Informed consent sheet

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Study Title: Electronic cough monitoring using artificial intelligence tools in patients with respiratory disease.

PROMOTER

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FUNDING

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Introduction

We are writing to you to inform you about a research study in which you are invited to participate. The study has been approved by the Research Ethics Committee of the University of Navarra.
With this document we want you to receive adequate information so that you can understand what the study is about and decide whether you want to participate in it or not. To do this, read this information sheet carefully and we will clarify any doubts that may arise after this. In addition, you can consult this with other people, if considered appropriate.

Voluntary Participation

You should know that your participation in this study is voluntary and that you can decide not to participate, or change your decision and withdraw your consent at any time, without affecting your relationship with your doctor or causing any harm to your treatment.

General Description

Coughing is a common and early symptom in most respiratory diseases. However, its adequate monitoring is limited by its subjectivity. In the absence of methods to objectively record the number

of times a patient coughs, physicians often rely entirely on data provided by patients, usually through self-filled questionnaires.

Having more accurate and objective information on the frequency and nature of coughs can provide physicians with important information about the cause of respiratory diseases, their progression, or response to treatment, as well as giving greater control to patients over their condition.

This study has 3 independent components, and you can choose in which of those you would like to participate:

Main study to determine Hyfe's clinical usefulness

This study aims to evaluate the usefulness of a mobile application, called Hyfe, that records and evaluates cough patterns, as an alternative to the currently existing cough recording methods. We want to compare the degree to which the records generated by Hyfe correlate with what the questionnaires filled out by the participants report. We also want to determine the precision with which Hyfe correctly differentiates cough from other similar sounds, in a subgroup of participants. We hope to record the cough of a group of patients who come to the Clinic of the University of Navarra and are diagnosed with diseases that cause cough. If necessary, each participant will be given a mobile phone that they will use to record their cough continuously for the duration of the study. In addition, you must indicate the intensity with which you cough each day, answering a single question through a web page, which you can access through the application.

You must also provide your contact information, as well as part of your medical history, to the doctor or nurse who formalizes your participation in the study. You will need to fill out a questionnaire on the influence of coughing on your quality of life, at the time of recruitment and during the second visit, before leaving the study.
Hyfe runs in the background on your mobile, and although it has continuous access to your mobile's microphone, it has been designed to only process sounds compatible with the characteristics of human coughing. When one of these sounds is detected and recorded by the application, an artificial intelligence algorithm studies it and in case of deciding that it is a cough episode, it is saved along with the information about the geographical location and the time it occurred.

Apart from the information provided by the application, we may also have access to your medical records at the Clínica Universidad de Navarra, in order to access information that could complement the data provided by Hyfe. These records include but are not limited to the results of the following laboratory tests

- Microbiology
    - COVID-19 tests.
    - Influenza PCR
    - Sputum culture.
- Hematology
    - Full blood count

    - D-dimer.
- Biochemistry
    - C reactive protein
    - Procalcitonin
    - CPK
    - LDH
    - Ferritin

Validation sub-study 1: Performance in controlled conditions

We want to determine the precision with which Hyfe differentiates cough from other sudden similar noises. Participants who take part in this component will be invited to visit an office at the University of Navarra, where they will have to stay for 30 minutes.

Validation sub-study 2: Performance in real-life conditions

Besides using a smartphone's built-in microphone, coughs can also be detected using a portable system called Hyfe Air. This system uses a wireless lapel microphone to register explosive sounds, which are then processed by the same artificial intelligence system used by the smartphone application. Participants who decide to take part in this second sub-study will help validate this tool in conditions similar to real-life.

Duration

For the main study, information will be collected for a period of 1 month, or if you are hospitalized, for the length of your stay at the Clinic. Researchers may ask you to extend your participation based on the evolution of the condition studied. During this period, and if you received a smartphone as part of the study, you should take it wherever you go.

Participants in the validation sub-study 1 will contribute with an extra 30 minute visit to the university's facilities.
Participants who take part in the validation sub-study 2 will be asked to use the smartphone application, a voice recorder, and the Hyfe Air wearable device for a variable period that might last from 6 to 24 hours.

Study procedures

You cannot participate in the study if you:

- Cannot, or do not want to share your cough-related codified data with datasets used to refine diagnostic algorithms.
- You cannot participate in the validation sub-studies if you are under 18 years-old.
- Are not a patient at the Clínica Universidad de Navarra (does not apply for participants exclusively taking part in the validation sub-studies).
- Do not have access to a Wi-fi network at your home or residence.

If you decide to participate, a doctor or nurse will help you log into the study application. If required, you will be provided a smartphone to download the application. You will have to connect this smartphone to your home's wifi network and carry it with you for most of the day. You must visit a

researcher before being discharged from the clinic (in case of being hospitalized), or after a month has elapsed since joining the study. You will receive an email with an appointment a few days before the date of this visit, in which you will have to return the mobile phone, in case one has been provided as part of this study.

If you are not provided with a smartphone, you will be asked to install Hyfe on your own mobile phone and use it to register at least 6 hours of records during the night, and while you sleep.

All study participants will have to fill out a Visual Analog Scale to indicate the intensity of their cough every night. This consists of a single question and takes about 2 minutes. At the time you are recruited into the study, and when you have finished your participation, you will also have to fill out a longer questionnaire, of 19 questions, about the characteristics of your coughs.
You can also be contacted via email to receive periodic updates on the status of the project and its preliminary results.

Participants who consent to take part in the validation sub-study 1 will contribute with a visit to the facilities of the university, which will take approximately 30 minutes. You will stay in a room and be asked to provide a series of voluntary sounds, while smartphones running Hyfe are placed in front of you. These sounds will be recorded and stored in a database (only your age and gender will be associated to these sounds, no other personal data will be linked to these files). The classification of the sounds made by Hyfe will then be compared to that performed by two external listeners, using the ID number assigned to each participant. This will allow us to objectively determine the accuracy of Hyfe detecting and classifying cough in a controlled setting.

Finally, participants who agree to take part in the validation sub-study 2 will have to use a smartphone, provided by the research team, and programmed to exclusively run Hyfe, for a variable period between 6 and 24 hours continuously. Participants will also be asked to use the Hyfe Air device, as well as a lapel microphone connected to a voice recorder during the entire monitoring period. Once the study is over, a researcher will count the number of coughs in your record, comparing it to that registered by Hyfe, and the Hyfe Air wearable device.

About Hyfe

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?
Hyfe 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 labelled as cough episodes are displayed by the app. Hyfe is a wellness status tool. Just like similar apps that count calories, steps or snores. Hyfe simply counts episodes of cough.

Benefits and risks of participating

Hyfe 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. Hyfe 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, Hyfe 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.

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 analyse the data will be password-protected and only authorised researchers will have access to them.

None of the MP3 recordings collected in the validation sub-studies will be shared with individuals external to the research team. They will be stored in password-protected servers and computers, only accessible to the research team.

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 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 times, 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 Carlos Chaccour, Tel number +34 628 659 003, 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.

Written informed consent form

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.

I accept to take part in the following components of the study:

- ○ The main study, which consists in the monitorization of my cough and the completion of the daily visual analogue scale for a period of 30 days.
- ○ The validation sub-study 1, which consists in recording a series of sounds a single time, and which will take approximately 30 minutes.
- ○ The validation sub-study 2, which consists in using Hyfe and the Hyfe Air device for a period between 6 and 24 hours.

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