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Digital Acoustic Surveillance for Early Detection of Respiratory Disease Outbreaks in Spain: A protocol for an observational study

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Abstract

Introduction

Cough is a landmark symptom of COVID-19 and other respiratory illnesses. However, objectively measuring its frequency and evolution is hindered by the lack of reliable and scalable monitoring systems. This can be overcome by newly developed artificial intelligence models that exploit the portability of smartphones. In the context of the ongoing COVID-19 pandemic, cough detection for respiratory disease syndromic surveillance represents a simple means for early outbreak detection and disease surveillance. In this protocol, we evaluate the ability of population-based digital cough surveillance to predict the incidence of respiratory diseases at population level in Navarra, Spain, while assessing individual determinants of uptake of these platforms.

Methods and analysis

Participants in the Cendea de Cizur, Zizur Mayor, or attending the local University of Navarra (Pamplona) will be invited to monitor their night-time cough using the smartphone app Hyfe Cough Tracker™. Detected coughs will be aggregated in time and space. Incidence of COVID-19, and other diagnosed respiratory diseases within the participants cohort, and the study area and population will be collected from local health facilities and used to carry out an ARIMA analysis on those independent time series. In a mixed-methods design, we will explore barriers and facilitators of continuous digital cough monitoring by evaluating participation patterns, socio demographic characteristics. Participants will fill an acceptability questionnaire and a subgroup will participate in focus group discussions.

Ethics and dissemination

Ethics approval was obtained from the ethics committee of the Centre Hospitalier de l'Université de Montréal, Canada and the Medical Research Ethics Committee of Navarre, Spain. Preliminary findings will be shared with civil and health authorities and reported to

individual participants. Results will be submitted for publication in peer-reviewed scientific journals and international conferences.

Trial Registration Number

clinicaltrials.gov/NCT04762693

Strengths and limitations of this study

1. This is the first study to evaluate the utility of artificial intelligence models and smartphone applications for cough detection at population level.
2. The studied approach has the potential to be rapidly scalable even within underdeveloped public health systems.
3. Qualitative methods will improve the understanding of barriers and facilitators affecting the uptake of cough detection smartphone applications and participation in acoustic surveillance programs.
4. Recorded coughs will be annotated with clinical diagnoses (when available) and will contribute to the training of cough-based disease-specific screening and diagnostic tools.
5. Success of this study is contingent on large-scale enrolment and high participant retention since a small sample size might not be sufficient to appropriately correlate the study population's cough trends and their relationship with the incidence of respiratory diseases at population level.

Introduction

Real-time tracking of the COVID-19 pandemic and detection of the emergence of novel variants or other respiratory pathogens represent challenges for public health authorities globally. Nonetheless, understanding local epidemiology is essential to disease control efforts. This is particularly true now that the world has moved into a COVID-19 endemic phase, with periodic outbreaks in multiple locations superimposed over ongoing community transmission. The ability to appropriately monitor disease incidence, however, is frequently limited by a lack of testing capacity, delays in health-seeking behaviours, as well as complexities related to timely aggregation of actionable surveillance data by public health authorities.

Although asymptomatic cases of COVID-19 and other respiratory communicable diseases are well described, cough remains a hallmark symptom of COVID-19 with as much as 75% of infected patients reporting cough as an early symptom. (1, 2) Additionally, coughing increases person to person transmission. Automatically detecting cough sounds is now possible thanks to the recent development of acoustics and artificial intelligence (AI) models which can be deployed on smartphone applications.(3) In brief, putative cough sounds (manifested as short and explosive noises) are recognized and captured by smartphones. Machine learning models trained on hundreds of thousands of annotated sounds are then used to distinguish cough from other sounds. Similar approaches were also taken one step further and shown to have value in COVID-19 specific cough recognition for disease screening and diagnosis. (4, 5)

We propose that COVID-19 surveillance and early outbreak recognition can be enhanced by digitally monitoring cough and detecting changes in its incidence at population level. We hypothesize such changes precede individual symptoms recognition, healthcare seeking behaviours, diagnosis and data aggregation within conventional disease surveillance systems. Indeed, digital cough monitoring data can be aggregated in real time providing constantly updated information on the emergence and activity of communicable respiratory diseases within populations. This approach would be of particular value in low- and middle-income

countries where (a) capturing passive data through health services is insufficient given unequal access to healthcare, and (b) active case detection and contact tracing capacity is limited. (6, 7)

To our knowledge, digital cough monitoring for early detection of respiratory disease outbreaks has never been performed. Provided the participation of a critical mass of active users is achieved, monitoring of aggregated cough data could provide a simple and inexpensive surrogate indicator for overall respiratory infections incidence, similar to, but more accurate than wastewater monitoring (8). This information could in turn guide public health interventions. If proven successful in the specific case of COVID-19, this study would establish a template for early and disease-agnostic detection of emerging pathogens, therefore contributing to health systems epidemic preparedness.

Primary research question

Can digital cough surveillance predict the incidence of respiratory diseases at population-level in Navarra, Spain?

Methods

Study design

This is a prospective observational study which will take place between November 2020 and October 2021 (Figure 1). Participants will be recruited in (a) the Cendea de Cizur, a municipality composed by a cluster of villages south of the city of Pamplona, (b) the neighbouring town of Zizur Mayor, in the Chartered Community of Navarra (Spain), as well as (c) in the different campuses of the University of Navarra (Pamplona), which collides with the municipalities.

All these communities are located within a 5 km range from each other, and there is a considerable geographical and social overlap between them, as the University of Navarra is the second most important employer in the area.

The 4,000 people living in the Cendea de Cizur are served by a public health center which receives 45,000 outpatients visits per year. Of these, approximately 12% are associated with respiratory diseases. Furthermore, the Clínica Universidad de Navarra is the main private healthcare provider in the region and offers medical care to a significant proportion of the population, as well as university students and workers. Both centres offer COVID-19 PCR testing. Together, those two healthcare facilities cover most of the population's healthcare needs and have digitalized medical record systems that facilitate the retrieval of medical data concerning the diagnosis of respiratory diseases among participants.

Recruitment strategies will include direct solicitation, community meetings, videos and advertisements in social media and university communication platforms. Those willing to participate will attend individual sessions with a study coordinator for counselling and training using the Hyfe Cough Tracker™ (Hyfe™) application, and for obtention of informed consent (Supplementary material). Participants will consent to be contacted regularly via email and telephone by the study team and will also fill an enrolment questionnaire (Supplementary material) where demographic and respiratory diseases medical data will be collected.

Primary objective

1. To assess the value of digital cough monitoring and acoustic surveillance in predicting COVID-19 and other respiratory diseases incidence at population level.

Secondary objective

2. To assess barriers and facilitators to participation in an acoustic surveillance program using a smartphone-based digital cough monitoring application.

Eligibility criteria

To be included in the study, participants must (i) be 13 years old or older, (ii) own a smartphone, (iii) be willing to install and use the Hyfe™ digital cough monitoring application, (iv) accept and comply with Hyfe™ privacy policy and terms of use, and (v) grant access to their medical records. To optimize population representativity, participants also need to (vi) visit the University of Navarra on a regular basis, either as a student, worker, or patient of the university clinic, or (vii) have a general interest in the study, and (viii) currently reside in Navarra. These criteria aim at ensuring a large sample size and the availability of needed medical records while concentrating recruitment in a geographically focused area.

Participant retention

To ensure participants' retention and promote continuous cough recording, we will use videos posted on social media, as well as emailed to participants, text messages and regular push notifications sent via the Hyfe™ application on participants' smartphones. Participants will also receive monthly emails with information regarding the current stage of the study and high-level preliminary results.

Digital cough monitoring

The cough detection application used in this study is Hyfe Cough Tracker™ (Hyfe™). (https://www.hyfeapp.com/). Hyfe™ runs in the background of smartphones operating systems, listens for and records short snippets (<0.5 seconds) of explosive, putative cough sounds and then classifies them as cough or non-cough, using a convolutional neural network model. Cough sounds are automatically matched with time and GPS coordinates which can be jittered to ensure participants' privacy. Hyfe™ is a research tool that has collected over 5 million putative cough sounds, of which over 1,000,000 have been classified as coughs or not by a human listener in order to train the AI model.

The analytical performance of Hyfe™ for cough detection was confirmed using this study's preliminary results from a subgroup of participants recruited in the Cendea de Cizur between November and December 2020. Analytical performance refers to whether the application is sensitive and specific for the classification of recorded sounds as coughs or non-coughs. During this period, nearly 700,000 putative cough sounds were registered, of which 119,876 were classified by human observers, revealing a sensitivity of 96.34% and a specificity of 96.54%, when using a cough-positivity threshold of 0.85 (Figure 2).

Upon enrolment, a study coordinator will assist participants in installing the Hyfe™ application. Once turned on, it will continuously monitor participants' cough. Participants can turn the application on and off at will but will be instructed to keep it active for at least six hours or while they sleep, every day for a minimum period of 30 days. In an adaptive design aimed at improving retention, participants will have the possibility of extending their participation to a 3-month and 6-month period.

Local epidemiology of respiratory disease

Digital medical data systems at the Zizur's health center and the Clínica Universidad de Navarra will be reviewed monthly to establish the incidence of the following respiratory, or cough-associated diseases in the participants cohort; COVID-19, influenza, respiratory syncytial virus (RSV), pneumonia, asthma, bronchitis, pharyngitis, chronic cough, chronic obstructive pulmonary disease (COPD), gastro-esophageal reflux disease (GERD), other nonspecific respiratory tract infections. Specifically, for COVID-19, daily incidence figures for the study area (Cendea de Cizur, Zizur Mayor, and Pamplona), and regional population, will also be obtained from local health authorities. Data will be aggregated and used to build local epidemic curves of respiratory diseases during the study period.

Barriers and facilitators to participation

A participation cascade informing on the number of solicited, enrolled, and actively recording participants will be tracked in real time throughout the study. The total number of user-hours using Hyfe™ will also be monitored in real time.

All participants will be asked to fill a satisfaction survey in which they will be asked about the usability of the app, the problems that they ran into, and their likelihood of using the app in the future. We will follow-up with a group of 25 participants who are willing to attend a focus group discussion (FGD) to better understand the barriers and facilitators affecting participation in the cough-surveillance system. The 25 participants will include some of whom deleted the application early on, who stopped using it after a month, and who had low satisfaction scores.

Patient and public involvement

This study pilots an experimental syndromic surveillance approach at population level. The municipal authorities of the Cendea de Cizur were informed about the nature of the study and provided feedback on the best approach to recruit local participants. Similarly, representatives of the University of Navarra's medical services collaborated on the design of the study protocol including the review of recruitment strategies as well as data collection, aggregation and reporting plans. No anticipated participants were involved in the study design. Study findings are to be reported in both English and Spanish to participants and key stakeholders at individual, municipality, and university levels during the surveillance phase.

Data analysis and sample size calculations

Syndromic surveillance as a surrogate marker of respiratory disease activity

Given the uncertainty around the incidence of the various respiratory diseases including COVID-19, throughout the study period, it is impossible to establish a target sample size

sufficient to either confirm or confute with statistical significance that cough monitoring at population level can predict incidence of respiratory diseases. We will endeavour to recruit the highest number of participants possible in order to achieve the best representation of the population.

First, cough data will be aggregated in time and space to create cough incidence curves and geospatial heat maps reflecting the frequency and density of cough among the studied population (Figure 3 and Figure 4). Second, epidemic curves reflecting the incidence of targeted respiratory illnesses within the participants cohort, and the number of COVID-19 cases diagnosed in the study area and population will be generated with data collected from the Clínica Universidad de Navarra, and Zizur's health center, as well as aggregated epidemiological records obtained from regional health authorities, respectively. Coughs per person-hour and clinical diagnoses data will be superposed in time. Finally, we will carry out an autoregressive moving average (ARIMA) analysis to compare the incidence of confirmed and forecasted respiratory diseases (including COVID-19) with the frequency of cough among study participants, measured as coughs per person-hour. ARIMA analysis is a type of time series analysis that uses past data to forecast the likely future behaviour of a variable. In brief, the variable of interest is regressed to its own lagged values, and autoregression and partial autocorrelation functions are used to model the stochastic nature of a time series. (9) Comparison and prediction analyses will be performed using epidemic curves from both the participants cohort and in the entire study area and population.

Perceptions and willingness to participate in syndromic surveillance

Mixed methods will be used to assess individual barriers and facilitators to participation in an acoustic surveillance program. Among all eligible individuals in the Cendea de Cizur, Zizur Mayor and in the University of Navarra who are invited to participate in the study, we will assess how many do install the cough detection application and keep using it through the

course of the study. Participants corresponding to specific user profiles based on duration and regularity of cough recording will be identified. We will then descriptively analyze the socio-demographic characteristics, and baseline health conditions of participants belonging to the different user profiles.

A subsample of participants will be contacted once a month, by telephone or text messaging, to obtain feedback from their experience using the app.

To assess population uptake of Hyfe™, as well as barriers and facilitators to participation, a convenience subsample of 25 participants will be recruited for focus group discussions. Following similar designs, FGDs will consist of two parts. (10) The first one will be aimed at understanding a participant's awareness of their cough frequency and temporality patterns, as well as the perceived importance of measuring these elements. Questions asked in this part will include (i) How much attention do you pay to your coughs on a daily basis? (ii) How important is it for you to know the number of times you cough per day? (iii) Will keeping track of your coughs help you improve your health? The second one will focus on the participant's experience using Hyfe™, as well as possible recommendations for developers to improve it. This part will include the following general questions: (i) What do you like about the app, (ii) What do you think of this app compared to other health apps, (iii) What doesn't work well, (iv) What keeps you committed (or not) to using the app, (v) What do you think the purpose of the app is, (vi) What advice do you have for the developers?

Risks and privacy

Recording sounds implies specific ethical and privacy concerns. These are, however, addressable at different levels. First, sound snippets recorded are too short (<0.5 seconds) to capture conversations or background sound. Participants can withdraw from the study at any time, and the application can be turned off or removed from smartphones freely. Our consent

process explicitly describes exactly what is and what is not recorded. The use of pre-generated unique identifiers to install and use the smartphone application ensures that only investigators can link cough data to personal identifiers. Contact information collected from participants will be kept in physical forms stored under lock, and password-protected files at the University of Navarra. Only the principal investigator, study coordinator, and research assistant will have access to this information.

Ethics and dissemination

This study protocol was approved by the ethics committee of the Centre Hospitalier de l'Université de Montréal, Canada (Reference numbers 2021-9247 20.253 & 2021-9270 20.226) and the Medical Research Ethics Committee of Navarra, Spain (Reference number PI107/2020). Any modifications to the approved protocol would be resubmitted to both committees.

Preliminary summary results of this study will be regularly shared with participants via email and through focal meetings. Final results will also be disseminated in open-access scientific journals and international conferences. A two-page summary of results will be prepared in Spanish and posted on the municipal and university website, and shared with local civil and health authorities, as well as with individual participants.

Discussion

The current COVID-19 pandemic highlights the incapacity of existing surveillance networks to rapidly curb the impact of emerging respiratory pathogens in the current globalized world. (11) This is particularly true in low- and middle-income countries, where diagnostic and contact-tracing efforts are limited by their crippling costs, and where epidemiological data aggregation infrequently translates into actionable information because of delays inherent to disaggregated and poorly digitalized health information systems. Continuous, individual-

based, and passive monitoring of cough among entire populations could represent inexpensive large-scale surveillance networks contributing to the early detection of outbreaks and enabling prioritized and focal delivery of limited resources.

AI and more specifically machine learning models, are increasingly used in disease surveillance and can maximize the impact of limited available resources. (12) Integration of such models with accurate digital epidemiological data was shown to provide reliable, near-real time estimations of influenza disease incidence. (13) The widespread distribution of smartphones coupled with the development of AI-enabled sound classification models now represent another new potential breakthrough in public health and epidemic preparedness. Beyond being able to detect cough, most smartphones have integrated geo-location functions. This allows the integration of acoustic records with geo-spatial and temporal data and increases the range of applications of acoustic surveillance systems for disease control. (14)

Apart from participating in a collective disease tracking and eradication effort, participants monitoring their cough also benefit from objective feedback on their own symptomatology. During a pandemic, such feedback could trigger appropriate healthcare seeking behaviours and self-quarantine further helping to limit disease transmission at community level.

Implementing such an innovative approach to disease surveillance is contingent on overcoming substantial challenges. Evidence suggests that users are typically willing to install mobile apps with a clearly perceived health benefit. But this is often limited by issues such as increased battery drainage, or disruption of daily activities by alerts and notifications. (15) Specifically, for acoustic surveillance apps, protecting user's privacy must also be a priority, in order to create the social trust needed to achieve a high uptake of these systems. To guarantee this, users must be able to clearly understand the nature of these applications, as

well as to control their functioning at will. This means that the quality of the data recorded will greatly depend on individual behaviours.

Despite proven technical capacity and tremendous potential in complementing surveillance systems, whether listed challenges can be overcome and whether digital cough monitoring can provide actionable public health information remains unknown. This study will address those questions. It will also generate operational expertise and qualitative knowledge on the facilitators to be exploited, and the barriers to be addressed in order to maximize uptake and impact prior to implementation on a wider scale.

Limitations and potential challenges

Enrolment and retention are expected to represent the major limitations of this project. Acoustic syndromic surveillance tools might be perceived as threatening for the privacy of potential participants. Furthermore, the quantity of cough data recorded will heavily rely on the regular use of the system by participants. The diversity of respiratory and non-respiratory conditions that can cause cough, as well as the consumption of medications to treat them, can make it difficult to link changes in cough frequency with epidemiological data. Finally, asymptomatic, or mild infections of SARS-CoV-2 and other respiratory pathogens, mean that a proportion of infected patients will not contribute to the cough-based surveillance system and are unlikely to seek medical attention, reducing available cough and epidemiological data necessary for the analysis. Those limitations and challenges reflect well the impediments to larger scale deployment of cough-based syndromic surveillance for any respiratory disease hence making this innovative study an ideal stress-test for such approach.

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Contributors

All authors meet criteria for authorship as per the BMJ Global Health policy and ICJME recommendations. Conceptualization (JCGF, JB, DD, NU, LYT, SGL, CCh), data curation (JCGF, JB, NU, CCh), formal analysis (JCGF, JB, NU, SGL, CCh), funding acquisition (SGL), investigation (JCGF, JCh, ALP, VO, IB, JBart, CCh), methodology (JCGF, JB, NU, SGL, CCh), supervision (JCGF, SGL, CCh), writing of the original draft (JCGF, CCh, SGL). All authors have read, reviewed, discussed, and approved the final manuscript and their respective representation in the authorship.

Data sharing statement

Aggregated deidentified datasets will be available upon completion of the study by reasonable request to the corresponding author.

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Competing interest

JB is the CEO of Hyfe™ Inc. Hyfe Inc had no role in the decision to submit this protocol for publication. All other authors declare no competing interests. Upon submission of this protocol for publication, JCG, SGL and CCh had full access to all the data available and assumed responsibility for the decision to submit the manuscript content for publication.

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Supplementary materials

1. Informed Consent Form
2. Assent form
3. Complementary medical questionnaire for participants
4. SPIRIT Checklist

Figure legends

Figure 1: Study design, timeline and monitoring plan for the study's primary objective.

Figure 2: Receiver operating characteristic (ROC) analysis showing an area under the curve (AUC) of 0.995 for the classification of cough in participants recruited between November and December 2020.

Figure 3: Coughs per person-hour registered in 62 participants between November 2020 and January 2021.

Figure 4: Heatmap of registered cough episodes in the municipalities of Zizur Mayor, Cendea de Cizur, and Pamplona between November 2020 and March 2021 (The Cendea de Cizur is an incontiguous municipality).

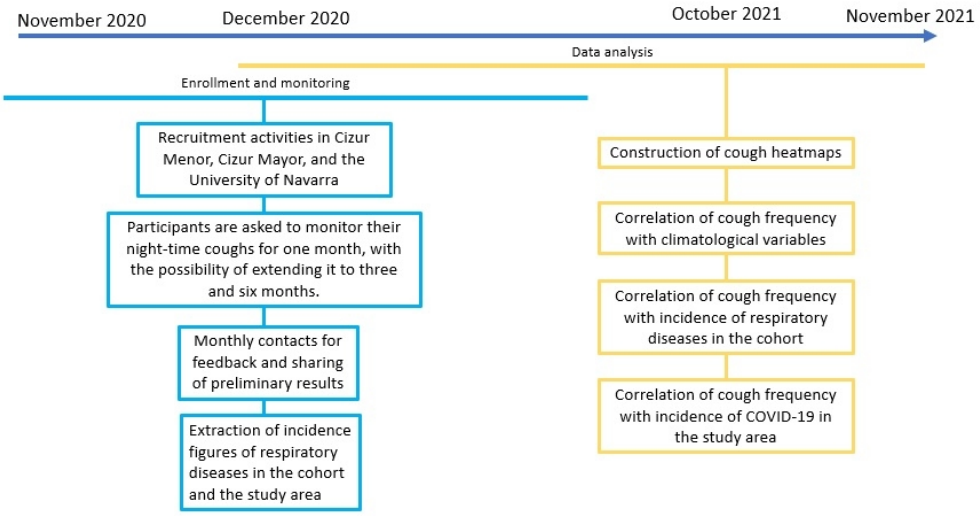

Figure 1

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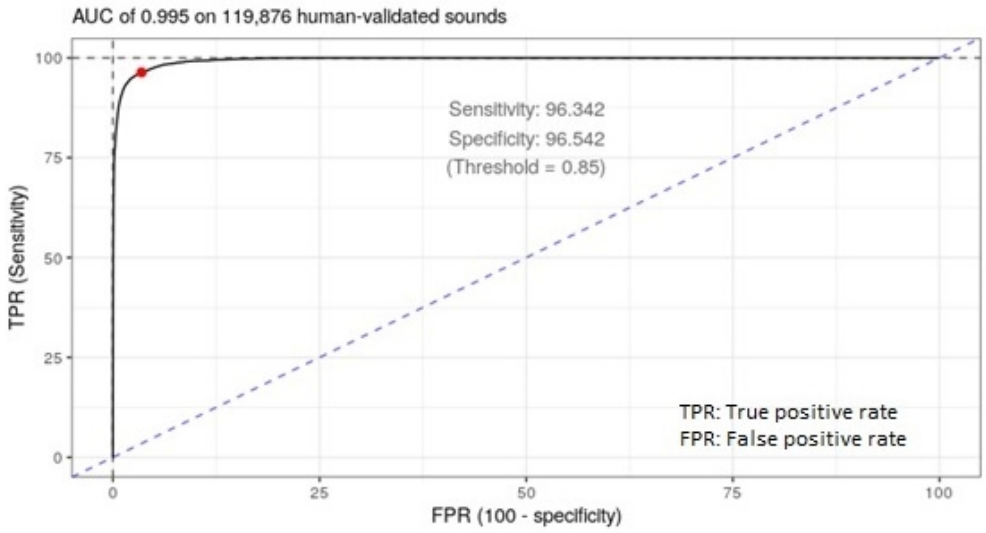

Figure 2

147x79mm (96 x 96 DPI)

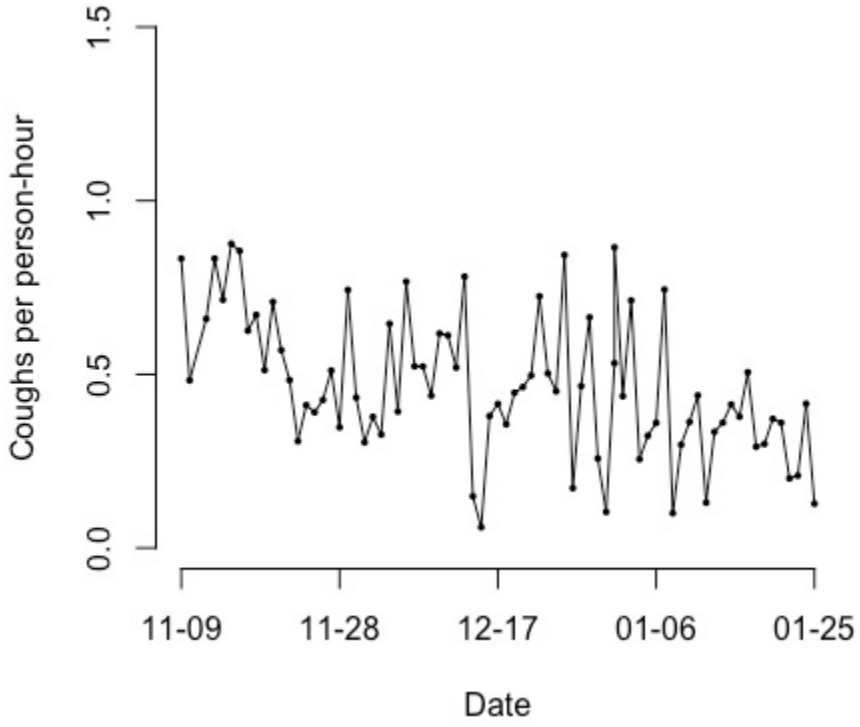

Figure 3

115x99mm (96 x 96 DPI)

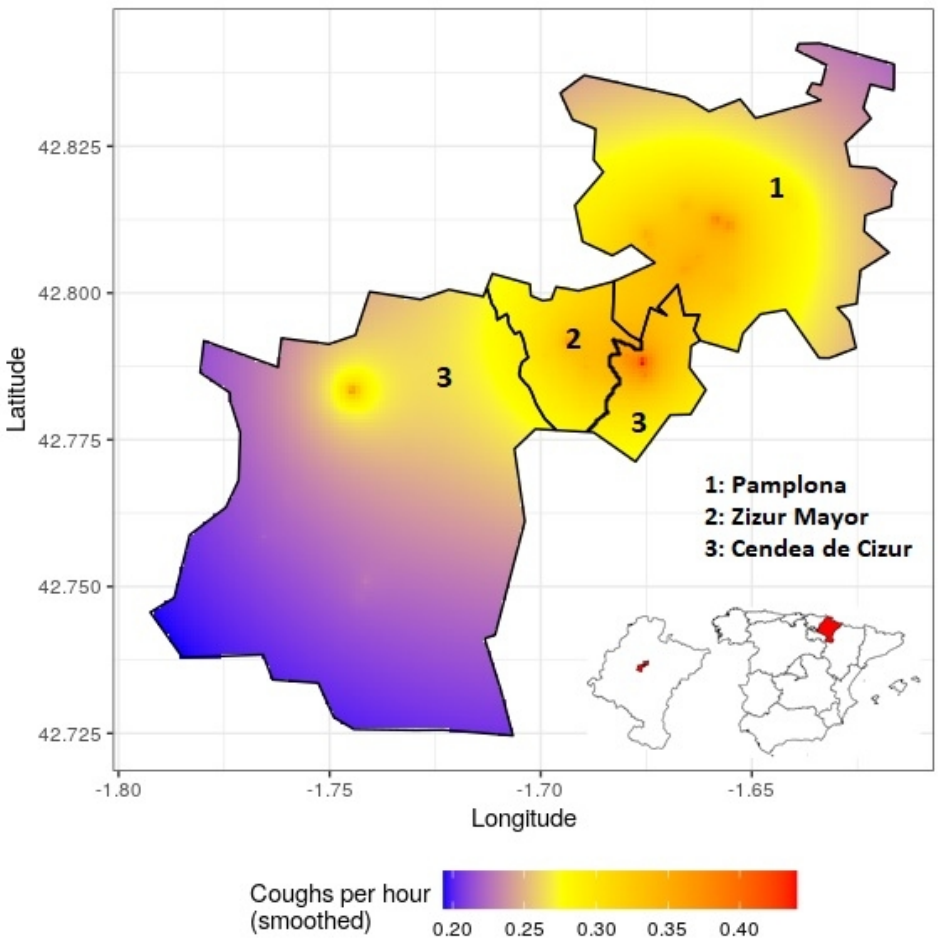

Figure 4

157x151mm (96 x 96 DPI)

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HOJA DE INFORMACIÓN Y CONSENTIMIENTO

Versión 3.0, 6 de enero de 2021

TÍTULO DEL ESTUDIO: Vigilancia acústica y monitorización digital de la tos a nivel poblacional para la detección temprana de brotes de enfermedades respiratorias. Un estudio observacional exploratorio.

CÓDIGO DEL PROMOTOR:

PROMOTOR

Clínica Universidad de Navarra/Universidad de Navarra, Avenida de Pío XII, 36

31008 Pamplona.

FINANCIACIÓN:

Este estudio está siendo financiado por el Centre Hospitalier de l'Université de Montréal (CHUM) y la fundación Patrick J. McGovern a través de una subvención otorgada al co-investigador Simon Grandjean Lapierre (*Early diagnosis of COVID-19 by utilizing Artificial Intelligence and Acoustic Monitoring*).

INVESTIGADOR PRINCIPAL

Carlos Chaccour

Teléfono +34 666 293 112

Email cchaccour@unav.es

INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por un Comité de Ética de la Investigación de la Universidad de Navarra, el comité de ética de la investigación con medicamentos de Navarra y el comité de ética del Centre Hospitalier de l'Universite de Montréal (CHUM), en Canadá.

Con este documento pretendemos que usted reciba la información adecuada para que pueda entender de qué se trata el estudio y decidir si desea o no participar en el mismo. Para ello, lea esta hoja informativa con atención y nosotros le aclararemos las dudas que puedan surgir después de la explicación. Además, puede consultar con las personas que considere oportuno.

PARTICIPACIÓN VOLUNTARIA

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Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

DESCRIPCIÓN GENERAL DEL ESTUDIO

Los coronavirus son un grupo de virus que causan infecciones respiratorias generalmente leves. Sin embargo, un miembro de este grupo, el SARS-Cov-2, es el responsable de provocar la COVID-19, una enfermedad potencialmente peligrosa que desde finales del 2019 se ha extendido a lo largo de todo el mundo.

Uno de los elementos necesarios para contener el avance de la pandemia de COVID-19 es entender su escala real. Esto es particularmente importante ahora que los brotes regulares en zonas en las que simultáneamente ocurre transmisión a una menor escala se han convertido en una realidad. Uno de los mayores obstáculos de los sistemas sanitarios es la limitada capacidad de hacer pruebas diagnósticas, lo que se traduce en retrasos en la búsqueda de atención médica, así como en la recolección de la información necesaria para planear intervenciones que limiten la expansión de la enfermedad.

La gran mayoría de pacientes con COVID-19 presentan tos como un síntoma temprano de la enfermedad. Este estudio pretende evaluar la utilidad de una aplicación para el móvil, llamada HyfeApp, que registra y evalúa patrones de tos, como complemento a las estrategias de vigilancia epidemiológica existentes. Para esto, estimamos que será necesario grabar y analizar episodios individuales de tos.

Por eso esperamos que el mayor número posible de habitantes instale la aplicación. Esta aplicación se ejecuta en segundo plano en el móvil. Aunque HyfeApp tiene acceso continuo al micrófono de su móvil, ha sido diseñada para procesar únicamente sonidos compatibles con las características de la tos humana. Cuando uno de estos sonidos es detectado y grabado por la aplicación, un algoritmo de inteligencia artificial lo estudia y en caso de decidir qué se trata de un episodio de tos, se guarda junto a la información sobre la ubicación geográfica y el momento en que ocurrió, que es proporcionada por el sistema GPS del móvil.

Aparte de la información suministrada por la aplicación, también revisaremos los registros médicos de aquellas personas dispuestas a participar que acudan a consulta en el sistema nacional de salud, o la Clínica Universidad de Navarra. El objetivo de esto es recolectar información sobre la presencia de tos durante la exploración médica, o el diagnóstico de alguna enfermedad respiratoria en alguna de las visitas. Solo se consultará información relacionada con alguna de las siguientes condiciones:

- Tos no específica.
- Infecciones del tracto respiratorio superior.
- Faringitis.
- Asma.
- Bronquitis.
- Enfermedad Broncopulmonar Obstructiva Crónica (EBPOC).
- COVID-19

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- Enfermedad por Reflujo Gastroesofágico (ERGE)
- Influenza
- Neumonía (por cualquier causa)
- Infección por virus sincitial respiratorio (VSR)
- Infecciones respiratorias inespecíficas.

Otros exámenes paraclínicos a ser recolectados incluyen:

- Microbiología
  - Pruebas de COVID-19
  - PCR para influenza
  - Cultivo de esputo
- Hematología
  - Hematología completa
  - Prueba del dímero D.
- Bioquímica
  - Proteína C reactiva
  - Procalcitonina
  - CPK
  - LDH
  - Ferritina

Aparte de la información obtenida de la app y sus registros médicos, también le pediremos a un grupo reducido de participantes que formen parte de discusiones grupales focalizadas, para explorar los desafíos que representa el uso continuo de HyfeApp, y su participación en el estudio. En caso de que se le solicite participar, usted podrá aceptar o negarse.

Duración

Se recolectará información inicialmente por un período de 1 mes, consultándosele en ese momento su disposición a seguir participando por 3 y 6 meses. Usted podrá negarse a seguir participando en el estudio en cualquier momento.

Procedimientos del estudio

Usted no puede participar en el ensayo si:

- No puede o no quiere aceptar compartir su información codificada, relacionada a sus registros de tos con bases de datos usadas para refinar los diagnósticos basados en perfiles acústicos.
- Si tiene menos de 13 años de edad.
- Si no tiene un teléfono inteligente capaz de ejecutar HyfeApp.
- Si no es un estudiante/trabajador de la Universidad de Navarra, o un paciente diagnosticado con una enfermedad causante de tos en la Clínica Universidad de Navarra.

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- Si no es residente en Navarra.

Si usted decide participar, un miembro de nuestro equipo lo ayudará a instalar la aplicación en su móvil. No serán necesarias nuevas visitas de parte del equipo de investigación, pero serán contactados una vez al mes para obtener comentarios sobre su experiencia usando la aplicación y ratificar su consentimiento y disposición a seguir participando en el estudio. También podrá ser contactado vía correo electrónico para recibir actualizaciones periódicas sobre el estado del proyecto y sus resultados preliminares.

LA APLICACIÓN HYFEAPP

HyfeApp es una aplicación móvil disponible para los sistemas operativos Android y iOS (Apple), desarrollada por un equipo multidisciplinario que incluye analistas de datos, desarrolladores de software y médicos especialistas en enfermedades infecciosas.

¿Qué hace HyfeApp?

HyfeApp se ejecuta constantemente en el segundo plano de su móvil, sin interferir con el funcionamiento de otras aplicaciones, pero teniendo acceso a su micrófono y grabando recortes de sonidos explosivos de menos de 0.5 segundos de duración. Ni las conversaciones, ni los sonidos de fondo son grabados. Estos recortes son enviados a un servidor, donde un algoritmo de inteligencia artificial identifica aquellos que presentan cambios súbitos y cortos en los decibeles, compatibles con episodios de tos. Posteriormente, otro algoritmo los procesa, evaluando otras características y determinando si efectivamente se trató de un episodio de tos. El servidor envía esta información de vuelta al móvil, de forma que los archivos clasificados como tos se incorporan a los registros mostrados por la aplicación.

HyfeApp es una herramienta que le proporciona información sobre su estado de bienestar. Tal como herramientas similares que cuentan calorías, registran el número de pasos o ronquidos. La única diferencia es que HyfeApp cuenta episodios de tos.

Beneficios y riesgos por su participación en estudio

HyfeApp le permitirá llevar un registro del número de veces que tose al día, así como evidenciar cambios con respecto a días anteriores. Sin embargo, no es una herramienta de diagnóstico o tratamiento médico. Por lo tanto, ni provee información o consejos médicos, ni sustituye de ninguna forma a los servicios sanitarios: HyfeApp no es un instrumento médico especializado. Si usted tiene alguna duda sobre su estado de salud, debe consultarlas con un médico o en caso de emergencia, llamar a los servicios respectivos inmediatamente .

Grabar sonidos desde un móvil inmediatamente genera dudas sobre la forma en que será manejada la información, y garantizada la privacidad de los participantes. Como hemos explicado anteriormente, HyfeApp no graba conversaciones ni sonidos de ambiente. Los segmentos de 0.5 segundos grabados por la aplicación no permiten identificar a los participantes. Sin embargo, algunos de estos sonidos pudiesen permitir identificar al participante si son interpretados en conjunto a otra metadata registrada por la aplicación (como el número de teléfono, por ejemplo). Por esta razón, toda la

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información transmitida por la aplicación estará encriptada y manejada según los protocolos de seguridad estándar empleados en este tipo de estudios. De esta forma, únicamente los investigadores podrán asociar los datos recolectados por la aplicación, a otros elementos que permitan identificar a los participantes.

No será remunerado por su participación en este estudio.

CONFIDENCIALIDAD

Toda la información recolectada en este estudio se mantendrá codificada, de forma que no pueda ser vinculada a sus datos personales. Solo el investigador principal y los co-investigadores sabrán su nombre y en cualquier documento o comunicación se usará un número de identificación personal asignado a cada participante. Los ordenadores utilizados para analizar los datos de este estudio tendrán contraseñas y solo investigadores autorizados podrán acceder a ellas.

La Universidad de Navarra, como responsable del tratamiento de datos, se compromete al cumplimiento de la Ley Orgánica del 3/2018, de 5 de diciembre y demás normativa de protección de datos en vigor. Por ello, es importante que conozca la siguiente información:

• Además de los derechos que ya conoce (acceso, modificación, oposición y cancelación de datos) ahora también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercer sus derechos, diríjase al Delegado de Protección de Datos de la institución en **[**protecciondedatosnav@unav.es**]**. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho/a.

• Tanto el Centro como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen a cumplir con la normativa de protección de datos en vigor. Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

• El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.

• Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar al Delegado de Protección de Datos del promotor **[**protecciondedatosnav@unav.es**].**

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COMPENSACIÓN ECONÓMICA

El promotor del estudio es el responsable de gestionar la financiación del mismo. Para la realización del estudio, el promotor ha firmado un contrato con el centro donde se va a realizar y con el médico del estudio.

Su participación en este estudio no le causará costes adicionales diferentes de los asociados a su tratamiento habitual. La asistencia rutinaria deberá ser pagada por la seguridad social, por su seguro médico o por usted mismo.

Usted no recibirá ninguna compensación económica por su participación en este estudio.

OTRA INFORMACIÓN RELEVANTE

Cualquier nueva información referente a la aplicación utilizada en el estudio y que pueda afectar su disposición para participar en el mismo, que se descubra durante su participación, le será comunicada lo antes posible.

Si usted decide retirar el consentimiento para participar en este estudio, no se añadirán nuevos datos a la base de datos y puede exigir la destrucción de cualquier información identificable previamente retenidas para evitar la realización de nuevos análisis.

También debe saber que puede ser excluido del estudio si el promotor y/o los investigadores del estudio lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso derivado de su participación, o porque consideren que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada del estudio

COMPARTIENDO LOS RESULTADOS

Usted tendrá acceso a todo el conocimiento generado por esta investigación en todo momento, solo debe preguntar al investigador principal. No compartiremos su nombre, estado de salud o dirección. Eventualmente, los resultados serán publicados, de forma tal que cualquier persona interesada en conocerlos, pueda acceder a ellos. Usted podrá solicitar información sobreel estado y los resultados del estudio, preguntándole directamente al investigador principal.

Al firmar el formulario de consentimiento adjunto, se compromete a cumplir con los procedimientos del estudio que se le han expuesto.

DERECHO A NEGARSE A PARTICIPAR O ABANDONAR EL ESTUDIO

- No tiene que participar en este estudio si no desea hacerlo.
- Tiene el derecho a NO firmar este formulario. Si no desea firmar este formulario, no podrá participar en este estudio de investigación. Esto se debe a que necesitamos su permiso por escrito antes de poder usar su información.
- Tiene el derecho a abandonar este estudio incluso después de haber aceptado participar. Si decide abandonar el estudio, no usaremos su información. En caso de decidir

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abandonar el estudio, por favor comuníquese con un miembro de nuestro personal. No tiene que explicar sus razones para abandonar el estudio.

A QUIÉN CONTACTAR

Si no está satisfecho con la forma en que se llevó a cabo este estudio, o tiene alguna duda, queja o pregunta sobre sus derechos como participante, por favor contacte a la oficina de atención al paciente de la Clínica Universidad de Navarra, por teléfono (+34 948 255 400) o correo electrónico (atpacientun@unav.es), para hablar con alguien independiente del equipo investigador.

Si tiene alguna duda sobre este estudio o sus procedimientos, ahora o en el futuro, puede comunicarse con: _____ . Teléfono: _____. Quién es el investigador principal del estudio. Puede llamar de lunes a viernes entre las 8:00 y las 17:00 horas.

Al firmar el formulario de consentimiento adjunto, se compromete a cumplir con los procedimientos del estudio que se le han expuesto.

Consentimiento Informado por escrito

TÍTULO DEL ESTUDIO: Vigilancia acústica y monitorización digital de la tos a nivel poblacional para la detección temprana de brotes de enfermedades respiratorias. Un estudio observacional exploratorio.

CÓDIGO DEL PROMOTOR:

Versión y fecha:

Yo, (nombre y apellidos)

.....

He leído la hoja de información que se me ha entregado.

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

He hablado con:

.....

(nombre y dos apellidos del investigador)

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

1º Cuando quiera

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2º Sin tener que dar explicaciones.

3º Sin que esto repercuta en mis cuidados médicos.

Presto libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información

Firma del investigador:

Nombre:

Fecha:

Firma del investigador:

Nombre:

Fecha:

Firma del participante:

Nombre:

Fecha:

Firma del Representante legal o Testigo imparcial (táchese lo que no proceda):

DNI:

Fecha:

A causa de:

Este documento se firmará por duplicado quedándose una copia el investigador y otra el participante.

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INFORMATION AND CONSENT SHEET

Version 3.0 (January 6th, 2021)

Study Title: Acoustic surveillance and digital cough monitoring at population level for early respiratory disease outbreak detection, an exploratory observational study

Promoter Code:

Promoter
Clínica Universidad de Navarra/Universidad de Navarra, Avenida de Pío XII, 36
31008 Pamplona

Funder: This study is funded by the Centre Hospitalier de l'Université de Montréal (CHUM) and the Patrick J. McGovern Foundation through a grant awarded to Co-Investigator Simon Grandjean Lapierre (*Early diagnosis of COVID-19 by utilizing Artificial Intelligence and Acoustic Monitoring*)

Main Researcher:
Carlos Chaccour
Teléfono +34 666 293 112
Email cchaccour@unav.es

Introduction
The objective of this document is to inform you about the characteristics of a research study you have been invited to participate in. The study has been approved by the Committee of Research Ethics of the Universidad de Navarra and the Committee of Medication Ethics of Navarra (Spain), as well as the ethics committee from the Centre Hospitalier de l'Université de Montréal (CHUM), in Canada.

This document aims to provide you with proper information, so you can understand this study and decide by yourself if you are willing to take part or not in it. Please read this information document carefully and we will answer any questions that might come up afterwards. You can also discuss this with people you trust before making a decision.

Voluntary Participation
You must know that your participation in this study is voluntary and you can decide not to take part, or change your mind and withdraw your consent at any time in the future. This will not affect your relationship with your healthcare provider, nor harm your access to proper medical treatment in any way.

General description of the study
Coronaviruses are a group of viruses that cause generally mild respiratory disease. However, a member of this group, the SARS-Cov-2, is responsible for causing COVID-19, a potentially dangerous disease that has spread across the globe since 2019.

One of the necessary interventions to contain the COVID-19 pandemic is understanding its real scale. This is particularly important now that new outbreaks are being regularly reported in areas with ongoing low-level transmission. A major limitation in this process is the limited diagnostic capabilities of many countries, which translates into delays in the search of medical attention and collection of necessary epidemiological data.

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Most patients with COVID-19 present cough as an early symptom of disease. This study aims to evaluate the usefulness of a mobile app called HyfeApp, which registers and studies cough patterns, as a complement to existing disease surveillance strategies. To do this, we will need to record and analyse episodes of cough in the town of Cizur Menor which has been selected as the location of the initial studies of this new platform.

For this reason, we need as many people as possible installing the app. This App runs in the background of your mobile phone. Although HyfeApp has continuous access to the mobile's mic, it has been designed to exclusively process sounds that match the characteristics of human cough. When one of these sounds is detected and recorded by the app, an artificial intelligence algorithm studies it and determines whether it is indeed an episode of cough.If so, the record is stored, along with time and geographical information provided by the mobile's GPS.

Besides the information from the app, we will also review the medical records of those participants who present for a medical consultation in the national health system or the Clinica Universidad de Navarra. The objective of this is to collect information about the presence of cough, or any respiratory disease during one of those visits. Data from your medical chart will be obtained by the investigators from your local clinic or hospital. This includes without being limited to information related to any of the following conditions will be reviewed:

- Non-specific cough
- Non-specific upper respiratory tract infections
- Pharyngitis
- Asthma
- Bronchitis
- Chronic Obstructive Pulmonary Disease (COPD)
- COVID-19
- Gastro-esophageal reflux disease (GERD)
- Influenza
- Pneumonia (any cause)
- Respiratory Syncytial virus
- Non-specific respiratory tract infections

Additional laboratory test data to be collected from the selected visits includes:

- Microbiology
  - COVID-19 tests
  - Flu PCR
  - Sputum culture
- Hematology
  - Full blood count
  - D-dimer test
- Biochemistry
  - C-reactive protein
  - Procalcitonin
  - CPK
  - LDH
  - Ferritin
- Radiology

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- Chest X-Ray
- Thorax CT-Scan

Besides the information from the app and medical charts, we will also solicit a restricted number of participants to participate in focus group discussions to explore the challenges related to using HyfeApp and participating in this study. If solicited, it will be your right to accept or refuse to participate in those focus groups.

Duration
Data will be initially collected for a one-month period. You will then be offered the opportunity to continue in the study for 3 and 6 months. You can refuse continuing in the study at any point.

Study Procedures
You will not be able to enroll in this study if you:

- Are incapable or unwilling to accept to share your codified cough data with multicenter databases aiming at refining acoustic-based diagnostics.
- Are under 13 years of age.
- Do not own a smartphone able to run HyfeApp.
- Are not a student/worker at the University of Navarra or a patient diagnosed with cough-related disease at the Clínica Universidad de Navarra.
- Are not a resident in Navarra.

In case you decide to take part, a member of our team will help you install the app on your mobile. No further visits from the research team will be necessary, but you might be contacted once a month to collect feedback on your experience using the app, as well as to confirm your willingness to continue in the study. You might also receive periodic updates via email, to keep you informed on the status of the project and relevant preliminary results.

About HyfeApp
HyfeApp is a mobile app available for Android and IOS (Apple) operating systems, developed by a multidisciplinary team of data scientists, software developers and infectious disease physicians.

What does HyfeApp do?
HyfeApp runs in the background of your mobile, without interfering with any other running app, but having constant access to your mic and recording explosive sound snips of 0.5 seconds or less. No conversations, nor ambient sounds are recorded. These sound snips are sent to a server, where an artificial intelligence algorithm processes them, evaluating their characteristics and determining if they were in fact, cough. The server then sends that data back to the mobile and the study investigator, so those files labeled as cough episodes are displayed by the app. HyfeApp is a wellness status tool. Just like similar apps that count calories, steps or snores. HyfeApp simply counts episodes of cough.

Benefits and risks of participating
HyfeApp will allow you to have a record of the number of times you cough every day, and of any changes compared to previous days. However, it is not a diagnostic or treatment tool. Therefore, it does not provide medical advice, nor replaces healthcare services. HyfeApp is not medical equipment. If you ever have doubts regarding your health condition or status, you should consult a doctor, or in case of emergency, communicate with proper emergency services.

We are aware that recording sounds from a mobile phone generates doubts regarding the handling of information and the participants' privacy. As explained before, HyfeApp does not record conversations or ambient sounds, and the 0.5 second sound snips are too short to identify

participants. However, if linked to other metadata (such as telephone numbers), these sounds could allow identification. For this reason, all the information transmitted by the app is encrypted and handled following standard safety protocols. This way, we can make sure that only the researchers can access potentially identifiable data.
You will not be paid for your participation.

Confidentiality
All the information collected in this study will be codified in such a way that it cannot be linked to your personal data. Only the principal and co-investigators involved in this study will know your name, and an ID number will be used to refer to you in every document or communication. The computers used to store and analyze the data will be password-protected and only authorised researchers will have access to them.

The Universidad de Navarra, as the data controller, complies with the Organic Law 3/2018, of December 5, and other Spanish data protection regulations in force. Therefore, it is important that you know the following information:

• In addition to the rights that you already know (access, modification, refusal and cancellation of data), you can now also limit the processing of incorrect data, request a copy, or have the data that you provided be transferred to a third party (portability) for the study. To exercise your rights, contact the Institution's Data Protection Officer at [protecciondedatosnav@unav.es]. You also have the right to contact the Data Protection Agency if you are not satisfied.

• Both the Center and the Promoter are respectively responsible for the processing of your data and undertake to comply with the data protection regulations in force. The data collected for the study will be identified by a code, so that information that can identify you is not included, and only your study doctor / collaborators will be able to relate said data to you and to your medical history. Therefore, your identity will not be revealed to any other person except to the health authorities, when required or in cases of medical emergency. The Research Ethics Committees, the representatives of the Health Authority in matters of inspection and the personnel authorized by the Sponsor, may only access to verify personal data, clinical study procedures and compliance with the rules of good clinical practice (always maintaining the confidentiality of the information).

• The Researcher and the Sponsor are obliged to keep the data collected for the study for at least 25 years after its completion. Subsequently, your personal information will only be kept by the center for the care of your health and by the promoter for other scientific research purposes if you have given your consent to do so, and if this is allowed by the law and applicable ethical requirements.

• If we transfer your encrypted data outside the EU to our group entities, service providers or scientific researchers who collaborate with us, the participant's data will be protected with safeguards such as contracts or other mechanisms by the protection authorities of data. If the participant wants to know more about it, he or she can contact the promoter's Data Protection Officer [protecciondedatosnav@unav.es].

Economic Compensation
The study promoter is responsible for managing the funds. Before doing a research study, the promoter must have signed a contract with the center where the study will take place, and the doctors

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who will conduct the study. Your participation in this study will not cost you any extra money beyond your standard medical procedures. Routine medical assistance will have to be paid by the social security network, your medical insurance, or yourself.

You will not receive any payment or monetary compensation for taking part in this study.

Other relevant information

Any new information regarding the app to be used in this study and that could affect your disposition to take part in it, discovered after you have decided to participate, will be communicated to you as soon as possible.

If you wish to withdraw your consent to take part in the study, no further personal data will be added to the database. You can also demand the destruction of any previously retained identifiable information, to prevent new analysis from being carried on.

You must also know that you could be excluded from the study if the promoter and/or researchers consider it to be adequate, either for your own safety, to prevent any adverse consequence deriving from your participation, or because they consider you are not complying with the established procedures. In any case, you will always receive a proper explanation of what caused your withdrawal from the study.

Sharing the results

At all time, you will have access to the knowledge we get from the research upon request to the principal investigator. We will not share your name, health status or where you live. After this, we will publish the results so that other interested people may learn from our research. You will be able to ask the status of this study and its findings by a direct request to the principal investigator.

Right to refuse or withdraw

You don't have to take part in this research study if you do not wish so. You have the right not to sign this form. If you do not sign this form, you cannot take part in this research study. This is because we need your written permission to use your information. You have the right to leave the research study. If you would like to leave the research study, please tell a member of the study staff. You do not need to explain why you want to leave.

Who to contact?

If you are not satisfied with the way this study was conducted, or if you have any concerns, complaints or general questions about your rights as a participant, please contact the Patient Attention Office at the Clínica Universidad de Navarra by phone (+34 948 255 400) or email atpacientun@unav.es to talk with someone independent of the research team.

If you have any questions about this study or study procedures now or in the future, you can call Dr. Carlos Chaccour. Tel number: 628 659 003 who is the Principal Investigator of the study. You can call Monday-Friday from 8.00 to 17.00 hrs.

By signing the following informed consent, you agree to comply with the previously explained study procedures.

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Written informed consent form

Study title: Acoustic surveillance and digital cough monitoring at population level for early respiratory disease outbreak detection, an exploratory observational study

Promoter code
Version and date:

I, (name and surname)
.....

Have read the information sheet presented above.
I have been allowed to ask questions about the study.
I have received sufficient information about the study to make a decision.

I have spoken to:
.....
(Name and surname of researcher)

I understand that my participation is voluntary.

I understand I can withdraw from the study:

1. Whenever I want to.
2. Without having to explain my reasons.
3. Without repercussions regarding my access to healthcare.

I freely and willingly accept to participate in this study. I give my consent for the access and usage of my data within the conditions previously detailed in the information sheet.

Researcher's signature

Name:

Date:

Researcher's signature	**Participant's signature**	**Signature of the legal representative or impartial witness (cross out if not applicable)**
Name:	**Name:**:	**DNI**:

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Date: **Date:**: **Date**:

Reason to sign:

This document will be signed in duplicate, one copy will be kept by the researcher and another one by the participant.

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ID del participante:

Hoja de información y autorización a menores de entre 13 y 18 años para participar en el estudio titulado:

Version 3.0 (6 de enero de 2021)

Vigilancia acústica y monitorización digital de la tos a nivel poblacional para la detección temprana de brotes de enfermedades respiratorias. Un estudio observacional exploratorio.

Este formulario de autorización es para aquellos menores de edad dispuestos a participar en el estudio observacional previamente descrito.

Promotor

Clínica Universidad de Navarra/Universidad de Navarra, Avenida de Pío XII, 36

31008 Pamplona.

Financiación: Este estudio está siendo financiado por el Centre Hospitalier de l'Université de Montreal (CHUM) y la fundación Patrick J. McGovern a través de una subvención otorgada al co-investigador Simon Grandjean Lapierre (*Early diagnosis of COVID-19 by utilizing Artificial Intelligence and Acoustic Monitoring*)

Investigador Principal

Carlos Chaccour

Teléfono +34 666 293 112

Email cchaccour@unav.es

Este formulario de autorización cuenta con dos partes:

- Hoja de información (para compartir la información relevante al proyecto con usted)
- Certificado de Autorización (donde se le solicitará su firma y la de su padre, madre o representante legal, en caso de que acepte participar).

Le será proveída una copia del Certificado de Autorización.

Parte I: Hoja de Información

Introducción

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por el Comité de Ética de la Investigación de la Universidad de Navarra, el comité de ética de la investigación con medicamentos de Navarra y el comité independiente de ética del Centre Hospitalier de l'Universite de Montreal (CHUM), en Canadá.

No es necesario que tome una decisión hoy. Puede tomarse el tiempo de hablar y discutir su participación con cualquier persona con la que se sienta cómodo haciéndolo.

Con este documento pretendemos que usted reciba la información adecuada para que pueda entender de qué se trata este estudio y decidir si quiere o no participar en el mismo. Es posible que haya palabras o información que no entienda. De ser así, siéntase libre de preguntar cualquier duda.

Generalidades del estudio

Los coronavirus son un grupo de virus que causan infecciones respiratorias generalmente leves. Sin embargo, un miembro de este grupo, el SARS-Cov-2, es el responsable de provocar la COVID-19, una enfermedad potencialmente peligrosa que desde finales del 2019 se ha extendido a lo largo de todo el mundo.

Uno de los elementos necesarios para contener el avance de la pandemia de COVID-19 es entender su escala real. Esto es particularmente importante ahora que los brotes regulares en zonas en las que simultáneamente ocurre transmisión a una menor escala se han convertido en una realidad. Uno de los mayores obstáculos de los sistemas sanitarios es la limitada capacidad de hacer pruebas diagnósticas, lo que se traduce en retrasos en la búsqueda de atención médica, así como en la recolección de la información necesaria para planear intervenciones que limiten la expansión de la enfermedad.

La gran mayoría de pacientes con COVID-19 presentan tos como un síntoma temprano de la enfermedad. Este estudio pretende evaluar la utilidad de una aplicación para el móvil, llamada HyfeApp, que registra y evalúa patrones de tos, como complemento a las estrategias de vigilancia epidemiológica existentes. Para esto, estimamos que será necesario grabar y analizar al menos 15,500 episodios individuales de tos.

Por eso esperamos que el mayor número posible de voluntarios instale la aplicación, la cual se ejecuta en segundo plano en el móvil. Aunque HyfeApp tiene acceso continuo al micrófono de su móvil, ha

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sido diseñada para procesar únicamente sonidos compatibles con las características de la tos humana. Cuando uno de estos sonidos es detectado y grabado por la aplicación, un algoritmo de inteligencia artificial lo estudia y en caso de decidir qué se trata de un episodio de tos, se guarda junto a información sobre la ubicación geográfica y el momento en que ocurrió, que es proporcionada por el sistema GPS del móvil.

Aparte de la información suministrada por la aplicación, revisaremos los registros médicos de aquellas personas dispuestas a participar que acudan a consulta en el sistema nacional de salud, o la Clínica Universidad de Navarra. El objetivo de esto es recolectar información sobre la presencia de tos durante la exploración médica, o el diagnóstico de alguna enfermedad respiratoria en alguna de las visitas. Solo se consultará información relacionada con alguna de las siguientes condiciones:

- Tos no específica.
- Infecciones del tracto respiratorio superior.
- Faringitis.
- Asma.
- Bronquitis.
- Enfermedad Broncopulmonar Obstructiva Crónica (EBPOC).
- COVID-19
- Enfermedad por Reflujo Gastroesofágico (ERGE)
- Influenza
- Neumonía (por cualquier causa)
- Infección por virus sincitial respiratorio (VSR)
- Infecciones respiratorias inespecíficas.

Otros exámenes paraclínicos a ser recolectados incluyen:

- Microbiología
  - pruebas de COVID-19
  - PCR para influenza
  - Cultivo de esputo
- Hematología
  - Hematología completa
  - Prueba del dímero D.
- Bioquímica
  - Proteína C reactiva
  - Procalcitonina
  - CPK
  - LDH
  - Ferritina

Aparte de la información obtenida de la app y sus registros médicos, también le pediremos a un grupo reducido de participantes que formen parte de discusiones grupales focalizadas, para explorar los desafíos que representa el uso continuo de HyfeApp, y su participación en el estudio. En caso de que se le solicite participar, usted podrá aceptar o negarse.

Duración

Se recolectará información inicialmente por un período de 1 mes, consultándosele en ese momento su disposición a seguir participando por 3 y 6 meses. Usted podrá negarse a seguir participando en el estudio en cualquier momento.

Procedimientos del estudio

Usted no puede participar en el ensayo si usted:

- No puede o no quiere aceptar compartir su información codificada relacionada a sus registros de tos con bases de datos globales usadas para refinar los diagnósticos basados en perfiles acústicos.
- Si no posee un teléfono inteligente en el que se pueda ejecutar HyfeApp.
- Tiene menos de 13 años de edad.
- No es un estudiante/trabajador de la Universidad, o un paciente diagnosticado con una enfermedad causante de tos en la Clínica Universidad de Navarra.
- Si no reside en Navarra.

Si usted decide participar, un miembro de nuestro equipo lo ayudará a instalar la aplicación en su móvil. No serán necesarias nuevas visitas de parte del equipo de investigación, pero serán contactados una vez al mes para obtener comentarios sobre su experiencia usando la aplicación y ratificar su consentimiento y disposición a seguir participando en el estudio. También podrá ser contactado vía correo electrónico para recibir actualizaciones periódicas sobre el estado del proyecto y sus resultados preliminares.

La aplicación HyfeApp

HyfeApp es una aplicación móvil disponible para los sistemas operativos Android y iOS (Apple), desarrollada por un equipo multidisciplinario que incluye analistas de datos, desarrolladores de software y médicos especialistas en enfermedades infecciosas.

¿Qué cosas hace HyfeApp?

HyfeApp se ejecuta constantemente en el segundo plano de su móvil, sin interferir con el funcionamiento de otras aplicaciones, pero teniendo acceso a su micrófono y grabando recortes explosivos de sonido de menos de 0.5 segundos de duración. Ni las conversaciones, ni los sonidos de fondo son grabados. Estos recortes son enviados a un servidor, donde un algoritmo de inteligencia artificial identifica aquellos que presentan cambios súbitos y cortos en los decibeles, compatibles con episodios de tos. Posteriormente, otro algoritmo los procesa, evaluando otras características y determinando si efectivamente se trató de un episodio de tos. El servidor envía esta información de

vuelta al móvil, de forma que los archivos clasificados como tos se incorporan a los registros mostrados por la aplicación.

HyfeApp es una herramienta que le proporciona información sobre su estado de bienestar. Tal como herramientas similares que cuentan calorías, registran el número de pasos o ronquidos. La única diferencia es que HyfeApp cuenta episodios de tos.

Beneficios y riesgos por su participación en estudio

HyfeApp le permitirá llevar un registro del número de veces que tose al día, así como evidenciar cambios con respecto a días anteriores. Sin embargo, no es una herramienta de diagnóstico o tratamiento médico. Por lo tanto, ni provee información o consejos médicos, ni sustituye de ninguna forma a los servicios sanitarios: HyfeApp no es un instrumento médico especializado. Si usted tiene alguna duda sobre su estado de salud, debe consultarlas con un médico o en caso de emergencia, llamar a los servicios respectivos inmediatamente .

Grabar sonidos desde un móvil inmediatamente genera dudas sobre la forma en que será manejada la información, y garantizada la privacidad de los participantes. Como hemos explicado anteriormente, HyfeApp no graba conversaciones ni sonidos de ambiente. Los segmentos de 0.5 segundos grabados por la aplicación no permiten identificar a los participantes. Sin embargo, algunos de estos sonidos pudiesen permitir identificar al participante si son interpretados en conjunto con otra metadata registrada por la aplicación (como el número de teléfono, por ejemplo). Por esta razón, toda la información transmitida por la aplicación estará encriptada y manejada según los protocolos de seguridad estándar empleados en este tipo de estudios. De esta forma, únicamente los investigadores podrán asociar los datos recolectados por la aplicación, a otros elementos que permitan identificar a los participantes.

Usted no recibirá un pago por su participación.

Participación Voluntaria

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar la autorización en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

Pagos y Compensación Económica

El promotor del estudio es el responsable de gestionar la financiación del mismo. Para la realización del estudio, el promotor ha firmado un contrato con el centro donde se va a realizar y con el médico del estudio.

Su participación en este estudio no le causará costes adicionales diferentes de los asociados a su tratamiento habitual. La asistencia rutinaria deberá ser pagada por la seguridad social, por su seguro médico o por usted mismo.

Ni usted ni sus padres/representantes recibirán un pago por su participación en este estudio.

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Otra Información

Cualquier nueva información referente a la aplicación utilizada en el estudio y que pueda afectar su disposición para participar en el mismo, que se descubra durante su participación, le será comunicada lo antes posible.

Si usted decide retirar el consentimiento para participar en este estudio no se añadirán nuevos datos a la base de datos y puede exigir la destrucción de cualquier información identificable previamente retenida, para evitar la realización de nuevos análisis.

También debe saber que puede ser excluido del estudio si el promotor y/o los investigadores del mismo lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso derivado de su participación, o porque consideren que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada del estudio.

Confidencialidad

Toda la información recolectada en este estudio se mantendrá codificada, de forma que no pueda ser vinculada a sus datos personales. Solo el investigador principal y los co-investigadores sabrán su nombre y en cualquier documento o comunicación se usará un número de identificación personal asignado a cada participante. Las computadoras utilizadas para analizar los datos de este estudio tendrán contraseñas y solo investigadores autorizados podrán acceder a ellas.

La Universidad de Navarra, como responsable del tratamiento de datos, se compromete al cumplimiento de la Ley Orgánica del 3/2018, de 5 de diciembre y demás normativa de protección de datos en vigor. Por ello, es importante que conozca la siguiente información:

• Además de los derechos que ya conoce (acceso, modificación, oposición y cancelación de datos) ahora también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercer sus derechos, diríjase al Delegado de Protección de Datos de la institución en [protecciondedatosnav@unav.es]. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho/a.

• Tanto el Centro como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen a cumplir con la normativa de protección de datos en vigor. Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

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• El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal sólo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.

• Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar al Delegado de Protección de Datos del promotor **[**protecciondedatosnav@unav.es**].**

Compartiendo los Resultados

Usted tendrá acceso a todo el conocimiento generado por esta investigación en todo momento, solo debe preguntar al investigador principal. No compartiremos su nombre, estado de salud o dirección. Eventualmente, los resultados serán publicados, de forma tal que cualquier persona interesada en conocerlos, pueda acceder a ellos. Usted podrá solicitar información sobre el status y los resultados del estudio, preguntándole directamente al investigador principal.

¿Quién aprobó esta investigación?

El estudio ha sido aprobado por el Comité de Ética de la Investigación de la Universidad de Navarra, el comité de ética de la investigación con medicamentos de Navarra y el comité independiente de ética del Centre Hospitalier de l'Universite de Montreal (CHUM), en Canadá.

Derecho a negarse a participar o abandonar el estudio

- No tiene que participar en este estudio si no desea hacerlo.
- Tiene el derecho a NO firmar este formulario. Si no desea firmar este formulario, no podrá participar en este estudio de investigación. Esto se debe a que necesitamos su permiso por escrito antes de poder usar su información.
- Tiene el derecho a abandonar este estudio incluso después de haber aceptado participar. Si decide abandonar el estudio, no usaremos su información. En caso de decidir abandonar el estudio, por favor comuníquese con un miembro de nuestro personal. No tiene que explicar sus razones para abandonar el estudio.

A quién contactar

Si no está satisfecho con la forma en que se llevó a cabo este estudio, o tiene alguna duda, queja o pregunta sobre sus derechos como participante, por favor contacte a la oficina de atención al paciente de la Clínica Universidad de Navarra, por teléfono (+34 948 255 400) o correo electrónico (atpacientun@unav.es), para hablar con alguien independiente del equipo investigador.

Si tiene alguna duda sobre este estudio o sus procedimientos, ahora o en el futuro, puede comunicarse con: Dr. Carlos Chaccour. Teléfono: 628 659 003. Quién es el investigador principal del estudio. Puede llamar de Lunes a Viernes entre las 8:00 y las 17:00 horas.

Parte II: Certificado de Autorización

Autorización del padre o representante legal

He leído o se me ha leído la información anterior. Se me permitió hacer preguntas al respecto y cualquier pregunta que haya hecho me fue contestada de forma satisfactoria.

☐ Autorizo que mi hijo/hija o representado legal participe en este proyecto de investigación.

☐ No autorizo que mi hijo/hija o representado legal participe en este proyecto de investigación y no he firmado la autorización presente a continuación.

Nombre del padre o representante legal:

Firma del padre o representante legal:

Fecha (dd/mm/aaaa)

Consentimiento del menor de edad

He leído o se me ha leído la información anterior. Se me permitió hacer preguntas al respecto y cualquier pregunta que haya hecho me fue contestada de forma satisfactoria.

☐ Acepto participar en este proyecto de investigación.

☐ No acepto participar en este proyecto de investigación y no he firmado la autorización presente a continuación.

En caso de que el menor acepte participar:

Nombre del menor de edad:

Firma del menor de edad

Fecha (dd/mm/aaaa):

En caso de no saber leer o escribir

Un testigo que sepa leer o escribir debe firmar (este individuo debería de ser posible, haber sido elegido por el participante, no su padre o representante, y no estar relacionado con el equipo de

investigación). Todo participante que no sepa leer o escribir debe presentar la huella digital de su pulgar.

Soy testigo de que este formulario fue leído de forma precisa al participante en potencia, y que dicho individuo tuvo la oportunidad para hacer preguntas. Confirmo que el individuo en cuestión ha autorizado su participación de forma voluntaria.

Nombre del testigo:

Firma del testigo:

Fecha (dd/mm/aaaa):

Huella digital del pulgar del participante:

Declaración del encargado de obtener la autorización

He leído de forma precisa la hoja de información al participante en potencia, y he hecho todo lo posible para asegurarme de que entendiera que se realizarán los siguientes procedimientos:

1. La aplicación HyfeApp deberá ser descargada en el móvil del participante.
2. La aplicación HyfeApp registrará y almacenará sonidos compatibles con la tos humana durante un período de un año, entre octubre de 2020 y septiembre de 2021.
3. En caso de acudir a una consulta en el sistema nacional de salud, la información médica del participante podrá ser accedida para buscar evidencia clínica de tos o alguna enfermedad respiratoria.

Confirmo que al participante se le ha dado la oportunidad de hacer preguntas sobre la investigación y que todas esas preguntas han sido contestadas de forma apropiada y de la mejor forma posible. Confirmo que el individuo no ha sido forzado a autorizar su participación, y que su consentimiento ha sido libre y voluntario.

Una copia de este certificado de autorización ha sido proporcionada al padre o representante legal del participante.

El padre o representante legal del participante ha firmado el consentimiento informado: Si____ No____

Nombre de la persona a cargo de obtener el consentimiento:

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Firma de la persona a cargo de obtener el consentimiento:

Fecha (dd/mm/aaaa):

Universidad de Navarra

English version

Participant ID:

Information sheet and assent form for the participation of minors aged 13-18 years in the research study titled:

Version 3.0 January 6th, 2021

Acoustic surveillance and digital cough monitoring at population level for early respiratory disease outbreak detection, an exploratory observational study

This assent form is meant for minors who are interested in taking part in the previously mentioned observational study. Please read this form carefully with your parents or legal guardian and ask any questions you might have.

Promoter

Clínica Universidad de Navarra/Universidad de Navarra, Avenida de Pío XII, 36
31008 Pamplona.

Funder

This study is funded by the Centre Hospitalier de l'Université de Montreal (CHUM) and the Patrick J. McGovern Foundation through a grant awarded to Co-Investigator Simon Grandjean Lapierre (*Early diagnosis of COVID-19 by utilizing Artificial Intelligence and Acoustic Monitoring*)

Main Researcher

Carlos Chaccour
Teléfono +34 666 293 112
Email cchaccour@unav.es

This document consists of two parts:

- Information sheet (meant to explain relevant information regarding the project).
- Assent form (where we will require your signature, and that of your parent or legal guardian, if you decide to take part in it).

You will be provided a copy of this document for your personal records.

Part I: Information sheet

Introduction

The objective of this document is to inform you about the characteristics of a research study you have been invited to participate in. The study has been approved by the Committee of Research Ethics of the Universidad de Navarra and the Committee of Medication Ethics of Navarra (Spain), as well as the independent ethics committee from the Centre Hospitalier de l'Université de Montreal (CHUM), in Canada.

This document aims to provide you with proper information, so you can understand this study and decide by yourself if you are willing to take part or not in it. Please read this information document carefully and we will answer any questions that might come up afterwards. You can also discuss this with people you trust before making a decision.

Objective of the research

Coronaviruses are a group of viruses that cause generally mild respiratory disease. However, a member of this group, the SARS-Cov-2, is responsible for causing COVID-19, a potentially dangerous disease that has spread across the globe since 2019.

One of the necessary interventions to contain the COVID-19 pandemic is understanding its real scale. This is particularly important now that new outbreaks are being regularly reported in areas with ongoing low-level transmission. A major limitation in this process is the limited diagnostic capabilities of many countries, which translates into delays in the search of medical attention and the collection of necessary epidemiological data.

Most patients with COVID-19 present cough as an early symptom of disease. This study aims to evaluate the usefulness of a mobile app called HyfeApp, which registers and studies cough patterns, as a complement to existing disease surveillance strategies. To do this, we will need to record and analyse about 15,500 individual episodes of cough. The town of Cizur Menor has been selected as the location of the initial studies of this new platform.

For this reason, we need as many people as possible installing the app, which runs in the background of your mobile. Although HyfeApp has continuous access to the mobile's mic, it has been designed to exclusively process sounds that match the characteristics of human cough. When one of these sounds is detected and recorded, an artificial intelligence algorithm studies it and where it determines it does sound like an episode of cough, the record is stored, along with geographical information and time, provided by the mobile's GPS.

Besides the information from the app, we will also review the medical records of those participants who present for a medical consultation in the national health system or the Clinica Universidad de Navarra. The objective of this is to collect information about the presence of cough, or any respiratory disease during one of those visits. Data from your medical chart will be obtained by the investigators from your local clinic or hospital. This includes without being limited to information related to any of the following conditions will be reviewed:

- Non-specific cough
- Non-specific upper respiratory tract infections
- Pharyngitis
- Asthma
- Bronchitis

- Chronic Obstructive Pulmonary Disease (COPD)
- COVID-19
- Gastro-esophageal reflux disease (GERD)
- Influenza
- Pneumonia (any cause)
- Respiratory Syncytial virus
- Non-specific respiratory tract infections

Additional laboratory test data to be captured from the selected visits includes:

- Microbiology
  - COVID-19 tests
  - Flu PCR
  - Sputum culture
- Hematology
  - Full blood count
  - D-dimer test
- Biochemistry
  - C-reactive protein
  - Procalcitonin
  - CPK
  - LDH
  - Ferritin

Besides the information from the app and medical charts, we will also solicit a restricted number of participants to participate in focus group discussions to explore the challenges related to using HyfeApp and participating in this study. If solicited, it will be your right to accept or refuse to participate in those focus groups.

Duration

Data will be initially collected for a one-month period. You will then be offered the opportunity to continue in the study for 3 and 6 months. You can refuse continuing in the study at any point.

Study Procedures

You will not be able to enroll in this study if you:

- Are incapable or unwilling to accept to share your codified cough data with multicenter databases aiming at refining acoustic-based diagnostics.
- Are under 13 years of age.
- Do not own a smartphone able to run HyfeApp.
- Are not a student/worker at the University of Navarra or a patient diagnosed with cough-related disease at the Clínica Universidad de Navarra.
- Are not a resident of Navarra

In case you decide to take part, a member of our team will help you install the app on your mobile. No further visits from the research team will be necessary. But you might be contacted once a month to collect feedback on your experience using the app, as well as to confirm your willingness to continue in the study. You might also receive periodic updates via email, to keep you informed on the status of the project and relevant preliminary results.

About HyfeApp

HyfeApp is a mobile app available for Android and IOS (Apple) operative systems, developed by a multidisciplinary team of data scientists, software developers and infectious disease physicians.

What does HyfeApp do?

HyfeApp runs in the background of your mobile, without interfering with any other running app, but having constant access to your mic and recording explosive sound snips of 0.5 seconds or less. No conversations, nor ambient sounds are recorded. These sound snips are sent to a server, where an artificial intelligence algorithm identifies those presenting sudden, shortchanges in decibel levels, compatible with cough episodes. Then, another algorithm processes them, evaluating its characteristics and determining if they were in fact, cough. The server then sends that data back to the mobile, so those files labeled as cough episodes are displayed by the app. HyfeApp is a wellness status tool. Just like similar apps that count calories, steps or snores. The only difference is that HyfeApp counts episodes of cough.

Benefits and risks of participating

HyfeApp will allow you to have a record of the number of times you cough every day, and of any changes compared to previous days. However, it is not a diagnostic or treatment tool. Therefore, it does not provide medical advice, nor replaces healthcare services. HyfeApp is not medical equipment. If you ever have doubts regarding your health condition or status, you should consult a doctor, or in case of emergency, communicate with proper emergency services.

We are aware that recording sounds from a mobile phone generates doubts regarding the handling of information and the participants' privacy. As explained before, HyfeApp does not record conversations or ambient sounds, and the 0.5 second sound snips are too short to identify participants. However, if linked to other metadata (such as telephone numbers), these sounds could allow identification. For this reason, all the information transmitted by the app is encrypted and handled following standard safety protocols. This way, we can make sure that only the researchers can access potentially identifiable data.

You will not be paid for your participation.

Voluntary participation

You must know that your participation in this study is voluntary and you can decide not to take part, or change your mind and resign your consent at any time in the future. This will not affect your relationship with your healthcare provider, nor harm your access to proper medical treatment in any way.

Economic Compensation

The study promoter is responsible for managing the funds. Before, doing a research study, the promoter must have signed a contract with the center where the study will take place, and the doctors who will conduct the study. Your participation in this study will not cost you any extra money beyond your standard medical procedures. Routine medical assistance will have to be paid by the social security network, your medical insurance, or yourself.

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You will not receive any payment or monetary compensation for taking part in this study.

Other information

Any new information regarding the app to be used in this study and that could affect your disposition to take part in it, discovered after you have decided to participate, will be communicated to you as soon as possible.

If you wish to withdraw your consent to take part in the study, no further personal data will be added to the database. You can also demand the destruction of any previously retained identifiable information, to prevent new analysis from being carried on.

You must also know that you could be excluded from the study if the promoter and/or researchers consider it to be adequate, either for your own safety, to prevent any adverse consequence deriving from your participation, or because they consider you are not complying with the established procedures. In any case, you will always receive a proper explanation of what caused your withdrawal from the study.

Confidentiality

All the information collected in this study will be codified in such a way that they cannot be linked to your personal data. Only the main researcher and co-researchers will know your name, and an ID number will be used to refer to you in every document or communication. The computers used to store and analyse the data will be password-protected and only authorised researchers will have access to them.

The Clínica Universidad de Navarra, as the data controller, complies with the Organic Law 3/2018, of December 5, and other Spanish data protection regulations in force. Therefore, it is important that you know the following information:

• In addition to the rights that you already know (access, modification, refusal and cancellation of data), you can now also limit the processing of incorrect data, request a copy, or have the data that you provided be transferred to a third party (portability) for the study. To exercise your rights, contact the Institution's Data Protection Officer at [protecciondedatosnav@unav.es]. You also have the right to contact the Data Protection Agency if you are not satisfied.

• Both the Center and the Promoter are respectively responsible for the processing of your data and undertake to comply with the data protection regulations in force. The data collected for the study will be identified by a code, so that information that can identify you is not included, and only your study doctor / collaborators will be able to relate said data to you and to your medical history. Therefore, your identity will not be revealed to any other person except to the health authorities, when required, or in cases of medical emergency. The Research Ethics Committees, the representatives of the Health Authority in matters of inspection and the personnel authorized by the Sponsor, may only access to verify personal data, clinical study procedures and compliance with the rules of good clinical practice (always maintaining the confidentiality of the information).

• The Researcher and the Sponsor are obliged to keep the data collected for the study for at least 25 years after its completion. Subsequently, your personal information will only be kept by the center for

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the care of your health and by the promoter for other scientific research purposes if you have given your consent to do so, and if this is allowed by the law and applicable ethical requirements.

• If we transfer your encrypted data outside the EU to our group entities, service providers or scientific researchers who collaborate with us, the participant's data will be protected with safeguards such as contracts or other mechanisms by the protection authorities of data. If the participant wants to know more about it, he or she can contact the promoter's Data Protection Officer [protecciondedatosnav@unav.es].

Sharing the results

At all time, you will have access to the knowledge we get from the research upon request to the principal investigator. We will not share your name, health status or where you live. After this, we will publish the results so that other interested people may learn from our research. You will be able to ask the status of this study and its findings by a direct request to the principal investigator.

Who approved this research?

The study has been approved by the Committee of Research Ethics of the Universidad de Navarra and the Committee of Medication Ethics of Navarra (Spain), as well as the independent ethics committee from the Centre Hospitalaire de l'Université de Montreal (CHUM), in Canada.

Right to refuse or withdraw

You don't have to take part in this research study if you do not wish so. You have the right not to sign this form. If you do not sign this form, you cannot take part in this research study. This is because we need your written permission to use your information. You have the right to leave the research study. If you would like to leave the research study, please tell a member of the study staff. You do not need to explain why you want to leave.

Who to contact?

If you are not satisfied with the way this study was conducted, or if you have any concerns, complaints or general questions about your rights as a participant, please contact the Patient Attention Office at the Clínica Universidad de Navarra by phone (+34 948 255 400) or email atpacientun@unav.es to talk with someone independent of the research team.

If you have any questions about this study or study procedures now or in the future, you can call Dr. Carlos Chaccour. Tel number 628 659 003 who is the Principal Investigator of the study. You can call Monday-Friday from 8.00 to 17.00 hrs.

Part II: Assent Form

Authorization from the parent or legal guardian

I have read, or have been read to the previous information. I was allowed to ask questions and I was provided with satisfactory answers to each one.

☐ I authorize my child/minor under my care to take part in this research project.

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☐ I do not authorize my child/minor under my care to take part in this research project and I have not signed the Assent Form presented below.

Name of parent or legal guardian:

Signature of parent or legal guardian:

Date (dd/mm/yyyy):

Consent from the minor

I have read or have been read to the previous information. I was allowed to ask questions and I was provided with satisfactory answers to each one.

☐ I accept to take part in this research project.

☐ I do not accept to take part in this research project and I have not signed the assent form presented below.

In case the minor accepts to participate:

Name of minor:

Signature of minor:

Date (dd/mm/yyyy):

If illiterate:

A literate witness must sign this form (when possible, this person should be chosen by the participant and not be related to the research team). Every illiterate participant must still present a fingerprint of his/her thumb.

I confirm this form was properly and accurately read to the potential participant and that said individual has voluntarily consented to participate in the study.

Name of witness:

Signature of witness:

Date (dd/mm/yyyy):

Participant's fingerprint (thumb):

Statement from the person responsible of getting written consent

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I have, to the best of my ability, read this information sheet to the potential participant and made my best effort to make sure he/she understood that the following procedures will be performed:

1. HyfeApp will be downloaded to the participant's mobile phone.
2. HyfeApp will register and store sounds that match the characteristics of human cough for a one-year period, between October 2020 and September 2021.
3. If the participant seeks medical attention through the national health network, his/her medical records could be accessed by the researchers to look for evidence of cough or any respiratory disease.

I confirm the participant has been allowed to ask questions and that all his/her questions have been answered to the best of my ability. I confirm the participant has not been coerced to take part in this study and that his consent was free and voluntary.

A copy of this form will be provided to the parent or legal guardian for personal records.

Has the parent or legal guardian signed the assent form?: Yes____ No____

Name of the person in charge of obtaining the participant's consent:

Signature of the person in charge of obtaining the participant's consent:

Date (dd/mm/yyyy):

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Cuestionario complementario de información médica

Versión 2.0 (6 de enero, 2021)

Información personal

Nombre:_____

Primer Apellido:_____

Segundo Apellido:_____

Fecha de nacimiento: _____

DNI: _____

Información de contacto:

Teléfono móvil:_____

Email:_____

Sistema operativo del móvil:

- ○ Apple
- ○ Android

Ciudad o pueblo_____ Avenida/Calle_____

Número_____ Escalera (izquierda o derecha, solo para departamentos)_____

Piso_____ Puerta_____

¿Usualmente usted recibe atención médica a través de cuál de los siguientes proveedores de salud?

- ○ Público (Seguridad Social/Osasunbidea)
- ○ Privado (Clínica Universidad de Navarra)
- ○ Ambos

¿Ha sufrido usted de alguna de las siguientes condiciones en el pasado, o sufre de alguna en la actualidad?

- ○ Tos de causa no específica o desconocida
- ○ Infecciones no especificadas de las vías respiratorias altas (Sinusitis, otitis, laringitis)
- ○ Faringitis
- ○ Asma
- ○ Bronquitis
- ○ Enfermedad broncopulmonar obstructiva crónica (EBPOC)
- ○ COVID-19
- ○ Enfermedad de Reflujo Gastroesofágico (ERGE)
- ○ Influenza estacional

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- ○ Neumonía (sin importar la causa)
- ○ Infección por virus sincitial respiratorio
- ○ Otras infecciones no especificadas del tracto respiratorio inferior
- ○ Fumador
- ○ Otra condición

En caso de haber seleccionado la ☒☒ ☒☒v ☒ ☒ ☒☒ ☒v explique a continuación a que se refiere:

_____
_____
_____

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English version

Medical Information Questionnaire for participants recruited at the University of Navarra

Version 2.0 (January 6th, 2021)

The following information must be filled by participants who have consented to take part in the study

Participant information

Name:_____

First surname:_____

Second surname:_____

DOB: _____

DNI: _____

Participant contact

Mobile phone:_____

Email:_____

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- ○ Apple
- ○ Android

Residence city_____ Street_____

Number _____ Stair (left or right, only for apartment buildings) _____

Floor_____ Door_____

Usually, you receive medical care from which of the following providers?

- ○ Public health network (Social Security/Osasunbidea)
- ○ Private (Clínica Universidad de Navarra)
- ○ Both

Please indicate if you have suffered from any of the following medical conditions

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- ○ Non-specific cough
- ○ Non-specific upper respiratory tract infections
- ○ Acute pharyngitis
- ○ Asthma
- ○ Bronchitis
- ○ Chronic Obstructive Pulmonary Disease (COPD)
- ○ COVID-19
- ○ Gastroesophageal Reflux Disease (GERD)
- ○ Influenza
- ○ Pneumonia (any cause)
- ○ Respiratory Syncytial Virus Disease
- ○ Another non-specific lower respiratory tract infection
- ○ Smoker
- ○ Other condition (please specify): _____

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Digital Acoustic Surveillance for Respiratory Disease Outbreak Early Detection: An Exploratory Observational Study in Navarra, Spain
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p. 3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	p. 19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p. 0
	5b	Name and contact information for the trial sponsor	p. 0
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	p. 19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p.5-6
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	p. 8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p.6-7

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained p. 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) p. 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered p.9-10,11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) p. 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended p. 12-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) p. 7-8, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations p. 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size p. 7

Methods: Assignment of interventions (for controlled trials)

Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions NA

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions p. 7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial NA
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol p. 7, 12-15.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols p. 9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol p.15-16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol p. 12-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) p. 15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) NA
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed NA

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct p. 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor NA

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval p. 16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) p. 16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) p. 7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial p. 15-16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site p. 19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Data share agreement included in the research agreement, but not included in the submission.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions p. 16
	31b	Authorship eligibility guidelines and any intended use of professional writers p. 19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Digital Acoustic Surveillance for Early Detection of Respiratory Disease Outbreaks in Spain: A protocol for an observational study

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Respiratory medicine
Keywords:	COVID-19, Respiratory infections < THORACIC MEDICINE, Epidemiology < TROPICAL MEDICINE

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Digital Acoustic Surveillance for Early Detection of Respiratory Disease Outbreaks in Spain: A protocol for an observational study

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Word count: 3471

Abstract

Introduction

Cough is a common symptom of COVID-19 and other respiratory illnesses. However, objectively measuring its frequency and evolution is hindered by the lack of reliable and scalable monitoring systems. This can be overcome by newly developed artificial intelligence models that exploit the portability of smartphones. In the context of the ongoing COVID-19 pandemic, cough detection for respiratory disease syndromic surveillance represents a simple means for early outbreak detection and disease surveillance. In this protocol, we evaluate the ability of population-based digital cough surveillance to predict the incidence of respiratory diseases at population level in Navarra, Spain, while assessing individual determinants of uptake of these platforms.

Methods and analysis

Participants in the Cendea de Cizur, Zizur Mayor, or attending the local University of Navarra (Pamplona) will be invited to monitor their night-time cough using the smartphone app Hyfe Cough Tracker™. Detected coughs will be aggregated in time and space. Incidence of COVID-19, and other diagnosed respiratory diseases within the participants cohort, and the study area and population will be collected from local health facilities and used to carry out an ARIMA analysis on those independent time series. In a mixed-methods design, we will explore barriers and facilitators of continuous digital cough monitoring by evaluating participation patterns, socio demographic characteristics. Participants will fill an acceptability questionnaire and a subgroup will participate in focus group discussions.

Ethics and dissemination

Ethics approval was obtained from the ethics committee of the Centre Hospitalier de l'Université de Montréal, Canada and the Medical Research Ethics Committee of Navarre, Spain. Preliminary findings will be shared with civil and health authorities and reported to

individual participants. Results will be submitted for publication in peer-reviewed scientific journals and international conferences.

Trial Registration Number

clinicaltrials.gov/NCT04762693

Strengths and limitations of this study

1. This is the first study to evaluate the utility of artificial intelligence models and smartphone applications for cough detection at population level.
2. The studied approach has the potential to be rapidly scalable even within underdeveloped public health systems.
3. Qualitative methods will improve the understanding of barriers and facilitators affecting the uptake of cough detection smartphone applications and participation in acoustic surveillance programs.
4. Recorded coughs will be annotated with clinical diagnoses (when available) and will contribute to the training of cough-based disease-specific screening and diagnostic tools.
5. Success of this study is contingent on large-scale enrolment and high participant retention since a small sample size might not be sufficient to appropriately correlate the study population's cough trends and their relationship with the incidence of respiratory diseases at population level.

Introduction

Real-time tracking of the COVID-19 pandemic and detection of the emergence of novel variants or other respiratory pathogens represent challenges for public health authorities globally. Nonetheless, understanding local epidemiology is essential to disease control efforts. This is particularly true now that the world has moved into a COVID-19 endemic phase, with periodic outbreaks in multiple locations superimposed over ongoing community transmission. The ability to appropriately monitor disease incidence, however, is frequently limited by a lack of testing capacity, delays in health-seeking behaviours, as well as complexities related to timely aggregation of actionable surveillance data by public health authorities.

Although asymptomatic cases of COVID-19 and other respiratory communicable diseases are well described, cough remains a common symptom of COVID- 19 (1, 2). A meta-analysis including data from over 24,000 adults with confirmed COVID-19 revealed cough as the second most prevalent symptom, being reported by 57% (CI: 54-60%) of all patients. (3) Additionally, cough is a key event in the transmission of COVID-19 and other respiratory pathogens.(4)

Given the intrinsic subjectivity of existing cough monitoring tools, mostly based in self-reported questionnaires, there is a great interest in developing an automated system to objectively register coughs. Attempts to achieve this date back to the 1950s, but until recently, important technologic constraints limited significant advances. (5)

Even now, detecting and classifying sounds as coughs without the input of a human observer, still represents a remarkable challenge. However, automatically detecting cough is now possible thanks to the development of acoustics and artificial intelligence (AI) models which can be incorporated into wearable devices. This has allowed the development of several alternatives, whose widespread deployment beyond a research context remains limited due to problems related to portability, the need to continuously record sound (which may

compromise patients' privacy), inconsistent sensitivity and specificity, high false positivity rates, and little financial incentives.(5)

Some of these limitations might be addressed by incorporating similar systems on smartphone applications, an approach that has just recently begun to be widely explored.(6, 7) In brief, putative cough sounds (manifested as short and explosive noises) are recognized and captured by smartphones. Machine learning models trained on hundreds of thousands of annotated sounds are then used to distinguish cough from other sounds.

We propose that COVID-19 surveillance and early outbreak recognition can be enhanced by digitally monitoring cough and detecting changes in its incidence at population level. We hypothesize such changes precede individual symptoms recognition, healthcare seeking behaviours, diagnosis, and data aggregation within conventional disease surveillance systems. Indeed, digital cough monitoring data can be aggregated in real time providing constantly updated information on the emergence and activity of communicable respiratory diseases within populations. This approach would be of particular value in low- and middle-income countries where (a) capturing passive data through health services is insufficient given unequal access to healthcare, and (b) active case detection and contact tracing capacity is limited. (8, 9)

To our knowledge, digital cough monitoring for early detection of respiratory disease outbreaks has never been performed. Provided the participation of a critical mass of active users is achieved, monitoring of aggregated cough data could provide a simple and inexpensive surrogate indicator for overall respiratory infections incidence, similar to, but more accurate than wastewater monitoring (10). This information could in turn guide public health interventions. If proven successful in the specific case of COVID-19, this study would establish a template for early and disease-agnostic detection of emerging pathogens, therefore contributing to health systems epidemic preparedness.

Primary research question

Can digital cough surveillance predict the incidence of respiratory diseases at population-level in Navarra, Spain?

Methods

Study design

This is a prospective observational study which will take place between November 2020 and October 2021 (Figure 1). Participants will be recruited in (a) the Cendea de Cizur, a municipality composed by a cluster of villages south of the city of Pamplona, (b) the neighbouring town of Zizur Mayor, in the Chartered Community of Navarra (Spain), as well as (c) in the different campuses of the University of Navarra (Pamplona), which collides with the municipalities.

All these communities are located within a 5 km range from each other, and there is a considerable geographical and social overlap between them, as the University of Navarra is the second most important employer in the area.

The 4,000 people living in the Cendea de Cizur are served by a public health center which receives 45,000 outpatients visits per year. Of these, approximately 12% are associated with respiratory diseases. Furthermore, the Clínica Universidad de Navarra is the main private healthcare provider in the region and offers medical care to a significant proportion of the population, as well as university students and workers. Both centres offer COVID-19 PCR testing. Together, those two healthcare facilities cover most of the population's healthcare needs and have digitalized medical record systems that facilitate the retrieval of medical data concerning the diagnosis of respiratory diseases among participants.

Recruitment strategies will include direct solicitation, community meetings, videos and advertisements in social media and university communication platforms. Those willing to participate will attend individual sessions with a study coordinator for counselling and training

using the Hyfe Cough Tracker™ (Hyfe™) application, and for obtention of informed consent. Information consent forms for adults and minors are available as supplementary material 1, and supplementary material 2, respectively. Participants will consent to be contacted regularly via email and telephone by the study team and will also fill an enrolment questionnaire (Supplementary material 3) where demographic and respiratory diseases medical data will be collected.

Primary objective

1. To assess the value of digital cough monitoring and acoustic surveillance in predicting COVID-19 and other respiratory diseases incidence at population level.

Secondary objective

2. To assess barriers and facilitators to participation in an acoustic surveillance program using a smartphone-based digital cough monitoring application.

Eligibility criteria

To be included in the study, participants must (i) be 13 years old or older, (ii) own a smartphone, (iii) be willing to install and use the Hyfe™ digital cough monitoring application, (iv) accept and comply with Hyfe™ privacy policy and terms of use, and (v) grant access to their medical records. To optimize population representativity, participants also need to (vi) visit the University of Navarra on a regular basis, either as a student, worker, or patient of the university clinic, or (vii) have a general interest in the study, and (viii) currently reside in Navarra. These criteria aim at ensuring a large sample size and the availability of needed medical records while concentrating recruitment in a geographically focused area. Accounting for differences between smartphone models' capabilities, upon recruitment, participants will also have to complete a microphone calibration process within the application. This is to make

sure their smartphones can accurately detect cough-like sounds. Participants who fail to complete this process will be excluded from the study.

Participant retention

To ensure participants' retention and promote continuous cough recording, we will use videos posted on social media, as well as emailed to participants, text messages and regular push notifications sent via the Hyfe™ application on participants' smartphones. Participants will also receive monthly emails with information regarding the current stage of the study and high-level preliminary results.

Digital cough monitoring

The cough detection application used in this study is Hyfe Cough Tracker™ (Hyfe™). (https://www.hyfeapp.com/). Hyfe™ runs in the background of smartphones operating systems, listens for and records short snippets (<0.5 seconds) of explosive, putative cough sounds and then classifies them as cough or non-cough, using a convolutional neural network model. Cough sounds are automatically matched with time and GPS coordinates which can be jittered to ensure participants' privacy. Hyfe™ is a research tool that has collected over 5 million putative cough sounds, of which over 1,000,000 have been classified as coughs or not by a human listener in order to train the AI model.

The analytical performance of Hyfe™ for cough detection (referred to whether the application is sensitive and specific for the classification of recorded sounds as coughs or non-coughs) was confirmed using this study's preliminary results from a subgroup of participants recruited in the Cendea de Cizur between November and December 2020.

Approximately 500 participants were contacted from an existing mailing list used in a previous epidemiological study, of these, 57 were enrolled. While participants were initially requested to keep Hyfe™ running continuously, they were later instructed to restrict their use to at least

6 hours during night-time, for 30 days, following complaints of increased battery consumption.

During this period, nearly 700,000 putative cough sounds were registered, of which 119,876 were classified by human observers, revealing a sensitivity of 96.34% and a specificity of 96.54%, when using a cough-positivity threshold of 0.85 (Figure 2).

These values, however, must be interpreted carefully, as specificity measured at the explosive sound level does not necessarily provide a full picture of diagnostic accuracy, particularly in loud environments, where the probability of an explosive sound being a cough is lower, and the false positivity rate might be considerably higher. Similarly, sensitivity does not account for non-explosive sounds, that are not captured by the system, and of which a non-zero number might be coughs.

Upon enrolment, a study coordinator will assist participants in installing the Hyfe™ application. Once turned on, it will continuously monitor participants' cough. Participants can turn the application on and off at will but will be instructed to keep it active for at least six hours or while they sleep, every day for a minimum period of 30 days. In an adaptive design aimed at improving retention, participants will have the possibility of extending their participation to a 3-month and 6-month period.

Local epidemiology of respiratory disease

Digital medical data systems at the Zizur's health center and the Clínica Universidad de Navarra will be reviewed monthly to establish the incidence of the following respiratory, or cough-associated diseases in the participants cohort; COVID-19, influenza, respiratory syncytial virus (RSV), pneumonia, asthma, bronchitis, pharyngitis, chronic cough, chronic obstructive pulmonary disease (COPD), gastro-esophageal reflux disease (GERD), other nonspecific respiratory tract infections. Specifically, for COVID-19, daily incidence figures for

the study area (Cendea de Cizur, Zizur Mayor, and Pamplona), and regional population, will also be obtained from local health authorities. Data will be aggregated and used to build local epidemic curves of respiratory diseases during the study period.

Barriers and facilitators to participation

A participation cascade informing on the number of solicited, enrolled, and actively recording participants will be tracked in real time throughout the study. The total number of user-hours using Hyfe™ will also be monitored in real time.

All participants will be asked to fill a satisfaction survey in which they will be asked about the usability of the app, the problems that they ran into, and their likelihood of using the app in the future. We will follow-up with a group of 25 participants who are willing to attend a focus group discussion (FGD) to better understand the barriers and facilitators affecting participation in the cough-surveillance system. The 25 participants will include some of whom deleted the application early on, who stopped using it after a month, and who had low satisfaction scores.

Patient and public involvement

This study pilots an experimental syndromic surveillance approach at population level. The municipal authorities of the Cendea de Cizur were informed about the nature of the study and provided feedback on the best approach to recruit local participants. Similarly, representatives of the University of Navarra's medical services collaborated on the design of the study protocol including the review of recruitment strategies as well as data collection, aggregation and reporting plans. No anticipated participants were involved in the study design. Study findings are to be reported in both English and Spanish to participants and key stakeholders at individual, municipality, and university levels during the surveillance phase.

Data analysis and sample size calculations

Syndromic surveillance as a surrogate marker of respiratory disease activity

Given the uncertainty around the incidence of the various respiratory diseases including COVID-19, throughout the study period, it is impossible to establish a target sample size sufficient to either confirm or confute with statistical significance that cough monitoring at population level can predict incidence of respiratory diseases. We will endeavour to recruit the highest number of participants possible in order to achieve the best representation of the population.

First, cough data will be aggregated in time and space to create cough incidence curves and geospatial heat maps reflecting the frequency and density of cough among the studied population (Figure 3 and Figure 4). Second, epidemic curves reflecting the incidence of targeted respiratory illnesses within the participants cohort, and the number of COVID-19 cases diagnosed in the study area and population will be generated with data collected from the Clínica Universidad de Navarra, and Zizur's health center, as well as aggregated epidemiological records obtained from regional health authorities, respectively. Coughs per person-hour and clinical diagnoses data will be superposed in time. Finally, we will carry out an autoregressive moving average (ARIMA) analysis to compare the incidence of confirmed and forecasted respiratory diseases (including COVID-19) with the frequency of cough among study participants, measured as coughs per person-hour. ARIMA analysis is a type of time series analysis that uses past data to forecast the likely future behaviour of a variable. In brief, the variable of interest is regressed to its own lagged values, and autoregression and partial autocorrelation functions are used to model the stochastic nature of a time series. (11) Comparison and prediction analyses will be performed using epidemic curves from both the participants cohort and in the entire study area and population.

Perceptions and willingness to participate in syndromic surveillance

Mixed methods will be used to assess individual barriers and facilitators to participation in an acoustic surveillance program. Among all eligible individuals in the Cendea de Cizur, Zizur Mayor and in the University of Navarra who are invited to participate in the study, we will assess how many do install the cough detection application and keep using it through the course of the study. Participants corresponding to specific user profiles based on duration and regularity of cough recording will be identified. We will then descriptively analyze the socio-demographic characteristics, and baseline health conditions of participants belonging to the different user profiles.

A subsample of participants will be contacted once a month, by telephone or text messaging, to obtain feedback from their experience using the app.

To assess population uptake of Hyfe™, as well as barriers and facilitators to participation, a convenience subsample of 25 participants will be recruited for focus group discussions. Following similar designs, FGDs will consist of two parts. (12) The first one will be aimed at understanding a participant's awareness of their cough frequency and temporality patterns, as well as the perceived importance of measuring these elements. Questions asked in this part will include (i) How much attention do you pay to your coughs on a daily basis? (ii) How important is it for you to know the number of times you cough per day? (iii) Will keeping track of your coughs help you improve your health? The second one will focus on the participant's experience using Hyfe™, as well as possible recommendations for developers to improve it. This part will include the following general questions: (i) What do you like about the app, (ii) What do you think of this app compared to other health apps, (iii) What doesn't work well, (iv) What keeps you committed (or not) to using the app, (v) What do you think the purpose of the app is, (vi) What advice do you have for the developers?

Risks and privacy

Recording sounds implies specific ethical and privacy concerns. These are, however, addressable at different levels. First, sound snippets recorded are too short (<0.5 seconds) to capture conversations or background sound. Participants can withdraw from the study at any time, and the application can be turned off or removed from smartphones freely. Our consent process explicitly describes exactly what is and what is not recorded. The use of pre-generated unique identifiers to install and use the smartphone application ensures that only investigators can link cough data to personal identifiers. Contact information collected from participants will be kept in physical forms stored under lock, and password-protected files at the University of Navarra. Only the principal investigator, study coordinator, and research assistant will have access to this information. Data transferred to other researchers will only include unique identifiers for individual participants, but no other personal information. All acoustic data and metadata collected by the application is stored in encrypted servers physically located in the United States. Data storage and access protocols are compliant with General Data Protection Regulation (GDPR), and only non-identifiable data information is stored by Hyfe.

Ethics and dissemination

This study protocol was approved by the ethics committee of the Centre Hospitalier de l'Université de Montréal, Canada (Reference numbers 2021-9247 20.253 & 2021-9270 20.226) and the Medical Research Ethics Committee of Navarra, Spain (Reference number PI107/2020). Any modifications to the approved protocol would be resubmitted to both committees.

Preliminary summary results of this study will be regularly shared with participants via email and through focal meetings. Final results will also be disseminated in open-access scientific journals and international conferences. A two-page summary of results will be prepared in

Spanish and posted on the municipal and university website, and shared with local civil and health authorities, as well as with individual participants.

Discussion

The current COVID-19 pandemic highlights the incapacity of existing surveillance networks to rapidly curb the impact of emerging respiratory pathogens in the current globalized world. (13) This is particularly true in low- and middle-income countries, where diagnostic and contact-tracing efforts are limited by their crippling costs, and where epidemiological data aggregation infrequently translates into actionable information because of delays inherent to disaggregated and poorly digitalized health information systems. Continuous, individual-based, and passive monitoring of cough among entire populations could represent inexpensive large-scale surveillance networks contributing to the early detection of outbreaks and enabling prioritized and focal delivery of limited resources.

AI and more specifically machine learning models, are increasingly used in disease surveillance and can maximize the impact of limited available resources. (14) Integration of such models with accurate digital epidemiological data was shown to provide reliable, near-real time estimations of influenza disease incidence. (15) The widespread distribution of smartphones coupled with the development of AI-enabled sound classification models now represent another new potential breakthrough in public health and epidemic preparedness. Beyond being able to detect cough, most smartphones have integrated geo-location functions. This allows the integration of acoustic records with geo-spatial and temporal data and increases the range of applications of acoustic surveillance systems for disease control. (16)

Apart from participating in a collective disease tracking and eradication effort, participants monitoring their cough also benefit from objective feedback on their own symptomatology.

During a pandemic, such feedback could trigger appropriate healthcare seeking behaviours and self-quarantine further helping to limit disease transmission at community level.

Implementing such an innovative approach to disease surveillance is contingent on overcoming substantial challenges. Evidence suggests that users are typically willing to install mobile apps with a clearly perceived health benefit. But this is often limited by issues such as increased battery drainage, or disruption of daily activities by alerts and notifications. (17) Specifically, for acoustic surveillance apps, protecting user's privacy must also be a priority, in order to create the social trust needed to achieve a high uptake of these systems. To guarantee this, users must be able to clearly understand the nature of these applications, as well as to control their functioning at will. This means that the quality of the data recorded will greatly depend on individual behaviours.

Despite proven technical capacity and tremendous potential in complementing surveillance systems, whether listed challenges can be overcome and whether digital cough monitoring can provide actionable public health information remains unknown. This study will address those questions. It will also generate operational expertise and qualitative knowledge on the facilitators to be exploited, and the barriers to be addressed in order to maximize uptake and impact prior to implementation on a wider scale.

Limitations and potential challenges

Enrolment and retention are expected to represent the major limitations of this project. Acoustic syndromic surveillance tools might be perceived as threatening for the privacy of potential participants. Furthermore, the quantity of cough data recorded will heavily rely on the regular use of the system by participants. The diversity of respiratory and non-respiratory

conditions that can cause cough, as well as the consumption of medications to treat them, can make it difficult to link changes in cough frequency with epidemiological data. Finally, asymptomatic, or mild infections of SARS-CoV-2 and other respiratory pathogens, mean that a proportion of infected patients will not contribute to the cough-based surveillance system and are unlikely to seek medical attention, reducing available cough and epidemiological data necessary for the analysis. Those limitations and challenges reflect well the impediments to larger scale deployment of cough-based syndromic surveillance for any respiratory disease hence making this innovative study an ideal stress-test for such approach.

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The authors want to thank the Municipality of the Cendea de Cizur, the University of Navarra and all participants for their trust and desire to participate in citizen science and altruistic population-level syndromic surveillance.

Contributors

All authors meet criteria for authorship as per the BMJ Global Health policy and ICJME recommendations. Conceptualization (JCGF, JB, DD, NU, LYT, SGL, CCh), data curation (JCGF, JB, NU, CCh), formal analysis (JCGF, JB, NU, SGL, CCh), funding acquisition (SGL), investigation (JCGF, JCh, AFM, VO, IB, JBart, CCh), methodology (JCGF, JB, NU, SGL, CCh), supervision (JCGF, SGL, CCh), writing of the original draft (JCGF, CCh, SGL). All authors have read, reviewed, discussed, and approved the final manuscript and their respective representation in the authorship.

Data sharing statement

Aggregated deidentified datasets will be available upon completion of the study by reasonable request to the corresponding author.

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Competing interest

JB is the CEO of Hyfe™ Inc. Hyfe Inc had no role in the decision to submit this protocol for publication. All other authors declare no competing interests. Upon submission of this protocol for publication, JCG, SGL and CCh had full access to all the data available and assumed responsibility for the decision to submit the manuscript content for publication.

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Supplementary materials

1. Informed Consent Form
2. Assent form
3. Complementary medical questionnaire for participants
4. SPIRIT Checklist

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Figure legends

Figure 1: Study design, timeline and monitoring plan for the study's primary objective.

Figure 2: Receiver operating characteristic (ROC) analysis showing an area under the curve (AUC) of 0.995 for the classification of cough in participants recruited between November and December 2020.

Figure 3: Coughs per person-hour registered in participants recruited between November 2020 and January 2021.

Figure 4: Heatmap of registered cough episodes in the municipalities of Zizur Mayor, Cendea de Cizur, and Pamplona between November 2020 and March 2021 (The Cendea de Cizur is an incontiguous municipality).

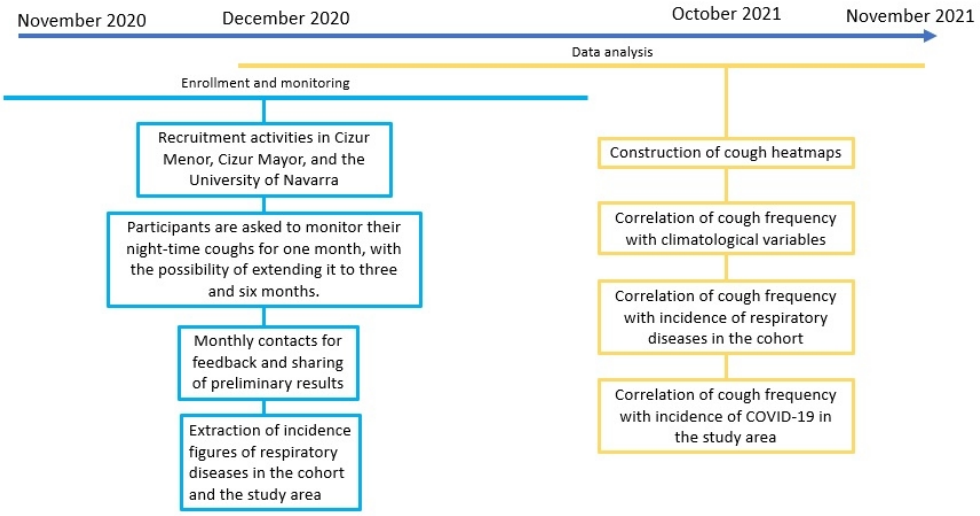

Figure 1

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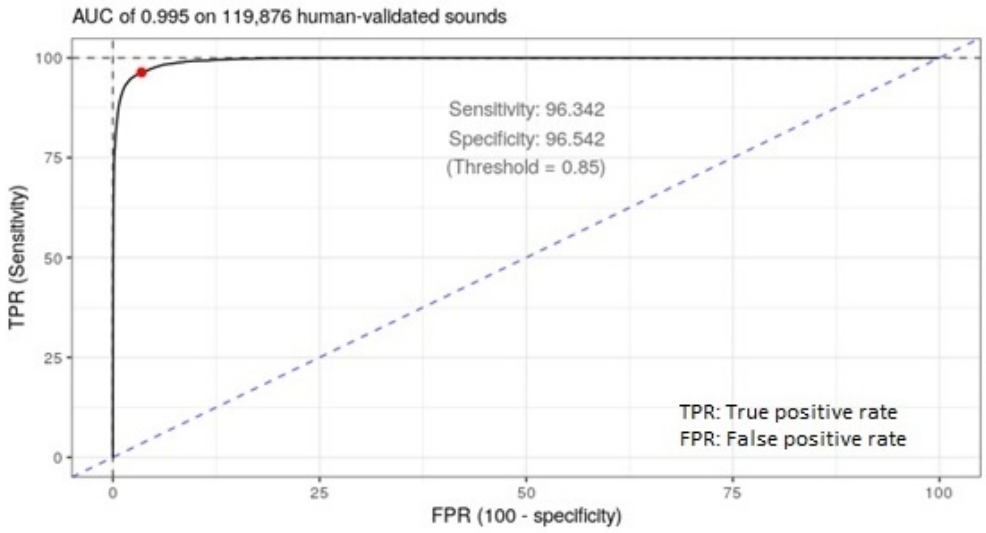

Figure 2

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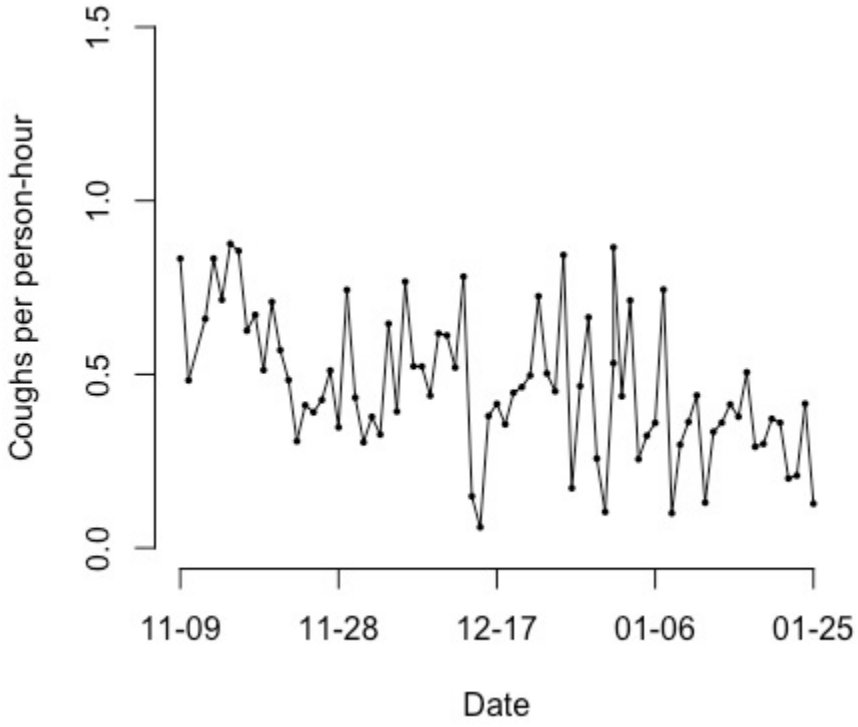

Figure 3

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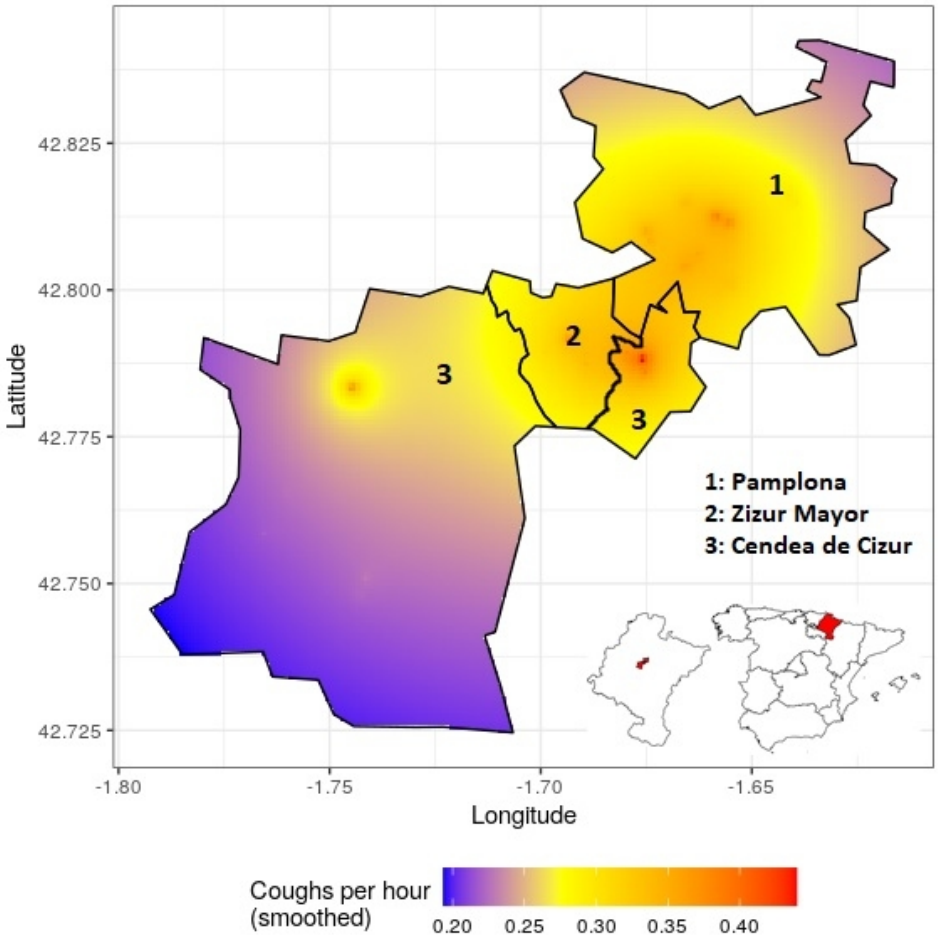

Figure 4

157x151mm (96 x 96 DPI)

Universidad de Navarra

HOJA DE INFORMACIÓN Y CONSENTIMIENTO

Versión 3.0, 6 de enero de 2021

TÍTULO DEL ESTUDIO: Vigilancia acústica y monitorización digital de la tos a nivel poblacional para la detección temprana de brotes de enfermedades respiratorias. Un estudio observacional exploratorio.

CÓDIGO DEL PROMOTOR:

PROMOTOR

Clínica Universidad de Navarra/Universidad de Navarra, Avenida de Pío XII, 36

31008 Pamplona.

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INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por un Comité de Ética de la Investigación de la Universidad de Navarra, el comité de ética de la investigación con medicamentos de Navarra y el comité de ética del Centre Hospitalier de l'Universite de Montréal (CHUM), en Canadá.

Con este documento pretendemos que usted reciba la información adecuada para que pueda entender de qué se trata el estudio y decidir si desea o no participar en el mismo. Para ello, lea esta hoja informativa con atención y nosotros le aclararemos las dudas que puedan surgir después de la explicación. Además, puede consultar con las personas que considere oportuno.

PARTICIPACIÓN VOLUNTARIA

Universidad de Navarra

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

DESCRIPCIÓN GENERAL DEL ESTUDIO

Los coronavirus son un grupo de virus que causan infecciones respiratorias generalmente leves. Sin embargo, un miembro de este grupo, el SARS-Cov-2, es el responsable de provocar la COVID-19, una enfermedad potencialmente peligrosa que desde finales del 2019 se ha extendido a lo largo de todo el mundo.

Uno de los elementos necesarios para contener el avance de la pandemia de COVID-19 es entender su escala real. Esto es particularmente importante ahora que los brotes regulares en zonas en las que simultáneamente ocurre transmisión a una menor escala se han convertido en una realidad. Uno de los mayores obstáculos de los sistemas sanitarios es la limitada capacidad de hacer pruebas diagnósticas, lo que se traduce en retrasos en la búsqueda de atención médica, así como en la recolección de la información necesaria para planear intervenciones que limiten la expansión de la enfermedad.

La gran mayoría de pacientes con COVID-19 presentan tos como un síntoma temprano de la enfermedad. Este estudio pretende evaluar la utilidad de una aplicación para el móvil, llamada HyfeApp, que registra y evalúa patrones de tos, como complemento a las estrategias de vigilancia epidemiológica existentes. Para esto, estimamos que será necesario grabar y analizar episodios individuales de tos.

Por eso esperamos que el mayor número posible de habitantes instale la aplicación. Esta aplicación se ejecuta en segundo plano en el móvil. Aunque HyfeApp tiene acceso continuo al micrófono de su móvil, ha sido diseñada para procesar únicamente sonidos compatibles con las características de la tos humana. Cuando uno de estos sonidos es detectado y grabado por la aplicación, un algoritmo de inteligencia artificial lo estudia y en caso de decidir qué se trata de un episodio de tos, se guarda junto a la información sobre la ubicación geográfica y el momento en que ocurrió, que es proporcionada por el sistema GPS del móvil.

Aparte de la información suministrada por la aplicación, también revisaremos los registros médicos de aquellas personas dispuestas a participar que acudan a consulta en el sistema nacional de salud, o la Clínica Universidad de Navarra. El objetivo de esto es recolectar información sobre la presencia de tos durante la exploración médica, o el diagnóstico de alguna enfermedad respiratoria en alguna de las visitas. Solo se consultará información relacionada con alguna de las siguientes condiciones:

- Tos no específica.
- Infecciones del tracto respiratorio superior.
- Faringitis.
- Asma.
- Bronquitis.
- Enfermedad Broncopulmonar Obstructiva Crónica (EBPOC).
- COVID-19

- Enfermedad por Reflujo Gastroesofágico (ERGE)
- Influenza
- Neumonía (por cualquier causa)
- Infección por virus sincitial respiratorio (VSR)
- Infecciones respiratorias inespecíficas.

Otros exámenes paraclínicos a ser recolectados incluyen:

- Microbiología
  - Pruebas de COVID-19
  - PCR para influenza
  - Cultivo de esputo
- Hematología
  - Hematología completa
  - Prueba del dímero D.
- Bioquímica
  - Proteína C reactiva
  - Procalcitonina
  - CPK
  - LDH
  - Ferritina

Aparte de la información obtenida de la app y sus registros médicos, también le pediremos a un grupo reducido de participantes que formen parte de discusiones grupales focalizadas, para explorar los desafíos que representa el uso continuo de HyfeApp, y su participación en el estudio. En caso de que se le solicite participar, usted podrá aceptar o negarse.

Duración

Se recolectará información inicialmente por un período de 1 mes, consultándosele en ese momento su disposición a seguir participando por 3 y 6 meses. Usted podrá negarse a seguir participando en el estudio en cualquier momento.

Procedimientos del estudio

Usted no puede participar en el ensayo si:

- No puede o no quiere aceptar compartir su información codificada, relacionada a sus registros de tos con bases de datos usadas para refinar los diagnósticos basados en perfiles acústicos.
- Si tiene menos de 13 años de edad.
- Si no tiene un teléfono inteligente capaz de ejecutar HyfeApp.
- Si no es un estudiante/trabajador de la Universidad de Navarra, o un paciente diagnosticado con una enfermedad causante de tos en la Clínica Universidad de Navarra.

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- Si no es residente en Navarra.

Si usted decide participar, un miembro de nuestro equipo lo ayudará a instalar la aplicación en su móvil. No serán necesarias nuevas visitas de parte del equipo de investigación, pero serán contactados una vez al mes para obtener comentarios sobre su experiencia usando la aplicación y ratificar su consentimiento y disposición a seguir participando en el estudio. También podrá ser contactado vía correo electrónico para recibir actualizaciones periódicas sobre el estado del proyecto y sus resultados preliminares.

LA APLICACIÓN HYFEAPP

HyfeApp es una aplicación móvil disponible para los sistemas operativos Android y iOS (Apple), desarrollada por un equipo multidisciplinario que incluye analistas de datos, desarrolladores de software y médicos especialistas en enfermedades infecciosas.

¿Qué hace HyfeApp?

HyfeApp se ejecuta constantemente en el segundo plano de su móvil, sin interferir con el funcionamiento de otras aplicaciones, pero teniendo acceso a su micrófono y grabando recortes de sonidos explosivos de menos de 0.5 segundos de duración. Ni las conversaciones, ni los sonidos de fondo son grabados. Estos recortes son enviados a un servidor, donde un algoritmo de inteligencia artificial identifica aquellos que presentan cambios súbitos y cortos en los decibeles, compatibles con episodios de tos. Posteriormente, otro algoritmo los procesa, evaluando otras características y determinando si efectivamente se trató de un episodio de tos. El servidor envía esta información de vuelta al móvil, de forma que los archivos clasificados como tos se incorporan a los registros mostrados por la aplicación.

HyfeApp es una herramienta que le proporciona información sobre su estado de bienestar. Tal como herramientas similares que cuentan calorías, registran el número de pasos o ronquidos. La única diferencia es que HyfeApp cuenta episodios de tos.

Beneficios y riesgos por su participación en estudio

HyfeApp le permitirá llevar un registro del número de veces que tose al día, así como evidenciar cambios con respecto a días anteriores. Sin embargo, no es una herramienta de diagnóstico o tratamiento médico. Por lo tanto, ni provee información o consejos médicos, ni sustituye de ninguna forma a los servicios sanitarios: HyfeApp no es un instrumento médico especializado. Si usted tiene alguna duda sobre su estado de salud, debe consultarlas con un médico o en caso de emergencia, llamar a los servicios respectivos inmediatamente .

Grabar sonidos desde un móvil inmediatamente genera dudas sobre la forma en que será manejada la información, y garantizada la privacidad de los participantes. Como hemos explicado anteriormente, HyfeApp no graba conversaciones ni sonidos de ambiente. Los segmentos de 0.5 segundos grabados por la aplicación no permiten identificar a los participantes. Sin embargo, algunos de estos sonidos pudiesen permitir identificar al participante si son interpretados en conjunto a otra metadata registrada por la aplicación (como el número de teléfono, por ejemplo). Por esta razón, toda la

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información transmitida por la aplicación estará encriptada y manejada según los protocolos de seguridad estándar empleados en este tipo de estudios. De esta forma, únicamente los investigadores podrán asociar los datos recolectados por la aplicación, a otros elementos que permitan identificar a los participantes.

No será remunerado por su participación en este estudio.

CONFIDENCIALIDAD

Toda la información recolectada en este estudio se mantendrá codificada, de forma que no pueda ser vinculada a sus datos personales. Solo el investigador principal y los co-investigadores sabrán su nombre y en cualquier documento o comunicación se usará un número de identificación personal asignado a cada participante. Los ordenadores utilizados para analizar los datos de este estudio tendrán contraseñas y solo investigadores autorizados podrán acceder a ellas.

La Universidad de Navarra, como responsable del tratamiento de datos, se compromete al cumplimiento de la Ley Orgánica del 3/2018, de 5 de diciembre y demás normativa de protección de datos en vigor. Por ello, es importante que conozca la siguiente información:

• Además de los derechos que ya conoce (acceso, modificación, oposición y cancelación de datos) ahora también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercer sus derechos, diríjase al Delegado de Protección de Datos de la institución en **[**protecciondedatosnav@unav.es**]**. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho/a.

• Tanto el Centro como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen a cumplir con la normativa de protección de datos en vigor. Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

• El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.

• Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar al Delegado de Protección de Datos del promotor **[**protecciondedatosnav@unav.es**].**

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COMPENSACIÓN ECONÓMICA

El promotor del estudio es el responsable de gestionar la financiación del mismo. Para la realización del estudio, el promotor ha firmado un contrato con el centro donde se va a realizar y con el médico del estudio.

Su participación en este estudio no le causará costes adicionales diferentes de los asociados a su tratamiento habitual. La asistencia rutinaria deberá ser pagada por la seguridad social, por su seguro médico o por usted mismo.

Usted no recibirá ninguna compensación económica por su participación en este estudio.

OTRA INFORMACIÓN RELEVANTE

Cualquier nueva información referente a la aplicación utilizada en el estudio y que pueda afectar su disposición para participar en el mismo, que se descubra durante su participación, le será comunicada lo antes posible.

Si usted decide retirar el consentimiento para participar en este estudio, no se añadirán nuevos datos a la base de datos y puede exigir la destrucción de cualquier información identificable previamente retenidas para evitar la realización de nuevos análisis.

También debe saber que puede ser excluido del estudio si el promotor y/o los investigadores del estudio lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso derivado de su participación, o porque consideren que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada del estudio

COMPARTIENDO LOS RESULTADOS

Usted tendrá acceso a todo el conocimiento generado por esta investigación en todo momento, solo debe preguntar al investigador principal. No compartiremos su nombre, estado de salud o dirección. Eventualmente, los resultados serán publicados, de forma tal que cualquier persona interesada en conocerlos, pueda acceder a ellos. Usted podrá solicitar información sobreel estado y los resultados del estudio, preguntándole directamente al investigador principal.

Al firmar el formulario de consentimiento adjunto, se compromete a cumplir con los procedimientos del estudio que se le han expuesto.

DERECHO A NEGARSE A PARTICIPAR O ABANDONAR EL ESTUDIO

- No tiene que participar en este estudio si no desea hacerlo.
- Tiene el derecho a NO firmar este formulario. Si no desea firmar este formulario, no podrá participar en este estudio de investigación. Esto se debe a que necesitamos su permiso por escrito antes de poder usar su información.
- Tiene el derecho a abandonar este estudio incluso después de haber aceptado participar. Si decide abandonar el estudio, no usaremos su información. En caso de decidir

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abandonar el estudio, por favor comuníquese con un miembro de nuestro personal. No tiene que explicar sus razones para abandonar el estudio.

A QUIÉN CONTACTAR

Si no está satisfecho con la forma en que se llevó a cabo este estudio, o tiene alguna duda, queja o pregunta sobre sus derechos como participante, por favor contacte a la oficina de atención al paciente de la Clínica Universidad de Navarra, por teléfono (+34 948 255 400) o correo electrónico (atpacientun@unav.es), para hablar con alguien independiente del equipo investigador.

Si tiene alguna duda sobre este estudio o sus procedimientos, ahora o en el futuro, puede comunicarse con: _____ . Teléfono: _____. Quién es el investigador principal del estudio. Puede llamar de lunes a viernes entre las 8:00 y las 17:00 horas.

Al firmar el formulario de consentimiento adjunto, se compromete a cumplir con los procedimientos del estudio que se le han expuesto.

Consentimiento Informado por escrito

TÍTULO DEL ESTUDIO: Vigilancia acústica y monitorización digital de la tos a nivel poblacional para la detección temprana de brotes de enfermedades respiratorias. Un estudio observacional exploratorio.

CÓDIGO DEL PROMOTOR:

Versión y fecha:

Yo, (nombre y apellidos)

.....

He leído la hoja de información que se me ha entregado.

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

He hablado con:

.....

(nombre y dos apellidos del investigador)

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

1º Cuando quiera

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2º Sin tener que dar explicaciones.

3º Sin que esto repercuta en mis cuidados médicos.

Presto libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información

Firma del investigador:

Nombre:

Fecha:

Firma del investigador:	**Firma del participante**:	**Firma del Representante legal o Testigo imparcial (táchese lo que no proceda)**:
Nombre:	**Nombre**:	**DNI**:
Fecha:	**Fecha**:	**Fecha**:
		A causa de:

Este documento se firmará por duplicado quedándose una copia el investigador y otra el participante.

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INFORMATION AND CONSENT SHEET

Version 3.0 (January 6th, 2021)

Study Title: Acoustic surveillance and digital cough monitoring at population level for early respiratory disease outbreak detection, an exploratory observational study

Promoter Code:

Promoter
Clínica Universidad de Navarra/Universidad de Navarra, Avenida de Pío XII, 36
31008 Pamplona

Funder: This study is funded by the Centre Hospitalier de l'Université de Montréal (CHUM) and the Patrick J. McGovern Foundation through a grant awarded to Co-Investigator Simon Grandjean Lapierre (*Early diagnosis of COVID-19 by utilizing Artificial Intelligence and Acoustic Monitoring*)

Main Researcher:
Carlos Chaccour
Teléfono +34 666 293 112
Email cchaccour@unav.es

Introduction
The objective of this document is to inform you about the characteristics of a research study you have been invited to participate in. The study has been approved by the Committee of Research Ethics of the Universidad de Navarra and the Committee of Medication Ethics of Navarra (Spain), as well as the ethics committee from the Centre Hospitalier de l'Université de Montréal (CHUM), in Canada.

This document aims to provide you with proper information, so you can understand this study and decide by yourself if you are willing to take part or not in it. Please read this information document carefully and we will answer any questions that might come up afterwards. You can also discuss this with people you trust before making a decision.

Voluntary Participation
You must know that your participation in this study is voluntary and you can decide not to take part, or change your mind and withdraw your consent at any time in the future. This will not affect your relationship with your healthcare provider, nor harm your access to proper medical treatment in any way.

General description of the study
Coronaviruses are a group of viruses that cause generally mild respiratory disease. However, a member of this group, the SARS-Cov-2, is responsible for causing COVID-19, a potentially dangerous disease that has spread across the globe since 2019.

One of the necessary interventions to contain the COVID-19 pandemic is understanding its real scale. This is particularly important now that new outbreaks are being regularly reported in areas with ongoing low-level transmission. A major limitation in this process is the limited diagnostic capabilities of many countries, which translates into delays in the search of medical attention and collection of necessary epidemiological data.

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Most patients with COVID-19 present cough as an early symptom of disease. This study aims to evaluate the usefulness of a mobile app called HyfeApp, which registers and studies cough patterns, as a complement to existing disease surveillance strategies. To do this, we will need to record and analyse episodes of cough in the town of Cizur Menor which has been selected as the location of the initial studies of this new platform.

For this reason, we need as many people as possible installing the app. This App runs in the background of your mobile phone. Although HyfeApp has continuous access to the mobile's mic, it has been designed to exclusively process sounds that match the characteristics of human cough. When one of these sounds is detected and recorded by the app, an artificial intelligence algorithm studies it and determines whether it is indeed an episode of cough.If so, the record is stored, along with time and geographical information provided by the mobile's GPS.

Besides the information from the app, we will also review the medical records of those participants who present for a medical consultation in the national health system or the Clinica Universidad de Navarra. The objective of this is to collect information about the presence of cough, or any respiratory disease during one of those visits. Data from your medical chart will be obtained by the investigators from your local clinic or hospital. This includes without being limited to information related to any of the following conditions will be reviewed:

- Non-specific cough
- Non-specific upper respiratory tract infections
- Pharyngitis
- Asthma
- Bronchitis
- Chronic Obstructive Pulmonary Disease (COPD)
- COVID-19
- Gastro-esophageal reflux disease (GERD)
- Influenza
- Pneumonia (any cause)
- Respiratory Syncytial virus
- Non-specific respiratory tract infections

Additional laboratory test data to be collected from the selected visits includes:

- Microbiology
  - COVID-19 tests
  - Flu PCR
  - Sputum culture
- Hematology
  - Full blood count
  - D-dimer test
- Biochemistry
  - C-reactive protein
  - Procalcitonin
  - CPK
  - LDH
  - Ferritin
- Radiology

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- Chest X-Ray
- Thorax CT-Scan

Besides the information from the app and medical charts, we will also solicit a restricted number of participants to participate in focus group discussions to explore the challenges related to using HyfeApp and participating in this study. If solicited, it will be your right to accept or refuse to participate in those focus groups.

Duration

Data will be initially collected for a one-month period. You will then be offered the opportunity to continue in the study for 3 and 6 months. You can refuse continuing in the study at any point.

Study Procedures

You will not be able to enroll in this study if you:

- Are incapable or unwilling to accept to share your codified cough data with multicenter databases aiming at refining acoustic-based diagnostics.
- Are under 13 years of age.
- Do not own a smartphone able to run HyfeApp.
- Are not a student/worker at the University of Navarra or a patient diagnosed with cough-related disease at the Clínica Universidad de Navarra.
- Are not a resident in Navarra.

In case you decide to take part, a member of our team will help you install the app on your mobile. No further visits from the research team will be necessary, but you might be contacted once a month to collect feedback on your experience using the app, as well as to confirm your willingness to continue in the study. You might also receive periodic updates via email, to keep you informed on the status of the project and relevant preliminary results.

About HyfeApp

HyfeApp is a mobile app available for Android and IOS (Apple) operating systems, developed by a multidisciplinary team of data scientists, software developers and infectious disease physicians.

What does HyfeApp do?

HyfeApp runs in the background of your mobile, without interfering with any other running app, but having constant access to your mic and recording explosive sound snips of 0.5 seconds or less. No conversations, nor ambient sounds are recorded. These sound snips are sent to a server, where an artificial intelligence algorithm processes them, evaluating their characteristics and determining if they were in fact, cough. The server then sends that data back to the mobile and the study investigator, so those files labeled as cough episodes are displayed by the app. HyfeApp is a wellness status tool. Just like similar apps that count calories, steps or snores. HyfeApp simply counts episodes of cough.

Benefits and risks of participating

HyfeApp will allow you to have a record of the number of times you cough every day, and of any changes compared to previous days. However, it is not a diagnostic or treatment tool. Therefore, it does not provide medical advice, nor replaces healthcare services. HyfeApp is not medical equipment. If you ever have doubts regarding your health condition or status, you should consult a doctor, or in case of emergency, communicate with proper emergency services.

We are aware that recording sounds from a mobile phone generates doubts regarding the handling of information and the participants' privacy. As explained before, HyfeApp does not record conversations or ambient sounds, and the 0.5 second sound snips are too short to identify

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participants. However, if linked to other metadata (such as telephone numbers), these sounds could allow identification. For this reason, all the information transmitted by the app is encrypted and handled following standard safety protocols. This way, we can make sure that only the researchers can access potentially identifiable data.
You will not be paid for your participation.

Confidentiality
All the information collected in this study will be codified in such a way that it cannot be linked to your personal data. Only the principal and co-investigators involved in this study will know your name, and an ID number will be used to refer to you in every document or communication. The computers used to store and analyze the data will be password-protected and only authorised researchers will have access to them.

The Universidad de Navarra, as the data controller, complies with the Organic Law 3/2018, of December 5, and other Spanish data protection regulations in force. Therefore, it is important that you know the following information:

• In addition to the rights that you already know (access, modification, refusal and cancellation of data), you can now also limit the processing of incorrect data, request a copy, or have the data that you provided be transferred to a third party (portability) for the study. To exercise your rights, contact the Institution's Data Protection Officer at [protecciondedatosnav@unav.es]. You also have the right to contact the Data Protection Agency if you are not satisfied.

• Both the Center and the Promoter are respectively responsible for the processing of your data and undertake to comply with the data protection regulations in force. The data collected for the study will be identified by a code, so that information that can identify you is not included, and only your study doctor / collaborators will be able to relate said data to you and to your medical history. Therefore, your identity will not be revealed to any other person except to the health authorities, when required or in cases of medical emergency. The Research Ethics Committees, the representatives of the Health Authority in matters of inspection and the personnel authorized by the Sponsor, may only access to verify personal data, clinical study procedures and compliance with the rules of good clinical practice (always maintaining the confidentiality of the information).

• The Researcher and the Sponsor are obliged to keep the data collected for the study for at least 25 years after its completion. Subsequently, your personal information will only be kept by the center for the care of your health and by the promoter for other scientific research purposes if you have given your consent to do so, and if this is allowed by the law and applicable ethical requirements.

• If we transfer your encrypted data outside the EU to our group entities, service providers or scientific researchers who collaborate with us, the participant's data will be protected with safeguards such as contracts or other mechanisms by the protection authorities of data. If the participant wants to know more about it, he or she can contact the promoter's Data Protection Officer [protecciondedatosnav@unav.es].

Economic Compensation
The study promoter is responsible for managing the funds. Before doing a research study, the promoter must have signed a contract with the center where the study will take place, and the doctors

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who will conduct the study. Your participation in this study will not cost you any extra money beyond your standard medical procedures. Routine medical assistance will have to be paid by the social security network, your medical insurance, or yourself.

You will not receive any payment or monetary compensation for taking part in this study.

Other relevant information

Any new information regarding the app to be used in this study and that could affect your disposition to take part in it, discovered after you have decided to participate, will be communicated to you as soon as possible.

If you wish to withdraw your consent to take part in the study, no further personal data will be added to the database. You can also demand the destruction of any previously retained identifiable information, to prevent new analysis from being carried on.

You must also know that you could be excluded from the study if the promoter and/or researchers consider it to be adequate, either for your own safety, to prevent any adverse consequence deriving from your participation, or because they consider you are not complying with the established procedures. In any case, you will always receive a proper explanation of what caused your withdrawal from the study.

Sharing the results

At all time, you will have access to the knowledge we get from the research upon request to the principal investigator. We will not share your name, health status or where you live. After this, we will publish the results so that other interested people may learn from our research. You will be able to ask the status of this study and its findings by a direct request to the principal investigator.

Right to refuse or withdraw

You don't have to take part in this research study if you do not wish so. You have the right not to sign this form. If you do not sign this form, you cannot take part in this research study. This is because we need your written permission to use your information. You have the right to leave the research study. If you would like to leave the research study, please tell a member of the study staff. You do not need to explain why you want to leave.

Who to contact?

If you are not satisfied with the way this study was conducted, or if you have any concerns, complaints or general questions about your rights as a participant, please contact the Patient Attention Office at the Clínica Universidad de Navarra by phone (+34 948 255 400) or email atpacientun@unav.es to talk with someone independent of the research team.

If you have any questions about this study or study procedures now or in the future, you can call Dr. Carlos Chaccour. Tel number: 628 659 003 who is the Principal Investigator of the study. You can call Monday-Friday from 8.00 to 17.00 hrs.

By signing the following informed consent, you agree to comply with the previously explained study procedures.

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Written informed consent form

Study title: Acoustic surveillance and digital cough monitoring at population level for early respiratory disease outbreak detection, an exploratory observational study

Promoter code
Version and date:

I, (name and surname)
.....

Have read the information sheet presented above.
I have been allowed to ask questions about the study.
I have received sufficient information about the study to make a decision.

I have spoken to:
.....
(Name and surname of researcher)

I understand that my participation is voluntary.

I understand I can withdraw from the study:

1. Whenever I want to.
2. Without having to explain my reasons.
3. Without repercussions regarding my access to healthcare.

I freely and willingly accept to participate in this study. I give my consent for the access and usage of my data within the conditions previously detailed in the information sheet.

Researcher's signature

Name:

Date:

Researcher's signature	**Participant's signature**	**Signature of the legal representative or impartial witness (cross out if not applicable)**
Name:	**Name:**:	**DNI**:

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Date: **Date:**: **Date**:
Reason to sign:

This document will be signed in duplicate, one copy will be kept by the researcher and another one by the participant.

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ID del participante:

Hoja de información y autorización a menores de entre 13 y 18 años para participar en el estudio titulado:

Version 3.0 (6 de enero de 2021)

Vigilancia acústica y monitorización digital de la tos a nivel poblacional para la detección temprana de brotes de enfermedades respiratorias. Un estudio observacional exploratorio.

Este formulario de autorización es para aquellos menores de edad dispuestos a participar en el estudio observacional previamente descrito.

Promotor

Clínica Universidad de Navarra/Universidad de Navarra, Avenida de Pío XII, 36

31008 Pamplona.

Financiación: Este estudio está siendo financiado por el Centre Hospitalier de l'Université de Montreal (CHUM) y la fundación Patrick J. McGovern a través de una subvención otorgada al co-investigador Simon Grandjean Lapierre (*Early diagnosis of COVID-19 by utilizing Artificial Intelligence and Acoustic Monitoring*)

Investigador Principal

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Este formulario de autorización cuenta con dos partes:

- Hoja de información (para compartir la información relevante al proyecto con usted)
- Certificado de Autorización (donde se le solicitará su firma y la de su padre, madre o representante legal, en caso de que acepte participar).

Le será proveída una copia del Certificado de Autorización.

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Parte I: Hoja de Información

Introducción

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por el Comité de Ética de la Investigación de la Universidad de Navarra, el comité de ética de la investigación con medicamentos de Navarra y el comité independiente de ética del Centre Hospitalier de l'Universite de Montreal (CHUM), en Canadá.

No es necesario que tome una decisión hoy. Puede tomarse el tiempo de hablar y discutir su participación con cualquier persona con la que se sienta cómodo haciéndolo.

Con este documento pretendemos que usted reciba la información adecuada para que pueda entender de qué se trata este estudio y decidir si quiere o no participar en el mismo. Es posible que haya palabras o información que no entienda. De ser así, siéntase libre de preguntar cualquier duda.

Generalidades del estudio

Los coronavirus son un grupo de virus que causan infecciones respiratorias generalmente leves. Sin embargo, un miembro de este grupo, el SARS-Cov-2, es el responsable de provocar la COVID-19, una enfermedad potencialmente peligrosa que desde finales del 2019 se ha extendido a lo largo de todo el mundo.

Uno de los elementos necesarios para contener el avance de la pandemia de COVID-19 es entender su escala real. Esto es particularmente importante ahora que los brotes regulares en zonas en las que simultáneamente ocurre transmisión a una menor escala se han convertido en una realidad. Uno de los mayores obstáculos de los sistemas sanitarios es la limitada capacidad de hacer pruebas diagnósticas, lo que se traduce en retrasos en la búsqueda de atención médica, así como en la recolección de la información necesaria para planear intervenciones que limiten la expansión de la enfermedad.

La gran mayoría de pacientes con COVID-19 presentan tos como un síntoma temprano de la enfermedad. Este estudio pretende evaluar la utilidad de una aplicación para el móvil, llamada HyfeApp, que registra y evalúa patrones de tos, como complemento a las estrategias de vigilancia epidemiológica existentes. Para esto, estimamos que será necesario grabar y analizar al menos 15,500 episodios individuales de tos.

Por eso esperamos que el mayor número posible de voluntarios instale la aplicación, la cual se ejecuta en segundo plano en el móvil. Aunque HyfeApp tiene acceso continuo al micrófono de su móvil, ha

sido diseñada para procesar únicamente sonidos compatibles con las características de la tos humana. Cuando uno de estos sonidos es detectado y grabado por la aplicación, un algoritmo de inteligencia artificial lo estudia y en caso de decidir qué se trata de un episodio de tos, se guarda junto a información sobre la ubicación geográfica y el momento en que ocurrió, que es proporcionada por el sistema GPS del móvil.

Aparte de la información suministrada por la aplicación, revisaremos los registros médicos de aquellas personas dispuestas a participar que acudan a consulta en el sistema nacional de salud, o la Clínica Universidad de Navarra. El objetivo de esto es recolectar información sobre la presencia de tos durante la exploración médica, o el diagnóstico de alguna enfermedad respiratoria en alguna de las visitas. Solo se consultará información relacionada con alguna de las siguientes condiciones:

- Tos no específica.
- Infecciones del tracto respiratorio superior.
- Faringitis.
- Asma.
- Bronquitis.
- Enfermedad Broncopulmonar Obstructiva Crónica (EBPOC).
- COVID-19
- Enfermedad por Reflujo Gastroesofágico (ERGE)
- Influenza
- Neumonía (por cualquier causa)
- Infección por virus sincitial respiratorio (VSR)
- Infecciones respiratorias inespecíficas.

Otros exámenes paraclínicos a ser recolectados incluyen:

- Microbiología
  - pruebas de COVID-19
  - PCR para influenza
  - Cultivo de esputo
- Hematología
  - Hematología completa
  - Prueba del dímero D.
- Bioquímica
  - Proteína C reactiva
  - Procalcitonina
  - CPK
  - LDH
  - Ferritina

Aparte de la información obtenida de la app y sus registros médicos, también le pediremos a un grupo reducido de participantes que formen parte de discusiones grupales focalizadas, para explorar los desafíos que representa el uso continuo de HyfeApp, y su participación en el estudio. En caso de que se le solicite participar, usted podrá aceptar o negarse.

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Duración

Se recolectará información inicialmente por un período de 1 mes, consultándosele en ese momento su disposición a seguir participando por 3 y 6 meses. Usted podrá negarse a seguir participando en el estudio en cualquier momento.

Procedimientos del estudio

Usted no puede participar en el ensayo si usted:

- No puede o no quiere aceptar compartir su información codificada relacionada a sus registros de tos con bases de datos globales usadas para refinar los diagnósticos basados en perfiles acústicos.
- Si no posee un teléfono inteligente en el que se pueda ejecutar HyfeApp.
- Tiene menos de 13 años de edad.
- No es un estudiante/trabajador de la Universidad, o un paciente diagnosticado con una enfermedad causante de tos en la Clínica Universidad de Navarra.
- Si no reside en Navarra.

Si usted decide participar, un miembro de nuestro equipo lo ayudará a instalar la aplicación en su móvil. No serán necesarias nuevas visitas de parte del equipo de investigación, pero serán contactados una vez al mes para obtener comentarios sobre su experiencia usando la aplicación y ratificar su consentimiento y disposición a seguir participando en el estudio. También podrá ser contactado vía correo electrónico para recibir actualizaciones periódicas sobre el estado del proyecto y sus resultados preliminares.

La aplicación HyfeApp

HyfeApp es una aplicación móvil disponible para los sistemas operativos Android y iOS (Apple), desarrollada por un equipo multidisciplinario que incluye analistas de datos, desarrolladores de software y médicos especialistas en enfermedades infecciosas.

¿Qué cosas hace HyfeApp?

HyfeApp se ejecuta constantemente en el segundo plano de su móvil, sin interferir con el funcionamiento de otras aplicaciones, pero teniendo acceso a su micrófono y grabando recortes explosivos de sonido de menos de 0.5 segundos de duración. Ni las conversaciones, ni los sonidos de fondo son grabados. Estos recortes son enviados a un servidor, donde un algoritmo de inteligencia artificial identifica aquellos que presentan cambios súbitos y cortos en los decibeles, compatibles con episodios de tos. Posteriormente, otro algoritmo los procesa, evaluando otras características y determinando si efectivamente se trató de un episodio de tos. El servidor envía esta información de

vuelta al móvil, de forma que los archivos clasificados como tos se incorporan a los registros mostrados por la aplicación.

HyfeApp es una herramienta que le proporciona información sobre su estado de bienestar. Tal como herramientas similares que cuentan calorías, registran el número de pasos o ronquidos. La única diferencia es que HyfeApp cuenta episodios de tos.

Beneficios y riesgos por su participación en estudio

HyfeApp le permitirá llevar un registro del número de veces que tose al día, así como evidenciar cambios con respecto a días anteriores. Sin embargo, no es una herramienta de diagnóstico o tratamiento médico. Por lo tanto, ni provee información o consejos médicos, ni sustituye de ninguna forma a los servicios sanitarios: HyfeApp no es un instrumento médico especializado. Si usted tiene alguna duda sobre su estado de salud, debe consultarlas con un médico o en caso de emergencia, llamar a los servicios respectivos inmediatamente .

Grabar sonidos desde un móvil inmediatamente genera dudas sobre la forma en que será manejada la información, y garantizada la privacidad de los participantes. Como hemos explicado anteriormente, HyfeApp no graba conversaciones ni sonidos de ambiente. Los segmentos de 0.5 segundos grabados por la aplicación no permiten identificar a los participantes. Sin embargo, algunos de estos sonidos pudiesen permitir identificar al participante si son interpretados en conjunto con otra metadata registrada por la aplicación (como el número de teléfono, por ejemplo). Por esta razón, toda la información transmitida por la aplicación estará encriptada y manejada según los protocolos de seguridad estándar empleados en este tipo de estudios. De esta forma, únicamente los investigadores podrán asociar los datos recolectados por la aplicación, a otros elementos que permitan identificar a los participantes.

Usted no recibirá un pago por su participación.

Participación Voluntaria

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar la autorización en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

Pagos y Compensación Económica

El promotor del estudio es el responsable de gestionar la financiación del mismo. Para la realización del estudio, el promotor ha firmado un contrato con el centro donde se va a realizar y con el médico del estudio.

Su participación en este estudio no le causará costes adicionales diferentes de los asociados a su tratamiento habitual. La asistencia rutinaria deberá ser pagada por la seguridad social, por su seguro médico o por usted mismo.

Ni usted ni sus padres/representantes recibirán un pago por su participación en este estudio.

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Otra Información

Cualquier nueva información referente a la aplicación utilizada en el estudio y que pueda afectar su disposición para participar en el mismo, que se descubra durante su participación, le será comunicada lo antes posible.

Si usted decide retirar el consentimiento para participar en este estudio no se añadirán nuevos datos a la base de datos y puede exigir la destrucción de cualquier información identificable previamente retenida, para evitar la realización de nuevos análisis.

También debe saber que puede ser excluido del estudio si el promotor y/o los investigadores del mismo lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso derivado de su participación, o porque consideren que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada del estudio.

Confidencialidad

Toda la información recolectada en este estudio se mantendrá codificada, de forma que no pueda ser vinculada a sus datos personales. Solo el investigador principal y los co-investigadores sabrán su nombre y en cualquier documento o comunicación se usará un número de identificación personal asignado a cada participante. Las computadoras utilizadas para analizar los datos de este estudio tendrán contraseñas y solo investigadores autorizados podrán acceder a ellas.

La Universidad de Navarra, como responsable del tratamiento de datos, se compromete al cumplimiento de la Ley Orgánica del 3/2018, de 5 de diciembre y demás normativa de protección de datos en vigor. Por ello, es importante que conozca la siguiente información:

• Además de los derechos que ya conoce (acceso, modificación, oposición y cancelación de datos) ahora también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercer sus derechos, diríjase al Delegado de Protección de Datos de la institución en [protecciondedatosnav@unav.es]. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho/a.

• Tanto el Centro como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen a cumplir con la normativa de protección de datos en vigor. Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

• El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal sólo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.

• Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar al Delegado de Protección de Datos del promotor **[**protecciondedatosnav@unav.es**].**

Compartiendo los Resultados

Usted tendrá acceso a todo el conocimiento generado por esta investigación en todo momento, solo debe preguntar al investigador principal. No compartiremos su nombre, estado de salud o dirección. Eventualmente, los resultados serán publicados, de forma tal que cualquier persona interesada en conocerlos, pueda acceder a ellos. Usted podrá solicitar información sobre el status y los resultados del estudio, preguntándole directamente al investigador principal.

¿Quién aprobó esta investigación?

El estudio ha sido aprobado por el Comité de Ética de la Investigación de la Universidad de Navarra, el comité de ética de la investigación con medicamentos de Navarra y el comité independiente de ética del Centre Hospitalier de l'Universite de Montreal (CHUM), en Canadá.

Derecho a negarse a participar o abandonar el estudio

- No tiene que participar en este estudio si no desea hacerlo.
- Tiene el derecho a NO firmar este formulario. Si no desea firmar este formulario, no podrá participar en este estudio de investigación. Esto se debe a que necesitamos su permiso por escrito antes de poder usar su información.
- Tiene el derecho a abandonar este estudio incluso después de haber aceptado participar. Si decide abandonar el estudio, no usaremos su información. En caso de decidir abandonar el estudio, por favor comuníquese con un miembro de nuestro personal. No tiene que explicar sus razones para abandonar el estudio.

A quién contactar

Si no está satisfecho con la forma en que se llevó a cabo este estudio, o tiene alguna duda, queja o pregunta sobre sus derechos como participante, por favor contacte a la oficina de atención al paciente de la Clínica Universidad de Navarra, por teléfono (+34 948 255 400) o correo electrónico (atpacientun@unav.es), para hablar con alguien independiente del equipo investigador.

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Si tiene alguna duda sobre este estudio o sus procedimientos, ahora o en el futuro, puede comunicarse con: Dr. Carlos Chaccour. Teléfono: 628 659 003. Quién es el investigador principal del estudio. Puede llamar de Lunes a Viernes entre las 8:00 y las 17:00 horas.

Parte II: Certificado de Autorización

Autorización del padre o representante legal

He leído o se me ha leído la información anterior. Se me permitió hacer preguntas al respecto y cualquier pregunta que haya hecho me fue contestada de forma satisfactoria.

☐ Autorizo que mi hijo/hija o representado legal participe en este proyecto de investigación.

☐ No autorizo que mi hijo/hija o representado legal participe en este proyecto de investigación y no he firmado la autorización presente a continuación.

Nombre del padre o representante legal:

Firma del padre o representante legal:

Fecha (dd/mm/aaaa)

Consentimiento del menor de edad

He leído o se me ha leído la información anterior. Se me permitió hacer preguntas al respecto y cualquier pregunta que haya hecho me fue contestada de forma satisfactoria.

☐ Acepto participar en este proyecto de investigación.

☐ No acepto participar en este proyecto de investigación y no he firmado la autorización presente a continuación.

En caso de que el menor acepte participar:

Nombre del menor de edad:

Firma del menor de edad

Fecha (dd/mm/aaaa):

En caso de no saber leer o escribir

Un testigo que sepa leer o escribir debe firmar (este individuo debería de ser posible, haber sido elegido por el participante, no su padre o representante, y no estar relacionado con el equipo de

investigación). Todo participante que no sepa leer o escribir debe presentar la huella digital de su pulgar.

Soy testigo de que este formulario fue leído de forma precisa al participante en potencia, y que dicho individuo tuvo la oportunidad para hacer preguntas. Confirmo que el individuo en cuestión ha autorizado su participación de forma voluntaria.

Nombre del testigo:

Firma del testigo:

Fecha (dd/mm/aaaa):

Huella digital del pulgar del participante:

Declaración del encargado de obtener la autorización

He leído de forma precisa la hoja de información al participante en potencia, y he hecho todo lo posible para asegurarme de que entendiera que se realizarán los siguientes procedimientos:

1. La aplicación HyfeApp deberá ser descargada en el móvil del participante.
2. La aplicación HyfeApp registrará y almacenará sonidos compatibles con la tos humana durante un período de un año, entre octubre de 2020 y septiembre de 2021.
3. En caso de acudir a una consulta en el sistema nacional de salud, la información médica del participante podrá ser accedida para buscar evidencia clínica de tos o alguna enfermedad respiratoria.

Confirmo que al participante se le ha dado la oportunidad de hacer preguntas sobre la investigación y que todas esas preguntas han sido contestadas de forma apropiada y de la mejor forma posible. Confirmo que el individuo no ha sido forzado a autorizar su participación, y que su consentimiento ha sido libre y voluntario.

Una copia de este certificado de autorización ha sido proporcionada al padre o representante legal del participante.

El padre o representante legal del participante ha firmado el consentimiento informado: Si____ No____

Nombre de la persona a cargo de obtener el consentimiento:

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Firma de la persona a cargo de obtener el consentimiento:

Fecha (dd/mm/aaaa):

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English version

Participant ID:

Information sheet and assent form for the participation of minors aged 13-18 years in the research study titled:

Version 3.0 January 6th, 2021

Acoustic surveillance and digital cough monitoring at population level for early respiratory disease outbreak detection, an exploratory observational study

This assent form is meant for minors who are interested in taking part in the previously mentioned observational study. Please read this form carefully with your parents or legal guardian and ask any questions you might have.

Promoter
Clínica Universidad de Navarra/Universidad de Navarra, Avenida de Pío XII, 36
31008 Pamplona.

Funder
This study is funded by the Centre Hospitalier de l'Université de Montreal (CHUM) and the Patrick J. McGovern Foundation through a grant awarded to Co-Investigator Simon Grandjean Lapierre (*Early diagnosis of COVID-19 by utilizing Artificial Intelligence and Acoustic Monitoring*)

Main Researcher
Carlos Chaccour
Teléfono +34 666 293 112
Email cchaccour@unav.es

This document consists of two parts:

- Information sheet (meant to explain relevant information regarding the project).
- Assent form (where we will require your signature, and that of your parent or legal guardian, if you decide to take part in it).

You will be provided a copy of this document for your personal records.

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Part I: Information sheet

Introduction

The objective of this document is to inform you about the characteristics of a research study you have been invited to participate in. The study has been approved by the Committee of Research Ethics of the Universidad de Navarra and the Committee of Medication Ethics of Navarra (Spain), as well as the independent ethics committee from the Centre Hospitalier de l'Université de Montreal (CHUM), in Canada.

This document aims to provide you with proper information, so you can understand this study and decide by yourself if you are willing to take part or not in it. Please read this information document carefully and we will answer any questions that might come up afterwards. You can also discuss this with people you trust before making a decision.

Objective of the research

Coronaviruses are a group of viruses that cause generally mild respiratory disease. However, a member of this group, the SARS-Cov-2, is responsible for causing COVID-19, a potentially dangerous disease that has spread across the globe since 2019.

One of the necessary interventions to contain the COVID-19 pandemic is understanding its real scale. This is particularly important now that new outbreaks are being regularly reported in areas with ongoing low-level transmission. A major limitation in this process is the limited diagnostic capabilities of many countries, which translates into delays in the search of medical attention and the collection of necessary epidemiological data.

Most patients with COVID-19 present cough as an early symptom of disease. This study aims to evaluate the usefulness of a mobile app called HyfeApp, which registers and studies cough patterns, as a complement to existing disease surveillance strategies. To do this, we will need to record and analyse about 15,500 individual episodes of cough. The town of Cizur Menor has been selected as the location of the initial studies of this new platform.

For this reason, we need as many people as possible installing the app, which runs in the background of your mobile. Although HyfeApp has continuous access to the mobile's mic, it has been designed to exclusively process sounds that match the characteristics of human cough. When one of these sounds is detected and recorded, an artificial intelligence algorithm studies it and where it determines it does sound like an episode of cough, the record is stored, along with geographical information and time, provided by the mobile's GPS.

Besides the information from the app, we will also review the medical records of those participants who present for a medical consultation in the national health system or the Clinica Universidad de Navarra. The objective of this is to collect information about the presence of cough, or any respiratory disease during one of those visits. Data from your medical chart will be obtained by the investigators from your local clinic or hospital. This includes without being limited to information related to any of the following conditions will be reviewed:

- Non-specific cough
- Non-specific upper respiratory tract infections
- Pharyngitis
- Asthma
- Bronchitis

- Chronic Obstructive Pulmonary Disease (COPD)
- COVID-19
- Gastro-esophageal reflux disease (GERD)
- Influenza
- Pneumonia (any cause)
- Respiratory Syncytial virus
- Non-specific respiratory tract infections

Additional laboratory test data to be captured from the selected visits includes:

- Microbiology
  - COVID-19 tests
  - Flu PCR
  - Sputum culture
- Hematology
  - Full blood count
  - D-dimer test
- Biochemistry
  - C-reactive protein
  - Procalcitonin
  - CPK
  - LDH
  - Ferritin

Besides the information from the app and medical charts, we will also solicit a restricted number of participants to participate in focus group discussions to explore the challenges related to using HyfeApp and participating in this study. If solicited, it will be your right to accept or refuse to participate in those focus groups.

Duration

Data will be initially collected for a one-month period. You will then be offered the opportunity to continue in the study for 3 and 6 months. You can refuse continuing in the study at any point.

Study Procedures

You will not be able to enroll in this study if you:

- Are incapable or unwilling to accept to share your codified cough data with multicenter databases aiming at refining acoustic-based diagnostics.
- Are under 13 years of age.
- Do not own a smartphone able to run HyfeApp.
- Are not a student/worker at the University of Navarra or a patient diagnosed with cough-related disease at the Clínica Universidad de Navarra.
- Are not a resident of Navarra

In case you decide to take part, a member of our team will help you install the app on your mobile. No further visits from the research team will be necessary. But you might be contacted once a month to collect feedback on your experience using the app, as well as to confirm your willingness to continue in the study. You might also receive periodic updates via email, to keep you informed on the status of the project and relevant preliminary results.

About HyfeApp

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HyfeApp is a mobile app available for Android and IOS (Apple) operative systems, developed by a multidisciplinary team of data scientists, software developers and infectious disease physicians.

What does HyfeApp do?

HyfeApp runs in the background of your mobile, without interfering with any other running app, but having constant access to your mic and recording explosive sound snips of 0.5 seconds or less. No conversations, nor ambient sounds are recorded. These sound snips are sent to a server, where an artificial intelligence algorithm identifies those presenting sudden, shortchanges in decibel levels, compatible with cough episodes. Then, another algorithm processes them, evaluating its characteristics and determining if they were in fact, cough. The server then sends that data back to the mobile, so those files labeled as cough episodes are displayed by the app. HyfeApp is a wellness status tool. Just like similar apps that count calories, steps or snores. The only difference is that HyfeApp counts episodes of cough.

Benefits and risks of participating

HyfeApp will allow you to have a record of the number of times you cough every day, and of any changes compared to previous days. However, it is not a diagnostic or treatment tool. Therefore, it does not provide medical advice, nor replaces healthcare services. HyfeApp is not medical equipment. If you ever have doubts regarding your health condition or status, you should consult a doctor, or in case of emergency, communicate with proper emergency services.

We are aware that recording sounds from a mobile phone generates doubts regarding the handling of information and the participants' privacy. As explained before, HyfeApp does not record conversations or ambient sounds, and the 0.5 second sound snips are too short to identify participants. However, if linked to other metadata (such as telephone numbers), these sounds could allow identification. For this reason, all the information transmitted by the app is encrypted and handled following standard safety protocols. This way, we can make sure that only the researchers can access potentially identifiable data.

You will not be paid for your participation.

Voluntary participation

You must know that your participation in this study is voluntary and you can decide not to take part, or change your mind and resign your consent at any time in the future. This will not affect your relationship with your healthcare provider, nor harm your access to proper medical treatment in any way.

Economic Compensation

The study promoter is responsible for managing the funds. Before, doing a research study, the promoter must have signed a contract with the center where the study will take place, and the doctors who will conduct the study. Your participation in this study will not cost you any extra money beyond your standard medical procedures. Routine medical assistance will have to be paid by the social security network, your medical insurance, or yourself.

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You will not receive any payment or monetary compensation for taking part in this study.

Other information

Any new information regarding the app to be used in this study and that could affect your disposition to take part in it, discovered after you have decided to participate, will be communicated to you as soon as possible.

If you wish to withdraw your consent to take part in the study, no further personal data will be added to the database. You can also demand the destruction of any previously retained identifiable information, to prevent new analysis from being carried on.

You must also know that you could be excluded from the study if the promoter and/or researchers consider it to be adequate, either for your own safety, to prevent any adverse consequence deriving from your participation, or because they consider you are not complying with the established procedures. In any case, you will always receive a proper explanation of what caused your withdrawal from the study.

Confidentiality

All the information collected in this study will be codified in such a way that they cannot be linked to your personal data. Only the main researcher and co-researchers will know your name, and an ID number will be used to refer to you in every document or communication. The computers used to store and analyse the data will be password-protected and only authorised researchers will have access to them.

The Clínica Universidad de Navarra, as the data controller, complies with the Organic Law 3/2018, of December 5, and other Spanish data protection regulations in force. Therefore, it is important that you know the following information:

• In addition to the rights that you already know (access, modification, refusal and cancellation of data), you can now also limit the processing of incorrect data, request a copy, or have the data that you provided be transferred to a third party (portability) for the study. To exercise your rights, contact the Institution's Data Protection Officer at [protecciondedatosnav@unav.es]. You also have the right to contact the Data Protection Agency if you are not satisfied.

• Both the Center and the Promoter are respectively responsible for the processing of your data and undertake to comply with the data protection regulations in force. The data collected for the study will be identified by a code, so that information that can identify you is not included, and only your study doctor / collaborators will be able to relate said data to you and to your medical history. Therefore, your identity will not be revealed to any other person except to the health authorities, when required, or in cases of medical emergency. The Research Ethics Committees, the representatives of the Health Authority in matters of inspection and the personnel authorized by the Sponsor, may only access to verify personal data, clinical study procedures and compliance with the rules of good clinical practice (always maintaining the confidentiality of the information).

• The Researcher and the Sponsor are obliged to keep the data collected for the study for at least 25 years after its completion. Subsequently, your personal information will only be kept by the center for

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the care of your health and by the promoter for other scientific research purposes if you have given your consent to do so, and if this is allowed by the law and applicable ethical requirements.

• If we transfer your encrypted data outside the EU to our group entities, service providers or scientific researchers who collaborate with us, the participant's data will be protected with safeguards such as contracts or other mechanisms by the protection authorities of data. If the participant wants to know more about it, he or she can contact the promoter's Data Protection Officer [protecciondedatosnav@unav.es].

Sharing the results

At all time, you will have access to the knowledge we get from the research upon request to the principal investigator. We will not share your name, health status or where you live. After this, we will publish the results so that other interested people may learn from our research. You will be able to ask the status of this study and its findings by a direct request to the principal investigator.

Who approved this research?

The study has been approved by the Committee of Research Ethics of the Universidad de Navarra and the Committee of Medication Ethics of Navarra (Spain), as well as the independent ethics committee from the Centre Hospitalaire de l'Université de Montreal (CHUM), in Canada.

Right to refuse or withdraw

You don't have to take part in this research study if you do not wish so. You have the right not to sign this form. If you do not sign this form, you cannot take part in this research study. This is because we need your written permission to use your information. You have the right to leave the research study. If you would like to leave the research study, please tell a member of the study staff. You do not need to explain why you want to leave.

Who to contact?

If you are not satisfied with the way this study was conducted, or if you have any concerns, complaints or general questions about your rights as a participant, please contact the Patient Attention Office at the Clínica Universidad de Navarra by phone (+34 948 255 400) or email atpacientun@unav.es to talk with someone independent of the research team.

If you have any questions about this study or study procedures now or in the future, you can call Dr. Carlos Chaccour. Tel number 628 659 003 who is the Principal Investigator of the study. You can call Monday-Friday from 8.00 to 17.00 hrs.

Part II: Assent Form

Authorization from the parent or legal guardian

I have read, or have been read to the previous information. I was allowed to ask questions and I was provided with satisfactory answers to each one.

☐ I authorize my child/minor under my care to take part in this research project.

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☐ I do not authorize my child/minor under my care to take part in this research project and I have not signed the Assent Form presented below.

Name of parent or legal guardian:

Signature of parent or legal guardian:

Date (dd/mm/yyyy):

Consent from the minor

I have read or have been read to the previous information. I was allowed to ask questions and I was provided with satisfactory answers to each one.

☐ I accept to take part in this research project.

☐ I do not accept to take part in this research project and I have not signed the assent form presented below.

In case the minor accepts to participate:

Name of minor:

Signature of minor:

Date (dd/mm/yyyy):

If illiterate:

A literate witness must sign this form (when possible, this person should be chosen by the participant and not be related to the research team). Every illiterate participant must still present a fingerprint of his/her thumb.

I confirm this form was properly and accurately read to the potential participant and that said individual has voluntarily consented to participate in the study.

Name of witness:

Signature of witness:

Date (dd/mm/yyyy):

Participant's fingerprint (thumb):

Statement from the person responsible of getting written consent

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I have, to the best of my ability, read this information sheet to the potential participant and made my best effort to make sure he/she understood that the following procedures will be performed:

1. HyfeApp will be downloaded to the participant's mobile phone.
2. HyfeApp will register and store sounds that match the characteristics of human cough for a one-year period, between October 2020 and September 2021.
3. If the participant seeks medical attention through the national health network, his/her medical records could be accessed by the researchers to look for evidence of cough or any respiratory disease.

I confirm the participant has been allowed to ask questions and that all his/her questions have been answered to the best of my ability. I confirm the participant has not been coerced to take part in this study and that his consent was free and voluntary.

A copy of this form will be provided to the parent or legal guardian for personal records.

Has the parent or legal guardian signed the assent form?: Yes____ No____

Name of the person in charge of obtaining the participant's consent:

Signature of the person in charge of obtaining the participant's consent:

Date (dd/mm/yyyy):

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Cuestionario complementario de información médica

Versión 2.0 (6 de enero, 2021)

Información personal

Nombre:_____

Primer Apellido:_____

Segundo Apellido:_____

Fecha de nacimiento: _____

DNI: _____

Información de contacto:

Teléfono móvil:_____

Email:_____

Sistema operativo del móvil:

- ○ Apple
- ○ Android

Ciudad o pueblo_____ Avenida/Calle_____

Número_____ Escalera (izquierda o derecha, solo para departamentos)_____

Piso_____ Puerta_____

¿Usualmente usted recibe atención médica a través de cuál de los siguientes proveedores de salud?

- ○ Público (Seguridad Social/Osasunbidea)
- ○ Privado (Clínica Universidad de Navarra)
- ○ Ambos

¿Ha sufrido usted de alguna de las siguientes condiciones en el pasado, o sufre de alguna en la actualidad?

- ○ Tos de causa no específica o desconocida
- ○ Infecciones no especificadas de las vías respiratorias altas (Sinusitis, otitis, laringitis)
- ○ Faringitis
- ○ Asma
- ○ Bronquitis
- ○ Enfermedad broncopulmonar obstructiva crónica (EBPOC)
- ○ COVID-19
- ○ Enfermedad de Reflujo Gastroesofágico (ERGE)
- ○ Influenza estacional

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- ○ Neumonía (sin importar la causa)
- ○ Infección por virus sincitial respiratorio
- ○ Otras infecciones no especificadas del tracto respiratorio inferior
- ○ Fumador
- ○ Otra condición

En caso de haber seleccionado la opción “Otra condición”, por favor explique a continuación a que se refiere:

_____
_____
_____

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English version

Medical Information Questionnaire for participants recruited at the University of Navarra

Version 2.0 (January 6th, 2021)

The following information must be filled by participants who have consented to take part in the study

Participant information

Name:_____

First surname:_____

Second surname:_____

DOB: _____

DNI: _____

Participant's mobile operating system:

- ○ Apple
- ○ Android

Participant contact

Mobile phone:_____

Email:_____

Residence city_____ Street_____

Number _____ Stair (left or right, only for apartment buildings) _____

Floor_____ Door_____

Usually, you receive medical care from which of the following providers?

- ○ Public health network (Social Security/Osasunbidea)
- ○ Private (Clínica Universidad de Navarra)
- ○ Both

Please indicate if you have suffered from any of the following medical conditions

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- ○ Non-specific cough
- ○ Non-specific upper respiratory tract infections
- ○ Acute pharyngitis
- ○ Asthma
- ○ Bronchitis
- ○ Chronic Obstructive Pulmonary Disease (COPD)
- ○ COVID-19
- ○ Gastroesophageal Reflux Disease (GERD)
- ○ Influenza
- ○ Pneumonia (any cause)
- ○ Respiratory Syncytial Virus Disease
- ○ Another non-specific lower respiratory tract infection
- ○ Smoker
- ○ Other condition (please specify): _____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Digital Acoustic Surveillance for Respiratory Disease Outbreak Early Detection: An Exploratory Observational Study in Navarra, Spain
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry…….. p. 3	✓
	2b	All items from the World Health Organization Trial Registration Data Set……NA	
Protocol version	3	Date and version identifier…… NA	
Funding	4	Sources and types of financial, material, and other support……. P. 18	
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors…….. p. 0, 18	
	5b	Name and contact information for the trial sponsor…….p.0	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities…… p. 18-19	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)…….. NA	
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention……. p.5-7	
	6b	Explanation for choice of comparators…….. p.5-7	
Objectives	7	Specific objectives or hypotheses…… p.8	
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)…….. p. 7	

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained……. p.7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)…… p.8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered….. p.9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)……. NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)……..p.9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial……..NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended……. p-12-14.
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended….. p. 7-8, Figure 1.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations…….p.12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size…….p.7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions……NA

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned……..NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions……..NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and How…… NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial…….NA
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol……..p.8,12-14.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols……p.9.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol…….p.13-14.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol……p.12-14.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)……..p.13.
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)……NA
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed……NA.

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial……NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct…….p.14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the Sponsor……..NA.

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval……..p.14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)……..p.14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)…….p.7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable……NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial……..p.14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site……..p.19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators…… Data share agreement included in the research agreement, but not in this submission.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation…….NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions…….p.14-15
	31b	Authorship eligibility guidelines and any intended use of professional writers……p.18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code……NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates……. Yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable……..NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.