Jun-2021

GENERAL COMMENTS	I am happy that my previous comments have been adequately addressed in the revised version of the manuscript.

REVIEWER	Hossain , Forsad University of Massachusetts Amherst
REVIEW RETURNED	16-Jun-2021

GENERAL COMMENTS	My comment was addressed, so I incline to accept the publication.