Tips to include SUPER SESI in your Breath Research Protocol

- Based on the standard defined by www.clinicaltrials.gov.
- Each section provides useful info on instrument and breath test procedures.

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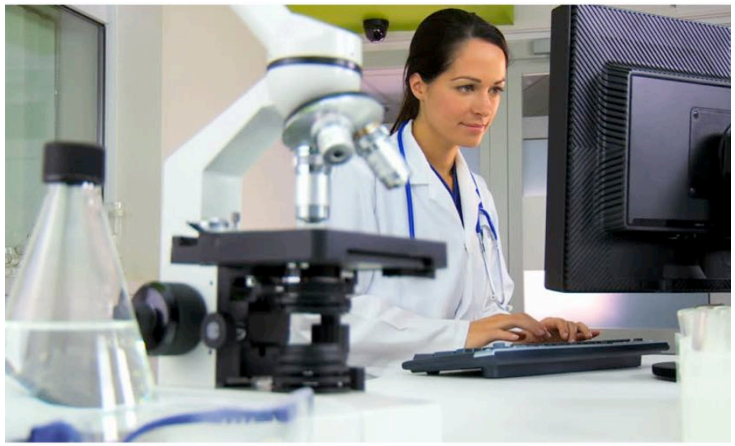
A. INTRODUCTION

Each clinical study is unique, organizing a clinical study, writing a research proposal and preparing a protocol are some of the most challenging tasks for researchers. Ultimately, getting things right is the responsibility of the Principal Investigator*.



The purpose of these sections is to present the information regarding Secondary Electro-Spray Ionization and SUPER SESI for breath analysis in a way that facilitates the preparation of your protocol.

B. ASPECTS TO CONSIDER WHEN PREPARING THE PROTOCOL OF YOUR CLINICAL STUDY

The following sections are arranged as the protocol registration data elements submitted to ClinicalTrials.gov for interventional studies (clinical trials) and observational studies. These sections are mostly adapted from 42 CFR Part 11. When applicable, each section provides useful information about the instrument and the breath test procedures.

* FIT does not take any responsibility on the accuracy or the applicability of these sections to any protocol of any clinical study.

1. STUDY IDENTIFICATION

Study Type *

The Principal Investigator is in charge of defining the type of study. SUPR SESI can be used in Observational studies and Interventional studies:

- **Interventional (clinical trial):** Participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health related outcomes, and SUPER SESI is used to measure the effect of the intervention on the composition of breath.

- **Observational:** Studies in human beings in which biomedical and/or health outcomes are assessed in pre-defined groups of individuals. Participants in the study may receive diagnostic, therapeutic, or other interventions, but the investigator does not assign specific interventions to the study participants. This includes when participants receive interventions as part of routine medical care, and a researcher studies the effect of the intervention. In these studies, SUPER SESI is used to measure the breath composition of the human beings participating in the study.

2. STUDY STATUS

Not affected.

3. SPONSORS/COLLABORATORS

Collaborators

Big data analysis is becoming essential in the understanding of clinical complex data-sets, and breath analysis is no exception to this trend. A breath analysis campaign based on SUPER SESI will produce huge amounts of data, which need to be analyzed by data scientists.

Fossil Ion Technology (FIT) is working to provide accurate and sophisticated algorithmic and Artificial Intelligence tools specifically tailored to analyze the data generated with SUPER SESI. FIT uses the acquired data to evaluate the quality of the systems and algorithms, to identify trends and bugs, and to fix them. These algorithms allow SUPER SESI users to assess their own data, to navigate it, and to extract significant information.

We encourage our customers to integrate a data-science specialist, or to collaborate with a data-science team to process the data.

To share the data with the data-science team, the data has to be properly anonymized and protected in accordance with local and international standards and legislation. Adequate means for transferring the data from the analyzer to the data science team have to be arranged.

In the protocol, it is important to state that data will be shared with the data-science partner who will analyze it. If you choose to work with FIT, we will also use meta-data from previous studies to complement and enhance the statistical significance of your Clinical study, and and we incorporate the new data in our data-base to enhance future clinical studies.

Our tip: get in contact with your partner/s before defining the protocol to address all confidentiality aspects and to define the specific procedures required to meet local legislation.

4. OVERSIGHT

Human Subjects Review

The identification of a new biomarker in breath could be very useful in many applications: it is fast, non-invasive, and breath is constantly produced by all living humans throughout their entire life-cycle.

- **Collecting data:** Breath analysis is non-invasive, and takes approximately 10 minutes. No harm is caused to the participants, and very little effort is required from them.
- **Analyzing and sharing data:** BIf you choose to share your data with FIT or other database: by sharing the data obtained in each clinical study, you will improve the statistical significance of your results, and the results obtained by the scientific community in the different clinical studies. Ultimately, this will result in a faster identification and validation of biomarkers. This will also help FIT to constantly improve its algorithms and instruments.

FDA Regulated Intervention

Super SESI is not an FDA-regulated device:

- SUPER SESI is not intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- SUPER SESI is not intended to affect the structure or any function of the body of man or other animals, and it does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and it is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

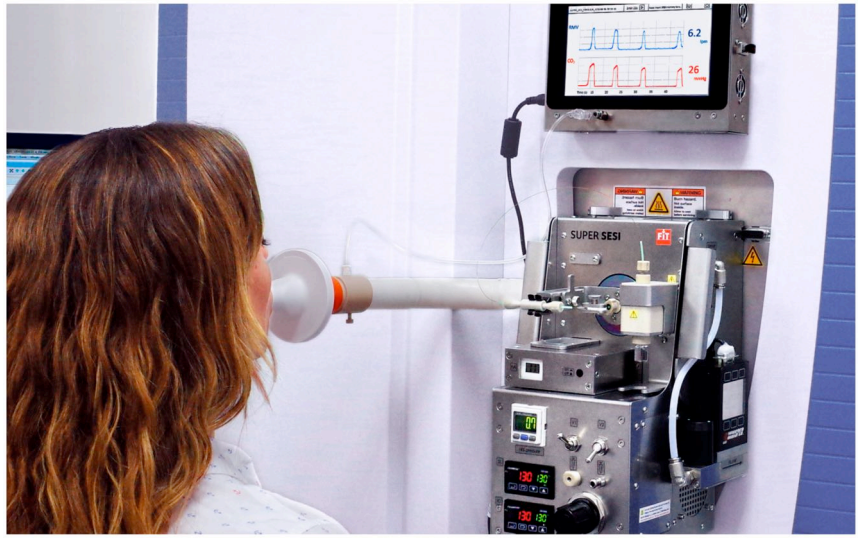
SUPER SESI is used to measure the chemical composition of breath.

5. STUDY DESCRIPTION

Detailed Description

Collecting data: Before the analysis, the participant is introduced to the system, and a disposable mouthpiece is provided to illustrate how he/she needs to exhale. No food, drinks (except for water), tooth brushing and chewing gum are allowed at least one hour before the test. SUPER SESI is coupled with a high resolution mass spectrometer and it is functioning in steady state. A disposable mouthpiece is located at the inlet, and EXHALION is used to guide the exhalation maneuver. The operator of the instrument initiates the acquisition and waits for 30 seconds while the participant is breathing normally.

The operator indicates when the participant has to exhale. At this point, the participant exhales while looking at EXHALION, that indicates the exhaled flow. The participant is required to exhale at a fixed flow rate between 5 and 10 Lpm during 20 seconds, after which the participant is required to breath normally for 30 seconds. Twelve exhalations are recorded in about 15 minutes. The acquisition is stored with an anonymized filename.



The mass spectrometer and the SUPER SESI are CE marked products, which must be operated in a laboratory environment by trained personnel. SUPER SESI is certified in accordance with Electrical Safety (IEC 61010), and Electro Magnetic Compatibility (IEC 61326). While exhaling into the system, participants must be accompanied by a trained professional in charge of the instruments.

Analyzing data: The mass spectrometer produces a full spectrum every 100 ms during the entire acquisition, each spectrum being a snapshot of the evolution of the signals measured for each species. Each breath analysis can take up to 100 Mbytes of data. A SUPER SESI-MS instrument can analyze the breath 48 participants per day (10 minutes per participant over 8h), and almost 1000 participants in a month. The total size an average campaign comprising 1000 participants is 100 Gigabytes. For this reason, big data analysis is required to pre-processes and post-process the data and to extract key features.

Our tip: define the data analysis plan before defining the protocol

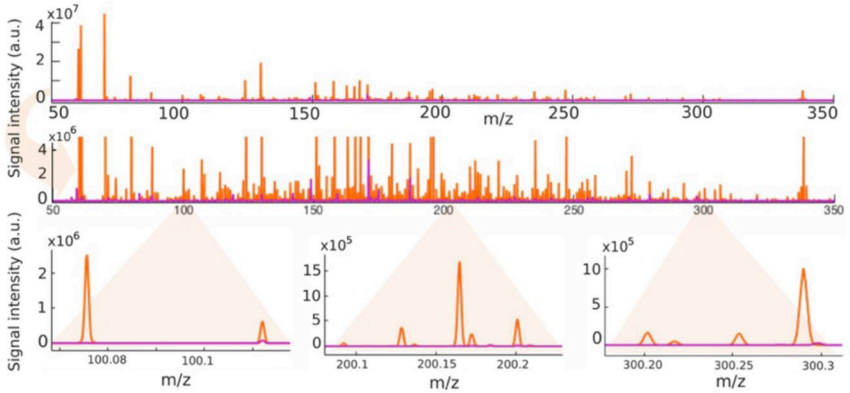


Fig. 2 Averaged spectra: Background represented in purple, exhaled breath signal represented in orange.

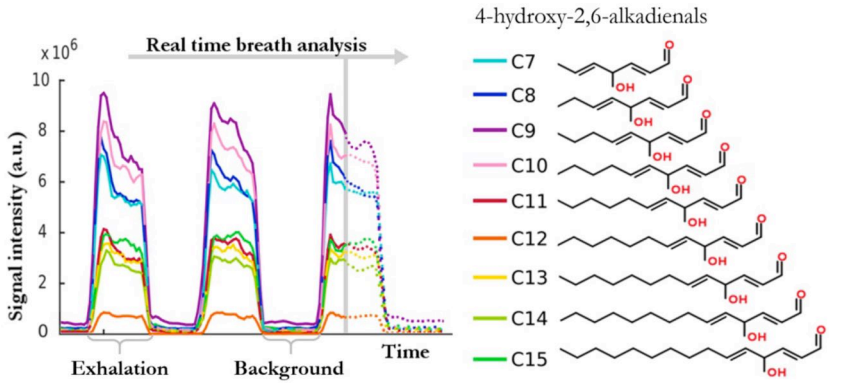


Fig. 3 Signal evolution corresponding to 4-hydroxy-2,6 alkadienals from 7 to 1 5 carbons, extracted from four direct consecutive exhalations.

6. CONDITIONS AND KEYWORDS

Keywords

Some possible keywords: exhaled breath, Signs and Symptoms.

7. STUDY DESIGN

Bio-specimen Retention:

Breath is analyzed online. It is not collected. No sample is thus retained.

8. ARMS, GROUPS, & INTERVENTIONS

Not affected.

9. OUTCOME MEASURES

Secondary Outcome Measure Information

Breath molecular analysis measured with SUPER SESI is a secondary outcome, being the primary outcome the standard diagnosis or set of syndromes of the condition being studied.

10. ELIGIBILITY

Eligibility Criteria

To participate in the study, participants must be able to follow the instructions to exhale into the system and to provide a steady pressure with a visual feedback.

11. CONTACTS, LOCATIONS, AND INVESTIGATOR INFORMATION

Not affected.

12. IPD SHARING STATEMENT

Plan to Share IPD & IPD Sharing Plan Description

FIT strongly encourages Principal Investigators to share the complete data set to allow for the continuous improvement of the analytical instrumentation and the breath data mining algorithms.

C. SUPER SESI

SUPER SESI is a highly sensitive ion source that harness the power of high resolution mass spectrometry to enable online ionization of low volatility metabolites.

- SUPERIOR TECHNOLOGY. Built upon Secondary Electro-Spray Ionization (SESI), SUPER SESI helpsmaking real-time analysis of volatile organic compunds (VOCs) a reality today.
- RELEVANT RESULTS. Due to its focus on low volatility species, SUPER SESI detects larger molecules, more relevant from a biological standpoint.
- EASY-TO-USE. SUPER SESI is designed under a plug and play philosophy and optimized for high performance commercial mass spectrometers (Thermo and Sciex).
- EASY-TO-CLEAN. SUPER SESI automates some cleaning procedures, and facilitates deep cleaning to keep contamination in check.

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