Co-funded by the European Union

Ref. Ares(2024)2372118 - 31/03/2024

vocorder

WP2 Specifications of the components, overall architecture and application use cases

D2.1 Report on the design of clinical settings validation

***VOCORDER**: Towards the ultimate breath analysis -based continuous healthcare*

VOCORDER CONSORTIUM

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Project title	Towards the ultimate breath analysis -based continuous healthcare
Project acronym	VOCORDER
Starting date	1 October 2023
End date	31 March 2027
Contract no.	101115442
Project Coordinator	MITERA
Deliverable no.	D2.1
Document name	VOCORDER_D2.1_ Report on the design of clinical settings validation.pdf
Deliverable name	Report on the design of clinical settingsvalidation
Work Package	WP2
Nature[1]	R
Dissemination[2]	PU
Lead Beneficiary	MITERA (MITERA)
Contributing beneficiary / beneficiaries	AIDEAS OU (AIDEAS), EREVNITIKO PANEPISTIMIAKO INSTITOUTO SYSTIMATON EPIKOINONION KAI YPOLOGISTON (ICCS), EIDGENOESSISCHE TECHNISCHE HOCHSCHULE ZUERICH (ETH), VRIJE UNIVERSITEIT BRUSSEL (VUB)
Reviewed by	EIDGENOESSISCHE TECHNISCHE HOCHSCHULE ZUERICH (ETH), METIS BALTIC (METIS)
Approved by	MITERA (MITERA)
Due date	31/03/2024
Actual submission date	31/03/2024

[1] **R** = Document, Report, **DMP** = Data Management Plan, **OTHER** = Other
[2] **PU** = Public, **SEN** = Sensitive, limited under the conditions of the Grant Agreement

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ABBREVIATIONS

Term	Explanation
AI	Artificial Intelligence
BRCA	Breast Cancer
CDC	Centers for Disease Control and Prevention
CFR	Case Fatality Rate
CKD	Chronic kidney disease
CNN	Convolutional Neural Network
COPD	Chronic obstructive pulmonary disease
CTR	Clinical Trial Regulation
DPIAs	Data Protection Impact Assessments

DPO	Data Protection Officer
ECCRI	Code of Conduct for Research Integrity
ECHR	European Convention for the Protection of Human Rights and Fundamental Freedoms
EMR	Electronic medical data
GA	Grant Agreement
GC-MS	Gas Chromatography Mass Spectrometry
GDPR	General Data Protection regulation
HR-MS	High-Resolution Mass Spectrometry
IARC	International Agency for Research on Cancer
ICT	Information Communication Technologies
ICU	Intensive Care Unit
IEC	Internal Ethics Committee
KNN	K-Nearest Neighbors
LSTM	Long Short-Term Memory
Mid-IR Array	Mid-infrared region of the electromagnetic spectrum usually covering the 4 – 10 □m range.
ML	Machine Learning
NB	Naive Bayes
NIST	National Institute of Standards and Technology
NSAIDs	Non-Steroidal Anti-Inflammatory drugs
PCA	Principal Component Analysis
QCL	Quantum cascade laser. Mid-infrared laser sources used in the VOCORDER
RWD	Real World Data
SESI-MS	Secondary Electrospray Ionization Mass Spectrometry

SSH	Social Sciences and Humanities
SVMs	Support Vector Machines
VOC	Volatile Organic Compounds

1. EXECUTIVE SUMMARY

This clinical study will explore the correlation analysis between volatile organic compounds (VOC) profiles in breath as detected by the VOCORDER breath analyser and Electronic medical data as collected by medical professionals. The obtained results are expected to be significant in refining the technology of breath analysis in the VOCORDER breath analyser for the early detection of diseases of interest.

The assessment of the device that will be produced within the framework of the VOCORDER project for breath analysis will take place at MITERA hospital in Athens, Greece. The clinical application of the device will be carried out in two phases: a preliminary phase **(baseline phase M12-M23)** and the final main phase to thoroughly evaluate the device **(validation phase M33-M39)**. During the baseline phase, samples taken from participants will be analyzed using Mass Spectrometry as a reference method. In the validation phase, the analysis will be conducted using both methods, namely the reference method and the VOCORDER method.

Implementing the first phase is necessary because gathering necessary data (clinical and laboratory) are required for developing Electronic Medical Records (EMR) and Artificial Intelligence (AI) algorithms. These will serve as the basis for evaluating the device's performance. The study will include both patients and healthy control groups from whom breath samples will be taken for analysis. The selected diseases in this study include lung cancer, stomach and colon cancer, breast cancer, kidney insufficiency and community-acquired or healthcare-associated acute infections.

2. STUDY DESIGN

2.1 The hypothesis

In the study of breathomics, several VOCs, VOC patterns and relationships among changes in VOC patterns are found to be related to different types of diseases. Therefore, changes in VOC patterns of the exhaled air correlate with particular conditions, as measured by specific disease-related VOC profiles.

2.2 Background and Objectives of the study

This clinical study is being conducted as part of the HORIZON-EIC-2022 PATHFINDER CHALLENGES-01-04 project entitled Vocorder, a new technology for breath analyses. **Breath sample collection for VOC analysis** (patients and control group), VOCs may already be present at a base level. However, the VOCORDER instrument will be capable of resolving those concentration differences caused by changes in the metabolism and discriminate against those which may already be present in the environmental air. Thus, the analyser will allow an in-situ time-resolved measurement of different gases (e.g., VOCs), recording their concentration profile within single breaths with minimal supervision and almost no strict methodology. However, in this validation phase strict methodology will be applied to ensure the validity of the approach and the unobtrusiveness of the method.

The breath analyses will be performed using laser-based breath analyser prototypes capable to detect small number of gases simultaneously. QCL mid-IR Array-based self-mixing analyser for the detection of VOCs with measurement range in the 10-100 ppb, limit of detection close to 1 ppb, resolution close to 1 ppb and accuracy near ± 1 ppb. Identification of compounds will rely on a NIST mass spectral library and **the comparison of their retention indices with the library of indices obtained for reference standards.** The initial breath analyser will be able to be tested in healthy and incubated patients alike, since the sampling tube can be connected to the ventilator directly, in addition to its original use.

This clinical study will address the correlation analysis between breath VOCs profiles as detected by the VOCORDER breath analyser and Electronic medical data collected by medical professionals. The obtained results are expected to be essential for tailoring the technology of breath analysis in the VOCORDER breath analyser towards the early detection of diseases of interest.

The main objectives of this clinical study are as follows:

1. To use the developed device in clinical setting and determine its operating parameters (respiratory volume, number, and frequency of clinical sampling).
2. To validate the performance of the device and its measurements produced in comparison with other relevant technologies and/or the established reference method.
3. To investigate the potential main correlations between the gases detected in breath analysis and the specific diseases chosen for this study.

2.3 Primary and secondary endpoint(s)

Primary endpoints:

To validate the effectiveness of the VOCORDER device in clinical practice and to promote further the technology of breath analyses.

Secondary endpoints:

1. Identify and define the operational parameters of the new technology of breath analyses in clinical practice.
2. Compare the performance and outcomes of VOCORDER technology against the GC-MS reference method.
3. Investigate the correlation between known pre-existing conditions and significant VOC biomarkers in exhaled breath for selected diseases.
4. Explore the potential of VOC biomarkers in exhaled breath for the early detection of diseases, facilitating timely diagnosis through correlation with key medical parameters.

2.4 Requirements for the conduct of the clinical study

2.4.1 Research center for the implementation and the current approval status of the Ethics Committees

The study will be conducted at MITERA Hospital. MITERA General Clinic, Maternity / Gynecological Clinic & Children's Hospital has established itself as a leading healthcare facility, serving as a comprehensive care center for individuals of all ages. With 45 years of operation, MITERA stands out as one of Greece's most esteemed private hospitals, offering a wide range of high-quality health services aimed at the prevention, diagnosis and treatment across various medical fields. MITERA is home to three clinics: the

General Clinic, the MITERA Maternity / Gynecological Clinic and the most comprehensive private pediatric clinic in Greece, the MITERA Children's Hospital. The commitment to providing exceptional nursing care and services is of high quality at MITERA Clinics, where a dedicated team of physicians, nurses, and midwives, backed by comprehensive administrative and technical support, are available around the clock, every day of the year, to address any medical emergency.

The hospital's Scientific Council has authorized the clinical study **(ANNEX 1).**

The study will be conducted by the MITERA research team.

2.4.2 Regulatory status

1. **The requirements of the General Data Protection Regulation (GDPR)** (**ANNEX 5**)
2. **Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016** on the protection of natural persons about the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC**• WP29: Opinion 05/2014** on anonymization techniques.
3. **The best practices of treatments/standard of care** will be followed. The patients will be diagnosed according to these best practices.
4. Even though the clinical study does not include drug treatments, the general principles of **Good Clinical Practice** will be followed to ensure ethical and scientific quality.
5. The principles defined in the guidelines of Health Technology Assessment agencies, such as **EUnetHTA**, will be considered, especially the following:
   - Comparators & Comparisons. Criteria for the choice of the most appropriate comparator(s).
   - Summary of current policies and best practice guidelines.
   - Endpoint Criteria for Relative Effectiveness Assessment: Clinical Endpoints
6. The study will be designed and analyzed in accordance with the **Statistical Principles for Clinical Trials** (CPMP/ICH/363/96), ICH Topic E9
7. **AEPD**: AEPD Guidelines on Personal Data Anonymisation Procedures will provide a framework for ensuring privacy and data protection.
8. **ENISA**: Recommendations will be followed to align technology developments with GDPR, particularly regarding data pseudonymization techniques.

9. The joint **AEPD-EDPS paper** on using hash functions for personal data pseudonymization will serve as a reference for data protection strategies.
10. **World Medical Association**: The Declaration of Helsinki on ethical principles for medical research involving human subjects

2.4.3 Ethics Status

VOCORDER embodies a dual role, functioning both as a research initiative and a clinical study that involves human participants. Therefore, it is subject not only to the rules regarding research ethical standards, but also must adhere to the ethical principles defined and established by the medical community. Moreover, it involves ground-breaking the interplay of disruptive and novel technologies, particularly Machine Learning (ML) and Artificial Intelligence (AI), introducing unique ethical challenges and considerations.

In the present section, adequate and thorough consideration will be given to all potential ethical concerns that could arise with VOCORDER. It aims to clarify the project's various aspects of VOCORDER, particularly, its innovative technological applications, while guidelines will be provided to the partners involved actively in VOCODER's research endeavors. In this Deliverable, we present initial considerations on the ethical issues that arise within VOCORDER's clinical study. The current analysis is closely associated with WP6 and Task 6.1, which will update and further elaborate on these matters at the implementation stage and with WP9, in the premises of which ethics checks will be conducted.

Research Ethics

Within VOCORDER, the concept of research ethics is delineated to encompass the procedural aspects that ensure the project's alignment with the principles applicable to Horizon Europe research. These standards address aspects of research integrity, such as fostering responsible research practices and managing the dynamics between researchers, participants, and society at large. It is imperative for VOCORDER partners to embody these principles and adhere to relevant legislation, ensuring their application throughout the project's research activities. Ethical adherence is crucial for all Horizon Europe projects, especially those involving human subjects, highlighting the necessity for the VOCORDER consortium to commit to key ethical principles.

The initial step toward ethical compliance includes clearly identifying the sources from which the ethical framework stems. This is crucial, enabling the anticipation and mitigation of potential risks that may appear and ensuring the abidance of the involved partners. Between those sources, the project's **Grant Agreement** (GA) is surely useful, along with **Regulation 2021/695**, established by Horizon Europe, serving both as the primary instruments in defining the project's ethical guidelines. Additionally, the European Commission provides additional **guidelines in social sciences and humanities (SSH)** and **in the ethical processing of personal data**[3] to assist researchers in conducting their work ethically. Finally, the **European Code of Conduct for Research Integrity** (ECCRI), issued by All European Academies (ALLEA), serves as an additional comprehensive manual to ensure compliance with those ethical requirements.

Grant Agreement

In Article 14 and ANNEX 5 of the GA, the ethical obligations of the beneficiaries are set. These vary from compliance with legislation to the respect of specific values. The project partners are mandated to follow ethical principles, including the highest standards of research integrity, as well as to comply with relevant EU, international, and national laws, such as the EU Charter of Fundamental Rights (Charter) and the European Convention for the Protection of Human Rights and Fundamental Freedoms (ECHR) and its supplementary Protocols. It is imperative to focus on principles such as proportionality, privacy, confidentiality, protection of personal data, non-discrimination, and the safeguarding of environmental and human health. Furthermore, the project will strictly adhere to the fundamental principle of research integrity, as outlined in the European Code of Conduct for Research Integrity. This encompasses ensuring the reliability, honesty, transparency, respect, accountability, protection of vulnerable persons, inclusiveness and justice, human dignity, and integrity throughout the research process. It also promotes openness, reproducibility, and traceability while refraining from any violations of research integrity described in the Code.

The scope of project activities is strictly limited to civil applications and explicitly excludes practices such as human cloning for reproductive purposes, genetic alteration of human heredity, creation of human embryos solely for research, or the destruction of human embryos. Research involving human embryos or embryonic stem cells is only

permissible under specified conditions or with explicit approval from the granting authority. Any research activities that elicit ethical concerns must conform to additional criteria set by ethics panels, including obtaining all necessary approvals or documents from relevant committees or authorities before commencing their tasks.

Regulation 2021/695

Article 19 of the Horizon Europe Regulation outlines the obligatory ethical standards for projects under its purview, specifically emphasizing:

1. Principle of proportionality
2. Principle of non-discrimination
3. Right to the physical and mental integrity of a person
4. Protection of environment and human health
5. Right to the protection of personal data
6. Right to privacy/ confidentiality

Entities participating in Horizon projects are obliged to furnish an ethics self-assessment, affirm adherence to ECCRI, ensure conformity of activities outside the EU with Member State legislation, and follow particular standards regarding licensing and ethical endorsements for initiatives involving human embryonic stem cells. Further measures include securing approvals from pertinent ethics committees before initiating such activities and undergoing ethics evaluations by the EU Commission, which operates as the funding entity. Article 20 focuses on maintaining confidentiality within research endeavors, mandating adherence to security measures, particularly in handling sensitive information. Similar to ethical protocols, proposals must include a security self-assessment. The Commission oversees the enforcement of these standards, performing necessary inspections and evaluations to maintain integrity and confidentiality in research projects.

EU Commission Guidelines on Ethics in Social Sciences and Humanities

The guidelines on ethics in SSH by the EU Commission serve as a reference for beneficiaries of Horizon projects, directing their research efforts with insights from the Nuremberg Code, the Helsinki Declaration, and the Belmont Report. Despite their origins in biomedical research, these documents encapsulate universal ethical principles relevant to any human-involved research. The guidelines emphasize the critical balance

between the potential risks of chosen research methodologies and their anticipated benefits. Lastly, the guidelines stress the necessity of obtaining informed consent from prospective research subjects as a standard practice. This ensures voluntary participation and informing individuals about the use of their personal data in analysis. Exceptions to this rule may occur when project methodologies require overriding these principles for societal benefits, provided there is a well-justified rationale and appropriate implementation of adequate protective measures.

European Code of Conduct for Research Integrity

Regulation 2021/695 specifically references the ECCRI, which is applicable across various scientific and academic domains. It acts as a cornerstone for fostering ethical research conduct and maintaining integrity throughout all phases of research, from inception to the dissemination of findings. Acknowledged by the Commission as the primary reference for research integrity in Horizon projects and as a standard for entities and researchers across Europe, the Code underscores core values. It emphasizes fundamental values such as a) reliability in ensuring the quality of research, reflected in the design, the methodology, the analysis, and the use of resources; b) honesty in developing, undertaking, reviewing, reporting, and communicating research in a transparent, fair, full and unbiased way; c) respect for colleagues, research participants, society, ecosystems, cultural heritage, and the environment and d) accountability covering the entire research lifecycle from idea generation to publication, including the management and organization of research, training, supervision, mentoring, and considering the broader impacts of the research. The Code also highlights instances of research misconduct, specifically highlighting fabrication, falsification, and plagiarism (categorized as FFP). Fabrication involves creating false results, falsification involves manipulating data without justification, and plagiarism involves using the work of other researchers and authors without paying proper attribution or without their prior authorisation.

EU Commission Guidelines on Ethics and Data Protection

In research settings, data protection mandates researchers to provide research subjects with comprehensive details regarding the handling of their personal data. It also necessitates organisations processing this data to guarantee its proper protection, minimisation, and deletion when no longer necessary. While Horizon research projects processing personal data are bound by EU and national data protection regulations, the

aim of this guidance note is to ensure that, beyond fulfilling legal requirements, all projects are steered by ethical considerations and the values and principles underpinning the EU acquis.

The areas associated with the handling of personal data and recognised to demand ethical consideration are the following:

1. Pseudonymisation and anonymisation
2. Data Protection principles to be integrated by design and by default
3. Informed consent for data processing
4. Special considerations for collecting data from children
5. Guidelines on the secondary use, transfer, security, and deletion of data
6. Data Protection Impact Assessments (DPIAs)
7. Profiling, tracking, surveillance, automated decision making and big data
8. Collection of personal data outside the European Union

Medical Ethics

As already noted, research engaging with individuals in the clinical realm must follow the dominant in the medical field ethical obligations. Regarding clinical studies, the **Declaration of Helsinki** sets the ethics framework for medical research (e.g. protection of life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects, protocols' design, role of research ethics committees, informed consent procedures, etc.) Relevant are also the principles enshrined in the **Oviedo Bioethics Convention** (Oviedo), the main purpose of is to protect individuals against exploitation arising out of treatment or research and it contains several detailed provisions on informed consent. In the EU sphere, the **EU Regulation 536/2014** on clinical trials on medicinal products for human use (CTR) and **EU Regulation 745/2017** on medical devices exist. At this point, it is important to note that when examining the pertinent ethical framework in relation to VOCORDER research involving human participants, a differentiation between clinical studies that involve testing medicinal products on humans and those observing humans using medical devices should take place. Since VOCORDER does not aim to test a medicinal product on human participants, the CTR does not apply. However, references to the CTR are regarded as guidelines and best practices and will be taken into consideration throughout

the implementation of the project. The **EU Directive 2011/24/EU** on the application of Patients' rights in cross-border healthcare grants certain rights to individuals who have acquired the status of patient in the EU.

Given the repetitive nature of ethical responsibilities and participant rights across these documents, a detailed, individual examination is not necessary. Instead, the VOCORDER project will address and elaborate on these ethical requirements holistically, ensuring comprehensive ethical compliance tailored to its specific research context.

Bioethical Principles

Across the most important and relevant to the VOCORDER project ethical principles in the medical sector are the ones of autonomy, beneficence, non-maleficence, and justice, which are going to be summarised and examined. These principles, while universally recognized, are nuanced, and require careful consideration to balance individual rights and broader interests. Normatively, they are dispersed across multiple sources on a global and on national level. These principles will be briefly presented and explained so as to operate as a navigator for the partners involved in the VOCORDER project.

To begin with, the principle of autonomy underscores the importance of reassuring and safeguarding patients' and participants' autonomy. The process of informed consent, which will be analyzed later, serves as a mechanism through which participating individuals can assert their autonomy in clinical care and research settings. Within the principle of beneficence physicians are obliged to pursue actions that enhance the welfare of their patients and act in their utmost interest. This involves not just preventing and treating diseases but also enhancing overall health and quality of life. Healthcare providers must aim to maximize the advantages while minimizing harm to the patient according to the principle of non-maleficence. The anticipated adverse impacts of any suggested intervention should always be evaluated in comparison to the intended positive effects. Finally, physicians must ensure an equitable distribution of medical goods and services among the patients, refraining from discrimination and decisions based on prejudicial assumptions or stereotypes.

Rights of Patients

While the provision of direct patient treatment is not one of the project's targets, patients constitute one of the main sources of the Real-World Data (RWD) used for the VOCORDER research. As such, they are entitled to certain rights under EU legislation, as outlined in the EU Directive 2011/24/EU, which addresses Patients' rights in cross-border healthcare. This directive ensures that patients receive the necessary information to make informed decisions about their healthcare and to exercise their rights effectively. In this regard, Article 4(2) specifies various obligations for healthcare service providers, including those utilizing Information Communication Technologies (ICT) solutions. These responsibilities encompass providing clear information regarding the availability, safety, and quality of healthcare services, clear disclosure of costs, outlining complaint procedures and mechanisms, providing information on professional liability, and detailing measures implemented to safeguard patients' personal data.

Informed Consent

In medical research, the principle of autonomy is fundamental, requiring that patients give informed consent prior to any research-related interventions on their bodies. Informed consent stands as the foundation of research ethics. Ensuring the attainment of valid, written, informed consent from research participants is of utmost importance. This principle is rooted in historical documents such as the Nuremberg Code and in the par. 25 of the Declaration of Helsinki, both stressing the necessity of voluntary consent in research. Presently, informed consent is widely recognized as a process wherein a patient is fully informed about the research details, including its purpose, potential risks, and benefits, and can make an informed decision regarding their participation. The Oviedo further elaborates on the requirement for informed consent in biomedical research. It dictates that participants must be adequately informed about the study, including its nature, risks, and benefits, before deciding whether to participate in it or not. Moreover, these documents emphasize that consent must be given voluntary and should be properly documented, with an understanding that participants have the freedom to withdraw at any point. In the context of the EU pharmaceutical sector, the CTR mandates informed consent for clinical trials, detailing the formalities and elements necessary for consent. Thus, it is crucial to distinguish between consent for trial participation and consent as a legal basis for processing personal data under the General Data Protection Regulation (GDPR). While informed consent serves as an ethical standard and procedural obligation under the CTR, it does not constitute a legal basis for data processing.

On the matter of providing information to the study participants the Declaration of Helsinki emphatically states in par. 26: "After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely given informed consent, preferably in writing". The information provided must be given in lay terms, ensuring that no form of pressure is applied to the potential individual participant nor their representatives. The method of communication should be tailored to suit the specific needs and circumstances of the research participants.

Ethical Committees

Medical research involving human participants mandates the approval of independent ethics committees, as per the CTR. According to the CTR in Article 2(11), an ethics committee is defined as an independent body established in a Member State in accordance with the local laws and empowered to give opinions for the purposes of the CTR, taking into account the views of laypersons, in particular patients or patients' organizations. As stated in par. 23 of the Declaration of Helsinki, the committee must operate transparently, maintain independence from the researcher, sponsor, or any undue influence, and possess appropriate qualifications. It should also take into account the laws and regulations of the countries where the research is conducted, along with relevant international norms and standards. Nevertheless, these considerations must not limit the protections afforded to research subjects as outlined in the Declaration. Their role extends to ongoing oversight of research projects to ensure continued compliance with ethical standards.

Disruptive technologies' ethics

VOCORDER aims to tackle intricate health challenges while paying special focus on ethical considerations. While it establishes a research ethics framework to steer clear of ethical breaches in human-involved research, its scope transcends mere compliance with ethical standards. The health status of the individual can be concluded by relying heavily on ML and AI signal processing with a 5 sec use of the device. VOCORDER also targets to add a new dimension to breath analysis by introducing explainable AI analytics and advanced data processing techniques. This presents ethical quandaries surrounding the utilization of AI in the medical realm.

The ethical framework of VOCORDER will explore how the consortium mitigates ethical risks arising from the fusion of health data and AI. It will explore various AI ethics issues,

including accountability and transparency, explainability, bias, and non-maleficence. Of particular focus is understanding how social and cultural factors impact diseases and algorithm development, including addressing hidden biases that may skew diagnoses. The project will also scrutinize biases in AI resulting from group composition and the failure to consider certain factors. The necessity of transparency and accountability for fostering trust raises ethical considerations concerning responsibility and informed consent. Moreover, the project will examine the role of clinicians, patient autonomy, and the risk of potential misuse in commercial exploitation. A template will be proposed in conjunction with the research ethics framework to evaluate the project's ethical stance concerning fundamental ethical questions arising in the AI sector and disruptive technologies in general.

One of the key considerations in applying AI to healthcare is complying with the principle of accountability. The accountability of diagnoses made entirely by or assisted by AI systems sheds light on ethical concerns. The matter of responsibility in case of errors has been vastly debated. At the same time, the opacity issue questions how clinicians can comprehend the reasoning behind a diagnosis, raising doubts about patient trust when the system's operation is not fully explainable and remains opaque even to the experts.

The integration of AI in healthcare introduces various biases, ranging from algorithmic design to inadequate data for comprehensive validation. These biases can involve statistical disparities, where dataset distributions deviate from real populations, and social biases, arising from inequitable representation in datasets. Historical biases can be traced stemming from entrenched perspectives, representation biases arise from underrepresented groups, and measurement biases result from favouring specific data or labels over others. Aggregation bias is observed when algorithms generalize diverse datasets uniformly, potentially distorting outcomes. In contrast, evaluation bias occurs in cases when benchmarks fail to represent the entire population, leading to flawed evaluations.

With the integration of AI in the VOCORDER research and the generation of the ‘deep-patient’, the principle of non-maleficence ensures the AI system is not misused beyond its intended purpose. One risk involves external cybersecurity attacks aiming to disrupt the system's functionality, posing a threat to the unintentional spread of personal and, thus, sensitive data. There is also the potential misuse of the system by external entities, either private or public ones, who may use it for profiling purposes without the knowledge

and consent of the individual or the researchers. As a consequence, ethical oversight should take place at all stages of the application of AI in the VOCORDER project.

Ensuring ethical compliance in VOCORDER

Specific measures have already and will be taken by the VOCORDER consortium before engaging in research activities that might be proven ethically challenging. Since numerous details must be specified at the time of drafting this deliverable, a precautionary approach has been adopted to prevent the underestimation of potential risks. Regardless of the progress, some steps need to be implemented, and those must be mentioned, but will monitor during the project's development.

Informed Consent and Information

Within VOCORDER, the responsible institution follows specific procedures and uses the consent form (ANNEX 6), ensuring compliance with the minimum information requirements for valid consent as outlined in the above frameworks. Participation in the VOCORDER research will be entirely voluntary for all individuals, with the right to withdraw from any stage of the research activities without facing any repercussions or penalties. A comprehensive information sheet outlining the purpose, procedure, risks, etc., of the VOCORDER research will be furnished to participants (ANNEX 6) along with the consent form. A protocol and draft templates for information consent forms can be retrieved in the respective ANNEX 6. They will also be added in the Data Management Plan. Physicians with appropriate scientific training and qualifications will give the information. The medical staff will be capable of answering questions posed by the individuals and explaining the process to be followed, what is requested from the participant, and the anticipated results. It will be ensured that potential participants have fully understood the information.

The consent will be given freely by the participants. It will be guaranteed that they do not feel obliged to or coerced in any way into giving consent. Participants will consent in writing, particularly by signing the informed consent form and information sheets presented below. If consent cannot be given in writing, for example, because of illiteracy, non-written consent must be formally documented and independently witnessed. Consent is a continuing process, especially in long-term trials like the one of VOCORDER. The responsible project partners will foster a continuous dialogue with participants and inform them of anything different/new related to the trial.

Incidental Findings Policy

As already outlined in D1.2 another aspect to consider in evaluating the compliance of research activities with ethics is the occurrence of incidental findings. Incidental findings refer to results that emerge outside the original intent of a test or procedure. Secondary findings, on the other hand, are actively sought but are not the primary focus of the test or procedure. 'Anticipated' incidental findings are those expected to be associated with a specific test or procedure, irrespective of their likelihood. On the contrary, 'unanticipated' incidental findings are unforeseen based on current scientific knowledge. Researchers may not anticipate such findings, but can prepare potential responses if unexpected discoveries arise, especially those with actionable or life-saving implications.

In human subject research, protocols for handling unexpected incidental findings need clear delineation. Researchers must specify whether participants will be informed of such findings or kept unaware. It is essential for researchers to anticipate the potential discovery of incidental findings and pre-emptively establish protocols. This includes proactive steps like obtaining participant consent and subsequent actions such as ensuring confidentiality and communicating findings to participants.

In VOCORDER, the project's activities will be governed by the following minimum set of rules regarding the incidental findings.

Frist, these incidental findings will be immediately referred the project's responsible partner for the clinical study (MITERA) and only if necessary to the Advisory Board members and the Internal Ethics Committee (IEC). They will assess their ethical ramifications and determine the appropriate course of action.

The following guidelines will govern the incidental findings:

a. Participants will provide informed consent to participate in the clinical study.

b. MITERA, the Scientific Board and the IEC will consider the deletion of any incidental findings.

c. The incidental findings will not be communicated to the participants.

The responsible partner for inspecting as well as guiding the consortium's partners regarding the project's ethical requirements/aspects will be VUB. These requirements may be revised and adjusted throughout the lifetime of the VOCORDER project.

Approval by Ethics Committee

Prior to the initiation of the clinical study which involves human participants, as well as of any pilot study, the responsible partner has obtained an ethics committee's approval. Any necessary authorization will also be sought for activities with ethical implications as required by national or EU law. The approval can be found in the present Deliverable (ANNEX 1).

To enhance oversight of ethical procedures throughout the project lifecycle, an IEC of VOCORDER will be established. This committee will play a dominant role in ensuring compliance to the ethical principle prescribed in legislation at all stages of the project, from protocol development to findings publication. Further, the committee will collaborate with local ethics committees in the six participating countries to address any participant complaints arising during the study. The IEC will be tasked with compiling and submitting safety and interim reports to the relevant national ethics committees when necessary.

Appointment of contact points for ethical and legal matters

In accordance with their respective activities and national regulatory framework, each partner involved in VOCORDER will appoint a Data Protection Officer (DPO) and/or designate a contact person responsible for addressing legal and ethical concerns related to the project's research activities.

Respect of ethical principles and relevant framework

It is essential to ensure that the VOCORDER follows its intended purpose and objectives strictly. All human subjects involved in the research must be treated equally, with due consideration given to any individual differences or special conditions. Participation of vulnerable groups should only occur if absolutely necessary for the research objectives, with appropriate measures in place to protect their rights. Evaluation of potential misuse of research findings is imperative, with measures in place to minimize any risk to participants. The physical and mental integrity of individuals will be respected and safeguarded throughout the research, with tailored attention to individual characteristics and vulnerabilities. Researchers will consistently demonstrate compliance with the clinical research protocol, which has been drafted and will be registered on the ClinicalTrials.gov data system and accountability is required in case of any possible violations. Processing of personal data must adhere to GDPR, with clear communication to data subjects regarding data processing purposes and storage duration. Special categories of data, especially medical data classified as sensitive, will be handled with extra care per GDPR guidelines, ensuring that data subjects' rights are respected and

data minimization principles are adopted. Robust security measures will be implemented to protect participants' data from unauthorized access. The privacy of research participants will be upheld, with individuals retaining control over their information. Confidentiality of disclosed information should be maintained, with disclosure permitted only for the project purposes and with the participant's prior consent.

To tackle the ethical challenges inherent in integrating AI into healthcare, the abidance the EU AI framework renders helpful. Since yet the AI Regulation has not entered into force, the project will follow the Ethics guidelines for trustworthy AI, introduced by the High-Level Expert Group on AI. They outline seven key ethical requirements applicable to various stakeholders; considerations for human oversight, technical robustness, privacy, transparency, diversity, non-discrimination, and societal wellbeing. Simultaneously, the WHO guidelines on Ethics & Governance of AI for Health, which underscore six more principles; protecting autonomy, promoting human wellbeing, ensuring transparency, fostering responsibility, ensuring inclusiveness, and promoting sustainability, will be examined.

Monitoring and reporting

Regular reports on ethics risk monitoring during project meetings will be provided. The formulation and distribution of an ethics questionnaire internally to the partners involved in the technical advancement is under consideration to ensure the alignment with the ethical requirements. The IEC will be responsible for addressing any question raised by the partners of the project at all instances and cooperate with the respective representative of legal and ethical matters defined by each entity. VOCORDER will assess its outcomes at all phases of the project implementation against these requirements to ensure comprehensive coverage.

2.5 Phases of the clinical study

The clinical study is *a prospective cohort study* and will be conducted in two phases:

- 1st Phase: Baseline phase (October 2024-August 2025)
- 2nd Phase: Validation phase – VOCORDED technology validation (May-December 2026)

2.5.1 Baseline phase

The implementation of this phase is considered necessary to define the basic operating parameters of the manufactured technology in order to allow the transition to the final validation of the device in the clinical field. The above objective will be achieved with the contribution of the artificial intelligence mechanism (WP.4) and the analysis of the raw data of the technological research teams involved in the design of the breath analyser. In this phase, patients and healthy controls are enrolled and the measurements of the gases produced are analysed using the GC-MS reference method.

2.5.2 Validation phase (VOCORDER validation phase)

During this stage, the VOCORDER technology undergoes clinical evaluation by both patients and healthy volunteers. The analysis involves measuring the gases emitted by the participants, utilizing both the standard reference method and the VOCORDER technology for comparison.

2.6 Diseases

The following diseases will be investigated:

1. Lung cancer
2. Gastric and colon cancer
3. Breast cancer
4. Kidney insufficiency
5. Infections - Pneumonia (community-acquired and hospital-acquired)

The selection of these diseases was based on the ETH team's review of existing literature (Task 2.1) and the subsequent adaptation of the findings to align with VOCORDER's capabilities to detect specific gas biomarkers for the early diagnosis of selected diseases (Task 2.2) **(ANNEX 2).**

2.7 Patients & Healthy control population

2.7.1 Healthy controls

At least 120 healthy controls of both sexes, aged between 20 and 75 years, who do not suffer from the diseases under investigation will be selected for participation in the study at the same time as the patients. At least 2-3 breath samples are expected to be taken from each prospective control on different days at the same time of day. The same

healthy controls will participate in both phases of the study, and the breath samples obtained will be analyzed using both methods.

The healthy volunteers are selected either from the hospital staff or from patients admitted to the hospital for another reason. The prospective controls will fill in a questionnaire with demographic and medical-history data after having been informed in detail (**ANNEX 6.part I**) about the study by the VOCORDER team of MITERA. The questionnaire **(ANNEX 4**) will be analyzed by the project team, and if it is concluded that the person can participate in the study, a consent form (**ANNEX 6.part II**) will be signed by the participant.

2.7.2 Patients population

2.7.2.1 Baseline phase

Patients: a total of 175 patients, 35 for each disease, aged 18-75 years of both genders, selected according to the following inclusion criteria:

1. Patients>18 years of age *of both genders*
2. They must be able to communicate and understand the information given to them by the MITERA staff.
3. Suffer from the disease under investigation.
4. The disease must be at the earliest possible stage, i.e., the patients must not yet have started treatment.
5. Patients should have no other serious comorbidities that affect the derived measurements. Patients will be selected in collaboration with the clinicians responsible for the treatment and/or hospitalisation of patients with the diseases under investigation.

Criteria 1, 2, and 3 are mandatory for enrollment in the study. For the enrollment of the patients in the study specific documentation of the disease should be available to the project team as following:

<u>For the cancer diagnosis is necessary to document the following:</u>

- The type of cancer is based on histopathological findings and specific indicators results.
- The stage of disease is based on radiological and hematological examinations.

<u>For the infections – pneumonia diagnosis is necessary to be determined the following:</u>

- The pneumonia diagnosis based on chest -X findings, clinical syndrome and the status of inflammatory indicators (day 1).
- The laboratory determination of the pathogen caused the clinical syndrome (if its possible to be isolated from clinical specimens)
- The clinical severity of the disease based on CURB 65/SMART COP score for patients with community or health acquired pneumonia respectively and Apache II for hospitalized patients in ICU.

For kidney insufficiency is necessary:

- Documentation of the Chronic Kidney Disease
- Determination of the disease stage according to CFR rates.
- Hemodialysis treatment

Exclusion criteria

- Lack of signed consent
- Lack of co-operation due to any reason
- Failure to follow the recommendations on the requirements prior to the breath sampling procedure
- Inability to provide a reliable breath sample
- Any treatment, specific diet, surgery, or other intervention having been initiated between obtaining samples for breath VOCs.

Once the patient has been informed (**ANNEX 6.part I**) by the MITERA team responsible for the project and has agreed to participate in the study, they must read and sign the relevant consent form for participation (**ANNEX 6.part II**). Similar questionnaires with the controls (data collection forms - **ANNEX 4**) will be completed for the patients participating in the study.

Sampling: At least two breath samples (1 L each) are taken from each patient under similar conditions and analyzed (e.g. on different days but at the same time of day). The breath samples will be analyzed in this phase using the reference method. In the final phase, they will be stored and analyzed using the VOCORDER method. The method of taking the breath sample will be according to the recommendations following the reference method (**ANNEX 3**).

2.7.2.2 Validation phase

Patients: The final phase of the clinical study will involve 100 patients, 20 for each disease. Patients will be selected according to the above criteria as in the baseline phase.

Sampling: Breath samples will be analyzed using both methodologies. At least two breath samples are taken from each patient under similar conditions and analyzed (e.g. on different days but at the same time of day). The method of taking the breath sample will be according to the recommendations following the reference method (**ANNEX 3**) and the VOCORDER-specific technical requirements.

Table 1 Description of the clinical phases

Clinical phases	**BASELINE PHASE**		**VALIDATION PHASE**	
Patients and healthy control population	Patients Group 1	Healthy controls	Patients Group 2	Healthy controls
Size of population (No)	175	120 (at least)	100	120
Methodology of breath analyses	SESI-MS and GC-MS reference method	SESI-MS and GC-MS reference method	SESI-MS and GC-MS reference method	SESI-MS and GC-MS reference method
			Vocorder technology	Vocorder technology

2.8 Methodology of breath analysis

During the initial baseline phase, the reference method of mass spectrometry will be used to analyze the exhaled breath of patients and healthy volunteers. Breath samples are collected in 1 L gas sampling bags and will be sent to the breath analysis laboratory at ETH Zurich for offline analysis **(ANNEX 3).**

In the subsequent validation phase, the clinical samples are analyzed using both methods, the VOCORDER technique and the reference method of mass spectrometry to ensure robust comparison and validation of the results.

2.9 Diseases and Data collection (AIDEAS, MITERA)

Furthermore, an extensive evaluation of risk factors for various health conditions reveals a complex interplay between genetic predisposition, environmental exposures, lifestyle choices, and underlying health conditions. For lung cancer, indisputably, the primary risk factor remains tobacco smoke, with about 85% of lung cancer cases being directly attributable to smoking, including secondhand smoke exposure (CDC, 2021). Radon exposure, occupational exposures to substances such as asbestos, certain metals, and diesel exhaust, as well as air pollution, further contribute to risk, alongside a family history of lung cancer (American Cancer Society, 2021).

Breast cancer's multifactorial etiology involves hormonal factors such as early menarche, late menopause, and hormone replacement therapy, combined with lifestyle factors like alcohol consumption, physical inactivity, and obesity. Genetic factors play a significant role, with mutations in the BRCA1 and BRCA2 genes markedly increasing risk. Furthermore, reproductive history, including age at first childbirth and breastfeeding, influences risk profiles (National Breast Cancer Foundation, 2021).

Gastric cancer risk is intricately connected to diet, Helicobacter pylori infection, smoking, and family history. The International Agency for Research on Cancer (IARC) recognizes H. pylori as a class I carcinogen for gastric cancer. Additionally, a diet rich in smoked foods, salted fish and meat, and pickled vegetables is associated with higher rates of gastric cancer, especially in regions like East Asia where these foods are dietary staples (World Cancer Research Fund, 2020).

Chronic kidney disease (CKD) and kidney insufficiency arise from conditions such as diabetes and hypertension, which are responsible for up to two-thirds of cases. Other risk factors include a family history of kidney disease, age over 60, and ethnicity, with African Americans, Native Americans, and Asian Americans at increased risk. Chronic use of NSAIDs and exposure to contrast dyes in imaging also pose risks (National Kidney Foundation, 2021).

Infections like pneumonia are influenced by an individual's immune status, with the very young, the elderly, and immunocompromised individuals being particularly susceptible. Environmental factors such as air quality, smoking, and exposure to respiratory irritants are essential, as are chronic respiratory diseases like asthma and Chronic obstructive pulmonary disease (COPD). Seasonal influenza can predispose individuals to bacterial pneumonia, illustrating the interrelationship between viral and bacterial infections (CDC,

2021). Understanding these risk factors is crucial for the development of preventive strategies, early detection methods, and the formulation of public health policies aimed at mitigating the impact of these diseases.

In conclusion, our comprehensive questionnaire will integrate a broad spectrum of demographic information and medical history details to assess the participant's health profile thoroughly. Demographic data such as age, gender, race/ethnicity, income, education level, occupation, marital status, and geographic location will offer a contextual background for individual health statuses. Medical history inputs, including weight, height, BMI, smoking habits, alcohol consumption, dietary habits, physical activity levels, comorbidities, and a detailed record of chronic diseases, infections, medication use, surgeries, and hospitalizations will provide a deeper insight into each participant's health risks. Additionally, we will assess psychological factors like depression and anxiety, as well as environmental and lifestyle influences such as occupational exposures, genetic predispositions, sleep patterns, and stress levels. This data will enable us to identify correlations and patterns that may contribute to disease prevalence and outcomes, as well as to the detected VOCs concentrations from the breath analyses. In addition, the concentrations of molecules produced by these diseases might vary due to endogenous processes such as the circadian rhythm or the health status of the subjects or due to additional external factors such as medication, usage of cosmetic products, or physical exercise. These factors will, where possible, be monitored.

2.10 Collection and uploading of clinical data.

The data will be collected by the MITEPA project team and stored in a computerised working folder within the hospital. The folder is only accessible to the MITERA project team. The patient-related data will then be anonymized and entered into a specially developed database shared with the other partners - authorized users **(ANNEX 6).** The database also includes the results using both methodologies.

2.11 Ensuring data protection.

The protection of the personal data of the patients participating in the study will be ensured within the framework of Greek legislation, the relevant European GDPR and the MITERA hospital regulations **(ANNEX 6)**.

2.12 Statistical Analysis planning and sample size calculation (ICCS)

According to the needs of the VOCORDER project a statistical analysis from the high-resolution spectra from breath samples data will be provided in Task 4.2. This analysis will utilize several AI techniques of different technologies for differentiating between classes of samples in terms of health-related latent properties, moreover, this automated process will identify correlations and dependencies among the selected diseases parameters, individual biomarker [1] bands and descriptors from the recorded data.

For the successful design approach and analysis of the clinical samples it is necessary to investigate the state-of-the-art approaches. Table 2 summarizes the reported Volatile Organic Compounds (VOCs) for the VOCORDER's diseases. VOCs can be used for detecting the VOCORDER's diseases based on statistical analysis using several kinds of machine learning algorithms (i.e., unsupervised, supervised, semi-supervised, and XAI) [2]. The following paragraphs of this section provide information about the current state-of-the-art machine learning approaches. The literature's described approaches will be used as prior knowledge for designing the machine learning models for the VOCORDER project after the successful collection of the clinical samples.

Table 2 Exhaled breath volatile organic compounds for the VOCORDER diseases.

Diseases	Reported Volatile Organic Compounds	Reference
Lung Cancer	Isopropanol Acetone Pentane Benzene	[3]
Gastric and Colon Cancer	Propanal Acetamide Isoprene 1,3-Propanediol Ethylene Methyl Isobutyl Ketone Acetic Acid m- Toluyl Aldehyde 1,2,5 Trimethylbenzene	[4]

Breast Cancer	(S)-1,2-propanediol Cyclopentanone Ethylene Carbonate 3-Methoxy-1,2-Propanediol 3-Methylpyridine Phenol Tetramethylsilane	[5]
Kidney Insufficiency	Cyclohexanol 3-Hydroxy-2-Butanone 3-Methyl Butanal Dimer of isoprene	[6]
Infections-Pneumonia	Methanol Acetaldehyde Propiolonitrile 2-Choloropyridine	[7]

2.12.1 Unsupervised AI Models

Unsupervised AI Principal Component Analysis (PCA) has been investigated as a solution to the detection of cancer from breath samples. In the work of Maiti et al. [8], it is discussed a case study of 63 volunteers composed of healthy and non-healthy samples, among them patients with kidney cancer, bladder cancer, and prostate cancer. Their data collection was based on laser-free broadband mid-infrared Fourier-transform spectroscopy for detecting cancer-sensitive metabolites gases (i.e., ethyl vinyl ketone, acetaldehyde, methyl butyrate, etc.). Their analysis, supported by supervised methods, indicated that these methodologies can be utilized for cancer detection. However, further research is required.

A similar research has been applied in the work of Aslam et al. [9]. In this case they investigated the diagnosis of early-stage gastric cancer based on unsupervised deep learning. They propose an innovative method for feature extraction based on a stacked sparse autoencoder for extracting discriminative features from unlabeled data of breath samples. Their results indicate that deep-stacked sparse autoencoder neural networks are able to achieve an overall accuracy of 98.7% for advanced gastric cancer classification and 97.3% for early gastric cancer detection using breath analysis.

The study by Alkhalifah et al. investigated cancer detection through VOCs analysis, analyzing 74 clinical breath samples using Gas Chromatography Mass Spectrometry from participants [10]. They propose an unsupervised clustering technique named VOCCluster for measuring mass spectra similarities of VOCs. Their work resulted in the VOCCluster approach achieving better scores compared to state-of-the-art algorithms such as DBSCAN and OPTICS.

2.12.2 Supervised and Semi-supervised AI Models

Supervised-based machine learning can be used as well for cancer detection. Begum et al. [11] investigates the identification of Leukemia based on cancer biomarkers. For their analysis, they considered Naive Bayes (NB), K-Nearest Neighbors (KNN) and Support Vector Machines (SVMs) algorithms for supervised learning. Their experimentation was performed by changing the size of the training set (i.e., used train sized of 20, 33 and 48 samples) and 33 samples for the test size. In all cases, the SVM algorithm scores were better than the other algorithms, however the authors concluded that future studies are necessary.

Zhou et al. [12] investigated the detection of Lung Cancer from 236 breath samples (176 healthy and 60 patients) using supervised learning. Each sample is composed of 308 features extracted from the chromatogram, while their experimental setup was based on the gradient boost decision trees algorithm. Using these parameters, they achieved an accuracy of 85% evaluated with 6-fold cross validation. Based on statistical bootstrap analysis 72% of the sampled are marked as “confident” with 93% accuracy of the confident samples in cross-validation.

Finally, semi-supervised machine learning has been applied effectively in the detection of lung-related diseases like SARS-CoV-2 [13]. Moreover, in the work of Shi et al. [14] it is proposed a semi-supervised deep transfer learning approach for detecting lung nodules that indicate lung cancer. These studies demonstrate the feasibility of using both supervised and semi-supervised learning methods for the detection of diseases based on breath analysis. However, all the aforementioned works concluded that further research is necessary to improve these technologies and provide a working solution capable of being used for medical treatment.

2.12.3 The VOCORDER's statistical analysis planning

The VOCORDER project aims to develop a device for the detection of several breath related diseases. To enable the detection and classification of these diseases, the project will explore a range of models, including supervised, unsupervised, and semi-supervised approaches. In addition, the VOCORDER project will utilize explainable AI [15], [16], [17] technology for trying to maximize the accuracy of the final models. At this stage, it is premature to detail specific statistical analyses due to the absence of measurements.

According to the literature, one viable strategy involves employing advanced classification techniques such as SVM, K-NN, NB, or Decision Trees to explore disease detection. A novel approach includes advanced artificial intelligence models, such as LSTM or CNN-based models. Explainable AI methods will also be applied not only to assess the likelihood of a disease but to elucidate the rationale behind the AI model's conclusions.

2.12.4 Sample size calculation

In VOCORDER's project endeavor to construct unbiased machine learning models to diagnose various diseases, we have meticulously calculated the requisite sample size, adhering to stringent statistical criteria. To analyze separate two-class problems, such as distinguishing between healthy individuals and those suffering from a specific disease, our objective is to achieve a sensitivity and specificity of at least 90%. This ambition necessitates a minimum of 35 subjects per class, underpinning the study with a confidence level of 95% and a margin of error set at 10%. While this margin exceeds the typically recommended 5% for disease-related research, it serves as our preliminary standard. With the inclusion of four distinct diseases in our study, the requirement escalates to a minimum of 35 subjects for each disease category. Furthermore, to reflect the demographic disparities in disease occurrence, such as the higher prevalence of breast cancer among women, the group of healthy participants needs to be significantly larger. This strategic sample size determination is pivotal for the successful development of unbiased and effective machine learning models.

3. CONCLUSIONS

With the specific design of this clinical study, we aim to achieve significant results regarding the evaluation of this new breath analysis technology, as well as the reference

method. The technologies for breath analysis will be evaluated at a clinical level in patients with diseases that cover a significant portion of human pathology, such as malignancies (lung, breast, and gastro and colon cancer), chronic and acute diseases (chronic Kidney Insufficiency and infections). The main goal of the clinical study is to take a step forward in the implementation of breath analysis technology in clinical practice using practical and user-friendly applications. The potential risks that may arise are mainly related to the possibility of not being able to complete the necessary number of patients per disease, which may lead to statistically significant results. Nonetheless, efforts will be made to supplement this patient number and to obtain as many breath samples for analysis as possible.

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ANNEX 1: SELECTED BIOMARKERS PER DISEASE (ETH)

ΜΗΤΕΡΑ
ΙΔΙΩΤΙΚΗ ΓΕΝΙΚΗ, ΜΑΙΕΥΤΙΚΗ-ΓΥΝΑΙΚΟΛΟΓΙΚΗ & ΠΑΙΔΙΑΤΡΙΚΗ ΚΛΙΝΙΚΗ Α.Ε.
ΗΜΕΡ. ΠΑΡΑΛΑΒΗΣ: 4/3/2024
ΑΡ. ΠΡΩΤΟΚΟΛΛΟΥ: 3716/1

Προς: **Επιστημονικό Συμβούλιο**

Θέμα: **Διενέργεια κλινικής μελέτης στο πλαίσιο του ευρωπαϊκού προγράμματος Vocorder- Towards the ultimate breath analysis -based continuous healthcare.**

Αξιότιμα μέλη του Επιστημονικού Συμβουλίου,

Το ΜΗΤΕΡΑ συμμετέχει στο ευρωπαϊκό πρόγραμμα (HORIZON) με τίτλο *Vocorder-Towards the ultimate breath analysis -based continuous healthcare* στο πλαίσιο του οποίου περιλαμβάνεται η διενέργεια κλινικής μελέτης. Στόχος του προγράμματος είναι η παραγωγή μιας εύχρηστης, φορητής συσκευής ανάλυσης της αναπνοής για τη διάγνωση/πρόγνωση συγκεκριμένων ασθενειών. Με την προτεινόμενη κλινική μελέτη στοχεύουμε στην αξιολόγηση της λειτουργίας της συσκευής που θα παραχθεί. Επιπλέον, η μελέτη αυτή αποτελεί μια σημαντική ευκαιρία ανάδειξης του ρόλου του ΜΗΤΕΡΑ και στο ερευνητικό πεδίο.

Για την κατανόηση του πλαισίου μέσα στο οποίο θα υλοποιηθεί η κλινική μελέτη ακολουθούν βασικές πληροφορίες για το έργο Vocorder:

Project name	Towards the ultimate breath analysis -based continuous healthcare
Project acronym	VOCORDER
Project Coordinator	MITERA
Call	HORIZON-EIC-2022-PATHFINDERCHALLENGES-01
Granting authority	European Innovation Council and SMEs Executive Agency
Project starting – end date	1 October 2023 - 31 March 2027 (42 Months)

Το VOCORDER στοχεύει στην ανάπτυξη καινοτόμων εξαρτημάτων αξιοποιώντας ανατρεπτικές τεχνολογίες απαραίτητων για την κατασκευή μιας αποτελεσματικής, φορητής και εύχρηστης και αξιόπιστης συσκευής ανάλυσης της αναπνοής. Το έργο αξιοποιεί πρόσφατες εξελίξεις στα λέιζερ μέσης υπέρυθρης ακτινοβολίας (mid-infrared lasers) για να αναπτύξει έναν αναλυτή αναπνοής πολλαπλών ειδών (αερίων) που μπορεί σε 5 sec με τη χρήση επεξεργασίας σήματος βασισμένης στην τεχνητή νοημοσύνη να συμπεράνει την κατάσταση της υγείας του ατόμου. Η εκπνεόμενη αναπνοή αποτελεί μια πολύ χρήσιμη πηγή καθώς μπορεί να ληφθεί σε μεγάλες ποσότητες, πρακτικά και ανώδυνα, περιέχει περισσότερες από 1.000 ουσίες οι οποίες μπορούν να χρησιμεύσουν ως αποτελεσματικοί βιοδείκτες, η μέτρηση της συγκέντρωσης των οποίων μπορεί να παρέχει μια σαφή πρόβλεψη της κατάστασης της υγείας του ατόμου, ενώ η διάγνωση ορισμένων ασθενειών ή παθολογικών διεργασιών στο ανθρώπινο σώμα μπορεί να προληφθεί έγκαιρα.

Στο Vocorder, το ΜΗΤΕΡΑ, κατέχει διευρυμένο ρόλο καθώς εκτός από την κλινική μελέτη έχει αναλάβει και το ρόλο του project coordinator από τον οποίο απορρέει η ευθύνη της παρακολούθησης των εργασιών για την επίτευξη των στόχων του έργου όπως έχει συμφωνηθεί με την Ευρωπαϊκή Ένωση.

ΒΑΣΙΛΕΙΟΣ ΣΙΟΥΛΑΣ
ΠΡΟΕΔΡΟΣ ΕΠΙΣΤΗΜΟΝΙΚΟΥ ΣΥΜΒΟΥΛΙΟΥ «ΜΗΤΕΡΑ»

Εγκρίνεται.
5/3/2024

Αναλυτικές πληροφορίες για το έργο περιλαμβάνονται στο επισυναπτόμενο αρχείο Grant Agreement.

Κλινική Μελέτη αξιολόγησης λειτουργίας της συσκευής VOCORDER

Η αξιολόγηση της συσκευής που θα παραχθεί στο πλαίσιο του προγράμματος VOCORDER για την ανάλυση της αναπνοής θα υλοποιηθεί στο νοσοκομείο ΜΗΤΕΡΑ. Πρόκειται για μία προοπτική μελέτη ασθενών – μαρτύρων. Δεν πρόκειται για παρεμβατική μελέτη και γι αυτό το λόγο ο κίνδυνος που προκύπτει για τους συμμετέχοντες είναι μηδενική.

Η κλινική εφαρμογή της συσκευής θα υλοποιηθεί σε δύο φάσεις, σε μία προκαταρκτική (baseline M13-M23) φάση και στην τελική κύρια φάση αξιολόγησης της συσκευής (intervention phase M33-M39). Στην πρώτη φάση τα δείγματα που θα παρθούν από τους συμμετέχοντες θα αναλυθούν με την μέθοδο αναφοράς Mass Spectromentry (MS) ενώ στην δεύτερη φάση η ανάλυση θα υλοποιηθεί και με τις δύο μεθόδους δηλαδή με την αναφοράς (MS) και με τη μέθοδο VOCORDER. Η αναγκαιότητα υλοποίησης της πρώτης φάσης προκύπτει από το γεγονός ότι απαιτούνται δεδομένα (κλινικά και εργαστηριακά για την ανάπτυξη των απαραίτητων ηλεκτρονικών βάσεων δεδομένων και αλγόριθμων τεχνητής νοημοσύνης βάσει των οποίων θα λειτουργήσει και η αξιολόγηση των παραγόμενων δεδομένων (VOCs) της συσκευής. Στην μελέτη θα συμμετάσχουν ασθενείς και υγιείς μάρτυρες από τους οποίους θα παρθούν τα δείγματα αναπνοής.

Τα νοσήματα που έχουν επιλεγεί να μελετηθούν είναι ο καρκίνος πνεύμονα, ο καρκίνος στόμαχου και παχέος εντέρου, ο καρκίνος μαστού, η χρόνια νεφρική ανεπάρκεια και οι οξείες λοιμώξεις κοινότητας ή συνδεόμενες με χώρους παροχής υγείας. Η επιλογή των νοσημάτων βασίστηκε στην μελέτη της υπάρχουσας βιβλιογραφίας για τους βιοδείκτες που συνδέονται με τη διάγνωση των διαφόρων νοσημάτων αλλά και με τη δυνατότητα της προς μελέτη συσκευής να ανιχνεύσει τα συγκεκριμένα αέρια-μόρια μέσω της ανάλυσης της αναπνοής.

Ο συνολικός αριθμός ασθενών να συμμετάσχει στην μελέτη ανά φάση είναι 175 στην 1η φάση και 100 στην 2η φάση. Ο αριθμός των υγειών μαρτύρων αφορά άτομα ηλικίας από 20-75 ετών και των δύο φύλων και υπολογίζεται τουλάχιστον στα 120 άτομα. Τα κριτήρια συμμετοχής των ασθενών και των υγειών μαρτύρων είναι καθορισμένα και η διαδικασία συμμετοχής τους είναι πλήρως εναρμονισμένη με το ευρωπαϊκό, εθνικό αλλά και τοπικό πλαίσιο περί ηθικής και δεοντολογίας καθώς και προστασίας προσωπικών δεδομένων. Οι συμμετέχοντες αφού ενημερωθούν λεπτομερώς από την ομάδα έρευνας του ΜΗΤΕΡΑ θα υπογράφουν σχετική φόρμα συγκατάθεσης. Τα δεδομένα των ασθενών θα καταχωρούνται κωδικοποιημένα από το προσωπικό του ΜΗΤΕΡΑ σε βάση δεδομένων του προγράμματος. Στην πλήρη βάση δεδομένων η οποία θα φυλάσσεται στο νοσοκομείο θα έχει πρόσβαση μόνο το προσωπικό του ΜΗΤΕΡΑ. Στην ανωνυμοποιημένη – κωδικοποιημένη βάση δεδομένων του προγράμματος θα έχουν πρόσβαση πιστοποιημένοι συνεργάτες.

Οι λεπτομέρειες του σχεδιασμού της κλινικής μελέτης περιγράφεται στο αντίστοιχο παραδοτέο του υποέργου (WP2- T2.3 Design of clinical settings validation for VOCORDER) το οποίο θα ολοκληρωθεί μέχρι τέλος Μαρτίου 2024 και θα αποσταλεί στο Επιστημονικό Συμβούλιο προς ενημέρωσή του.

Η Ομάδα έρευνας του ΜΗΤΕΡΑ για την υλοποίηση της κλινικής μελέτης συντονίζεται από την ιατρό Φλώρα Κοντοπίδου. Στην ερευνητική ομάδα θα συμμετάσχουν επιπλέον ένας επαγγελματίας υγείας και ένας διοικητικός υπάλληλος του ΜΗΤΕΡΑ.

Η έγκριση της μελέτης από το Επιστημονικό Συμβούλιο του νοσοκομείου αποτελεί βασική προϋπόθεση υλοποίησής της. Επιπλέον, η επιτυχής διεξαγωγή της απαιτεί την συνεργασία διάφορων ιατρικών κλινικών ειδικοτήτων ώστε να επιτευχθεί ο στόχος της συμμετοχής του απαραίτητου αριθμού ασθενών. Για όλους τους παραπάνω λόγους η έγκριση και στήριξη του Επιστημονικού Συμβουλίου σε αυτό το εγχείρημα είναι μέγιστης σημασίας.

Είμαστε στη διάθεσή σας για οποιεσδήποτε περαιτέρω διευκρίνηση.

Εκ μέρους της ομάδας έρευνας έργου VOCORDER,

Ζωή Ζαχαρούλη

Project Office Manager

ANNEX 2: SELECTED BIOMARKERS PER DISEASE (ETH)

This section's table presents a selection of Volatile Organic Compounds (VOCs) associated with specific diseases, chosen for testing in a clinical environment. The selection process for these biomarkers was informed by previous research, taking into account factors such as the number of patients and control subjects involved in the studies, the analytical methods employed, the identified biomarkers, their concentrations, and the reported specificities and sensitivities.

Table 3 Biomarkers per disease

	Lung cancer	Gastric/Colon cancer	Breast cancer	Kidney insufficiency	Infections - Pneumonia
Acetone	X	X		X	X
Ammonia				X	
Ethanol	X			X	
Ethylene		X	X	X	
Isoprene	X	X	X	X	
Methanol	X		X		X

ANNEX 3: BREATH SAMPLE COLLECTION AND ANALYSIS (ETH)

Breath measurements. Chemical analysis of exhaled breath will be carried out using a state-of-the-art instrument based on a secondary electrospray ionization (SESI) source purchased from Fossil Ion Technology SL, coupled with a high-resolution mass spectrometry (HR-MS) system (Q Exactive Orbitrap, ThermoFisher Scientific). SESI-MS is a well-established and robust analytical technology especially developed for in-depth breath characterization. Its applicability has already been demonstrated in clinical studies previously published by ETH Zurich. In addition, an orthogonal method based on gas chromatography coupled with mass spectrometry (GC-MS) will be used to elaborate on breath component identification.

Breath sampling will be performed using Tedlar gas sampling bags. The participants will be requested to exhale into two 1 L gas sampling bags and fill up to 80 % of their capacity. The collected breath samples will be transferred to the lab for analysis using SESI-MS and GC-MS.

During an off-line breath measurement using SESI-MS, a sampling bag desampling system allows collected breath molecules to pass through a short-length heated sample transfer line into the ionization chamber. In the SESI chamber, a high voltage is applied to a working solution (primary electrospray solvent – in our case, formic acid 0.1% in water) to generate a mist of charged droplets that interacts with breath molecules for charge transfer and ionization. The produced charged breath molecules are then introduced into the mass analyzer for mass-to-charge separation and detection. Measurements are carried out both in the positive and negative ion mode, which facilitates the determination of protonated and deprotonated species, respectively. The sample transfer line and the ionization chamber are continuously heated to prevent water condensation and absorption of low-volatility metabolites on the walls. During measurements, a nano-ampere meter is used to monitor the stability of the electrospray. Mass calibration and tuning of the system in both ionization modes are performed once per week or more often if required. The stability of the whole system is monitored daily by introducing gaseous standards (e.g., acetone) at known concentrations using a gas standard generation system that additionally allows quantification calculations of target metabolites. Mass spectra are recorded in the entire mass range of interest and individual mass windows covering different *m/z* ranges. The mass windows are then stitched together using built-in-house preprocessing algorithms. This approach has been specifically developed and optimized to expand analytical capabilities regarding the number of features that can be detected by the mass analyzer and for sensitivity enhancement.

The real-time measuring capabilities and the non-invasive characteristics of the SESI-MS allow time-resolved biological and metabolic responses to stimuli of interest. SESI-MS operates at ambient pressure and does not suffer from fragmentation issues (as high energies are not involved), enabling tandem mass spectrometric (MS^2) analysis and reliable compound identification. It is characterized by operational simplicity, high resolving power (240,000), high mass accuracy, outstandingly high sensitivity (detection limits down to sub ppt), and low limits of quantification (LOQ). In addition, SESI allows the analysis of high molecular weight compounds (up to 1000 Da) with high polarity, delivering clear molecular discrimination and identification in the mass region of our interest.

For offline breath analysis using GC-MS, breath samples collected in 1L bags will be transferred to stainless-steel tubes filled with absorbent materials using a portable mini

gas pump. The tubes will then be sealed and stored in a refrigerator until they are transported to the laboratory. There, the samples will undergo analysis with a standard thermal desorption system linked to a GC-MS. For future use, the samples will be stored at a temperature of -80°C.

High-resolution MS. Orbitrap technology is a valuable tool in the chemical analysis of complex samples with unknown compositions. An advantage of using high-resolution MS is that many different compound classes can be detected where prior knowledge of chemical content is not necessary. Its large dynamic range enables the measurement of both low-level and abundant compounds that may be present, given sufficient ionization efficiency. Molecular formulae of detected features can be generated by using high mass accuracy and isotopic abundance ratios. At the same time, structural information can be revealed by dissociating the compound with tandem MS.

Identification of metabolites. A strategic feature of the Orbitrap is the possibility to obtain tandem mass spectra (MS^2) for selected ions through collision-induced dissociation. This feature undoubtedly increases the chemical specificity of the instrument allowing the distinction between isomers, important for molecular identification and quantification. On the other hand, MS^2 provides a robust means to interrogate the compounds' functional groups. This is essential for better comprehension of important physical and chemical properties of detected features, such as volatility. Representative databases for compounds' identification include METLIN MS^2 (http://metlin.scripps.edu), the Human Metabolome Database (HMDB, http://www.hmdb.ca), and the Madison Metabolomics Consortium Database (MMCD; http://mmcd.nmrfam.wisc.edu/).

Quantification of breath metabolites. Quantification of selected exhaled breath metabolites of interest is of major importance, and it is associated with analytical performance, accuracy, reproducibility, linearity, reliability, and stability. To quantify detected exhaled breath metabolites (e.g., acetone, isoprene, etc.), we will utilize a range of built-in-house or commercial systems for the controllable generation of gaseous standards in a chemical environment simulating human exhaled breath. Our first device is a reference gas system based on the controlled mixing of streams of gases (analyte of interest and dilution gas) stored in gas cylinders and of humid air developed at the ETHZ. The second gas standard production device is built in-house and is based on the controlled evaporation of a liquid analyte and its diffusion into a controlled humidity

carrier gas stream. This system contains multiple evaporation chambers, allowing the independent and simultaneous generation of gas standards from individual compounds or multi-component mixtures in a fully automated and programmable way. This system expands the generation range of gas standards from any volatile and semi-volatile organic compound in the liquid phase, replacing the need for multiple gas cylinders and enabling great control over accurate gas mixing. Finally, our third calibration system is a modified commercial calibration gas generator based on permeation tubes technology (OVG-4, Owlstone Medical Ltd, UK). The different systems for generating traceable gaseous standards allow our quantification methodology to flexibly adapt and achieve different concentration levels of metabolites of interest (from low ppt to high ppm), enhancing further standardization of breath analysis procedures and establishing an essential component for the on-line calibration of breath sensors.

ANNEX 4 : VOCODER'S QUESTIONNAIRE (AIDEAS, MITERA)

Demographics	
Age	The current age, considered as a continuous variable
Gender	Male, female, or other gender identities
Race/Ethnicity	Categorized according to racial or ethnic backgrounds
Income	Yearly income
Education Level	The highest degree or level of school completed
Occupation	The type of profession or job held
Marital Status	Includes single, married, divorced, widowed, etc.
Number of pregnancies	For female
Geographic Location	Urban vs. rural
Accommodation in nursing home or hospitalization in a Long-term facility	Yes/No
Medical history	
Weight	Current Body Weight
Height	Current height
BMI	Body Weight, Height and Composition
Smoking	Yes/No
Alcohol Consumption	Yes/No
Balanced nutrition	Yes/No
Physical Activity	Yes/No
Co-morbidities	Yes/No
Chronic Diseases	The presence of conditions like hypertension, diabetes, or autoimmune diseases
Chronic Disease of lung	Yes/No
COVID -19	The last positive Rapid or molecular test for SARS-CoV2

Post- COVID syndrome	Yes/No
Chronic Infections	Past infections that can influence current health status, such as HIV or hepatitis, tuberculosis etc.
Medication Use	Long-term use of certain medications can have adverse effects
Previous antimicrobial treatment	Last 6 months
Known acquisition from pathogens of interest	MDROs, fungi, virals,
Surgeries or Hospitalizations	Previous surgeries and previous hospitalization their outcomes
Depression	Yes/No
Anxiety	Yes/No
Occupational Exposures	Exposure to certain chemicals or environments can increase risk for diseases
Genetic Predisposition	A family history of certain conditions
Sleep Patterns	Poor sleep or not
Stress Levels	Existence of chronic stress
Current medical status – hospitalization	
Breast Cancer	Yes/No
Lung cancer	Yes/No
Gastric and colon cancer	Yes/No
Kidney insufficiency	Yes/No
Pneumonia	Yes/No
Suspected case of COVID-19?	Yes/No
The patient is hospitalized?	Yes/No
If yes, in which clinical ward	……
Date of admission	_/_/_

ANNEX 5. A DATA PROTECTION FRAMEWORK (VUB)

Table 4 Relevant Data Protection Legislation for VOCORDER

Council of Europe (CoE)	
ECHR (Article 8)	Right to respect for private and family life, home and correspondence
1. Everyone has the right to respect for his private and family life, his home and his correspondence. 2. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic wellbeing of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others.	
Convention 108 and 108+	Data Protection
The Convention 108, established in 1981, is the first binding international treaty addressing data protection. It applies to both public and private sector data processing across all CoE member states. In 2018, Convention 108 was updated (Convention 108+) to address contemporary challenges posed by the digital era and globalised data processing operations, aiming to enhance the security of personal data exchanges.	
European Union (EU)	
Charter of Fundamental Rights and the Treaty on the Functioning of the European Union (Article 8)	Right to protect personal data
1. Everyone has the right to the protection of personal data concerning him or her. 2. Such data must be processed fairly for specified purposes and on the basis of the consent of the person concerned or some other legitimate basis laid down by law. Everyone has the right of access to data which has been collected concerning him or her, and the right to have it rectified. 3. Compliance with these rules shall be subject to control by an independent authority.	
GDPR	Rules on the processing of personal data
The GDPR, enacted in May 2018, serves as the principal legal framework safeguarding individuals' personal data and its free movement within the European Union, replacing Directive 95/46/EC. It applies to both automated and non-automated processing activities involving personal data within the EU, regardless of where the processing occurs, ensuring protection for EU residents' data. However, the regulation excludes non-personal data, data of deceased persons or legal entities, and personal data processed for purely personal reasons or within households without professional or commercial ties.	

In addition to legal provisions, the European Union's independent bodies, namely the European Data Protection Supervisor (EDPS) and the European Data Protection Board (EDPB), offer crucial guidance for the implementation of data protection laws. The EDPS functions as the EU's autonomous authority on data protection, with key responsibilities including supervising personal data processing by EU institutions, providing advisory services on data protection matters, and monitoring new technologies concerning data protection issues. Similarly, the EDPB, established by the GDPR, serves as an independent European entity aiming to ensure consistent application of data protection regulations across the EU and fostering cooperation among data protection authorities.	
Opinions	
EC, Green paper SWD (2014)	European Commission Green Paper on mobile Health ("mHealth")
EDPB 3/2019	EDPB Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR)
EDPB2021	A Preliminary Opinion on data protection and scientific research
EDPS 2020	Response to the request from the European Commission for clarifications on the consistent application of the GDPR, focusing on health research
Recommendations	
Recommendation No. R (97) 5	Council of Europe, Committee of Ministers, Recommendation No. R (97) 5 on the Protection of Medical Data
CM/Rec (2019) 2	Council of Europe Recommendation CM/Rec (2019)2 of the Committee of Ministers to member States on the protection of health-related data
EDBP R01/2020	Recommendations 01/2020 on measures that supplement transfer tools to ensure compliance with the EU level of protection of personal data (Version 2.0)
Guidelines	
WP251	Article 29 Guidelines on Automated individual decision-making and Profiling for the purposes of Regulation 2016/679

WP259	Article WP29 Guidelines on consent under Regulation 2016/679
EDPB 01/2019	EDPB Guidelines 1/2019 on Codes of Conduct and Monitoring Bodies under Regulation 2016/679
EDPB 04/2019	EDPB Guidelines 4/2019 on Article 25 Data Protection by Design and by Default
EDPB 03/2020	EDPB Guidelines 03/2020 on the processing of data concerning health for the purpose of scientific research in the context of the COVID-19 outbreak
EDPB 05/2020	EDPB Guidelines 05/2020 on consent under Regulation 2016/679
EDPB 07/2020	EDPB Guidelines 07/2020 on the concepts of controller and processor in the GDPR
EDPB 10/2020	EDPB Guidelines 10/2020 on restrictions under Article 23 GDPR
EDPB 01/2021	EDPB Guidelines 01/2021 on Examples regarding Data Breach Notification
AEPD-EDPS	10 misunderstandings related to anonymization
EDPB-EDPS 5/2021	EDPB-EDPS Joint Opinion 5/2021 on the proposal for a Regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (Artificial Intelligence Act)
EDPB-EDPS 03/2022	EDPB-EDPS Joint Opinion 03/2022 on the Proposal for a Regulation on the European Health Data Space
National Legislations	
Greece	
Greek Constitution (Article 9A)	All persons have the right to be protected from the collection, processing and use, especially by electronic means, of their personal data, as specified by law. The protection of personal data is ensured by an independent authority, which is

	constituted and operates as specified by law.
Law 4624/2019	Measures for implementing Regulation (EU) 2016/679 and transposition of Directive (EU) 2016/680
Hellenic Data Protection Authority ('HDPA') is the competent national regulatory authority and is entitled to supervise the application of data protection rules in Greece.	
Germany	
German Federal Data Protection Act ('BDSG')	Measures for implementing Regulation (EU) 2016/679
Germany has 17 different Data Protection Authorities. The Federal Data Protection Authority is primarily in charge of Federal public entities. The rest 16 data protection authorities preside over private organizations operating in their jurisdiction, within each Federal State.	
France	
French Act No. 2018-493 of 20 June 2018 and Ordinance No. 2018-1125 of 12 December 2018	Measures for implementing Regulation (EU) 2016/679
The French data protection authority (the Commission nationale de l'informatique et des libertés, 'CNIL') acts as the French supervisory authority for data protection issues.	
Belgium	
Act of July 30, 2018 on the Protection of Natural Persons with Regard to the Processing of Personal Data	Measures for implementing Regulation (EU) 2016/679
The Belgian DPA replacing its predecessor, the Privacy Commission, was established by the Act of December 3, 2017, Establishing the Data Protection Authority.	
Lithuania	
Law No. XIII-1426 of 30 June 2018	Law on Legal Protection of Personal Data
The State Data Protection Inspectorate ('VDAI'), is the Lithuanian authority responsible for data protection issues.	
Estonia	
Personal Data Protection Act and Personal Data Protection Implementation Act 2018	Measures for implementing Regulation (EU) 2016/679

The body responsible for enforcing the data privacy legislation in Estonia is the Data Protection Inspectorate (‘DPI’).	
Switzerland	
Federal Act on Data Protection of 25 September 2020 (‘FADP’) and Ordinance on the Federal Act on Data Protection	General Data Protection Framework (aligned with GDPR, the Council of Europe's Modernised Convention for the Protection of Individuals with Regard to the Processing of Personal Data and Directive (EU) 2016/680)
The Federal Data Protection and Information Commissioner (‘FDPIC’) supervises businesses, organisations, and Federal public authorities' compliance with their respective obligations under the FADP and the Ordinance. The data protection supervisory authorities of the Cantons supervise the data processing activities of Cantonal and communal authorities in accordance with the Cantonal data protection acts.	

Handling personal data in VOCORDER

Under EU data protection legislation, only personal data falls within the scope of data protection regulations. Researchers collecting personal data (‘data about individuals’) must adhere to the relevant data protection pieces of legislation. Hence, as an initial measure to ascertain the legal duties and liabilities of the consortium regarding data protection, it is essential to pinpoint the categories of data undergoing processing. The following three categories can be identified:

- **Personal Data** (Article 4(1) and Recital 26 GDPR): Personal data means any information relating to an identified or identifiable natural person. Put simply, personal data enables the identification of individuals either directly or indirectly. Under the term both direct identifiers and indirect identifiers refer to any other information linked or linkable to an individual. A standard for assessing identifiability, emphasizing the reasonable likelihood of identification through available means is also introduced by GDPR. Actual identification or intent isn't necessary, nor is data possession by the same entity processing the information.
- **Special Categories of Personal Data** (Article 9 GDPR): Special categories of personal data are also known as ‘sensitive data’ and refer to information deemed riskier to individuals, thus warranting enhanced protection. This category includes ‘personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, or trade union membership, as well as the processing of genetic data, biometric data for uniquely identifying a person, data concerning

health, or data concerning a person's sex life or sexual orientation' (par (1)). Processing such special categories of data is prohibited by default, with only a limited number of conditions under which such processing renders lawful (par (2)).

- **Medical / Health Data** (Article 4(15) and Recital 35 GDPR): 'Data concerning health' means personal data related to the physical or mental health of a natural person, including the provision of health care services, which reveal information about their past / present/ future health status according to GDPR. Health data falls under the special categories of data, rendering its processing initially prohibited. Member States retain the authority to impose additional conditions or restrictions, particularly concerning genetic, biometric, or health-related data.

The VOCORDER project utilises various data for training the ML algorithms and building on the VOCORDER device. Those can be non-personal data, referring to information that cannot lead to the identification of a specific individual. In those cases, data protection regulations do not apply. They can also be personal data, notably data that has the potential to directly or indirectly identify an individual. In these instances, data protection rules are applicable. Both non-sensitive personal data and special categories of personal data will be used.

More specifically, demographic data will be collected both from patients and from healthy individuals. The term refers to all non-clinical data about a patient or a healthy person, including their name, date of birth, sex, race, contact details, etc. Among them, personal and special categories of data can be included, which will be collected through a questionnaire and an interview of the involved parties. Additionally, data on the clinical status, including information about comorbidities, long-term diseases, and, in general, information relating to the health situation of a person will be collected.

Data Processing in VOCORDER

Definition

In GDPR (Article 4(2)) terms, 'processing' means any operation or set of operations that is performed on personal data or sets of personal data, whether or not by automated means, such as collection, recording, organization, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restriction, erasure, or destruction. Although data processing activities are still under discussion for the

organisation of the clinical study in the context of the VOCORDER, the processing activities will be described briefly as they are shaped for the time being. Thus, they will be revised according to the necessary changes for the smoother implementation of the project.

VORODER's data processing activities can be summarised as follows:

- Data Collection: This stage involves gathering personal data from sample collection, questionnaires and personal interviews. Patients and healthy participants are informed about their participation and the objectives of the project beforehand and consent to the processing of their personal data (WP 2 and 6).
- Data preparation: The data collected will be digitalized in a pre-defined way based on the relevant SOPs and uploaded in the system of the MITERA for the purposes of VOCORDER project.
- De-personalisation: After the data is collected and uploaded anonymisation or pseudonymisation techniques will be applied to protect personal data, such as but not limited to encryption.
- Data Storage: All data and associated metadata will be stored anonymously in the project's database repository, adhering to all privacy and security measures for data protection.
- Data Transfers: No international transfer of personal data will be conducted in VOCORDER. Possible data transfer is anticipated between the partners. Data transfer will have undergone de-personalisation.
- Data Exploitation: Data will constitute the input of ML algorithms that partners responsible for the device development will employ (WP4).
- Data Destruction: Destruction of data involves the deletion or erasure of data from systems or files to prevent recovery, ensuring data protection and privacy.

Data Controller and Data Processor

Data 'controller' is indicative of the natural or legal person, public authority, agency or other body which, alone or jointly with others, determines the purposes and means of the processing of personal data, where the purposes and means of such processing are determined by Union or Member State law, the controller or the specific criteria for its nomination may be provided for by EU or national law (Article 4(7) GDPR). The defining factor of controllership lies in the ability to dictate or impact the objectives and methods of data processing and can be associated with a singular task within the data processing

cycle or with multiple sets of operations. If multiple parties are jointly involved in determining the purpose and methods of a data processing activity, they are considered joint controllers (Article 26 GDPR).

Data 'processor' means a natural or legal person, public authority, agency, or other body that processes personal data on behalf of the controller (Article 4(8) GDPR). The processor, distinct from the controller, is tasked with executing specific duties on behalf of the controller. While instructions may vary in specificity, the processor's role is primarily defined by its impact on decision-making. The classification of processor or controller is contingent upon the specific processing activities involved, allowing for distinct roles across different datasets and processing phases.

It is crucial to identify controllers, processors, and joint controllerships to determine the distribution of responsibilities for complying with data protection legislation. The VOCORDER project comprises three distinct groups of beneficiaries based on their roles: Medical Partner (MITERA), Technical Partners (ARGOS, AIDEAS, CAILABS, ICCS, EULAMBIA), and Supporting Partners (VUB, METIS, NEURALTECH). Medical Partners spearhead the collection and utilization of data and, in collaboration with Technical Partners, determine the operations of the VOCORDER device. The consortium also includes a third category of entities overseeing legal, ethical, dissemination, and exploitation tasks. While all partners collectively agree to engage in medical and scientific research, not all bear equal responsibility for every data processing activity during the project since their contribution differs. Considering the sensitive nature of the personal data involved and to uphold principles of transparency and accountability, the consortium should establish a data processing arrangement to delineate and assign relevant responsibilities to each partner according to their respective role.

Risks of the processing

The term 'risk' is defined in the NIS 2 Directive as the potential for loss or disruption caused by an incident and is to be expressed as a combination of the magnitude of such loss or disruption and the likelihood of occurrence of the incident" (Article 6(9)). Potential disruptions encompass unauthorized or accidental disclosures (confidentiality breach), alterations (integrity breach), and loss or destruction of personal data (availability breach). The GDPR emphasises risk management and security assessment, linking them directly to the responsibilities of data controllers. They are obligated to promptly notify supervisory authorities of breaches, providing comprehensive information such as

the categories of data subjects affected, potential consequences, and measures taken to address the breach. Notifying the data subjects is required when the breach poses a high risk to their rights and freedoms. Nonetheless, exemptions exist when appropriate measures have been implemented or notification would be disproportionate.

The VOCORDER consortium must identify risks that could impact the personal data processed in the project and update them regularly. In addition, the procedure for handling personal data breaches will be agreed upon, possibly in the form of a protocol or a strategy.

Security of the processing

To counterbalance the risks proposed above, researchers must pay special attention to the security of processing, by implementing some measures described indicatively in Articles 32-34 and Recital 83 of the GDPR. Those include: a) the pseudonymization and encryption of personal data; b) the ability to ensure the ongoing confidentiality, integrity, availability, and resilience of processing systems and services; c) the ability to restore the availability and access to personal data promptly in the event of a physical or technical incident; d) a process for regularly testing, assessing, and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing. The notification process to be followed by the data controller when a data breach occurs is also featured and, particularly, to the affected data subject. This set of obligations sets the template under which data controllers and occasionally data processors should operate to comply with their obligation to keep the data they are processing secure.

VOCORDER's Data Management Plan delineates the processing of personal data within the project and will be revised and updated to reflect up-to-date practices. As recommended, an efficient way to establish clear responsibilities in data processing for the project would be to draft a data processing agreement. Towards the goal of data security, the anonymization or pseudonymization of data, as well as the employment of appropriate technical measures to prevent unauthorized access to it will have an important impact. The testing and evaluation of the efficacy of technical and organisational security measures should be constant and depicted in the project's documents.

De-personalization in VOCORDER

AnonymiseZ or Anonymous data are regarded as ‘data that do not (or no longer) relate to identifiable individuals. The (re-)identification of the individuals involved is made impossible, and this inability is permanent, extending even to the researchers conducting the study. Such data do not qualify as personal data under GDPR and thus fall outside the scope of data protection laws. Therefore, anonymisation constitutes a processing activity aiming at removing all identifying elements from a set of personal data to ensure the data subject cannot be identified. For data to be considered anonymous, no elements should remain in the information that could, with reasonable effort, be used to re-identify the involved individuals. Once data have been effectively anonymised, they cease to be classified as personal data. When achieving complete anonymisation is not technically feasible due to the inability to suppress the risk of re-identification, pseudonymisation will be implemented along with necessary technical and organisational measures. Even then, anonymisation can be considered as a protective measure.

Pseudonymised data is data that has undergone pseudonymisation. Pseudonymisation is called the processing of personal data in a manner that renders it impossible to attribute to a specific individual without additional information, provided that this additional information is kept separate and is subject to technical and organisational measures to prevent attribution to an identified or identifiable person (Article 4(5) GDPR). Despite being pseudonymised, such data is still considered personal data, and as such, the GDPR remains fully applicable. So, pseudonymisation is a processing activity designed to mitigate risks to the data subject by rendering their identification impossible without the use of supplementary information. Unlike anonymisation, it does not render a data subject unidentifiable; therefore, pseudonymised data remains subject to the legal data protection framework.

Under the context of VOCORDER, de-personalisation will take place. The responsible physicians and staff of MITERA after data collection will cater for its de-personalisation and secure storage. A likelihood test for anonymisation is crucial, along with proper justification of the results. In cases when it would be necessary to reidentify the participants so as to draw conclusions on the effectiveness of the medical device in identifying diseases and monitoring the health status and anonymisation renders impossible, pseudonymisation should be preferred. Data processing by other VOCORDER partners rather than the medical one will occur after their de-personalisation, using anonymisation, pseudonymisation and encryption techniques. Throughout the project's entirety, it is advisable to employ pseudonymisation as the

default approach for the data collected and uploaded. Finally, MITERA should pledge to prevent the re-identification of the individuals to whom the data pertains for purposes other than those strictly mentioned in the VOCORDER project's goals and objectives.

Data Protection Principles in VOCORDER

A) Lawfulness, Fairness and Transparency (Article 5(1)(a) GDPR): Personal data shall be processed lawfully, fairly and in a transparent manner in relation to the data subject ('lawfulness, fairness and transparency')

Lawfulness

By the principle of lawfulness, all processing of personal data must be grounded on one or more legal bases outlined in Article 6(1) of the GDPR, which includes: obtaining free, voluntary, and specific consent from the data subject; (b) fulfilling contractual obligations with the data subject; (c) adhering to legal obligations imposed on the controller; (d) safeguarding the vital interests of the data subject or another individual; (e) conducting activities in the public interest or exercising official authority; (f) pursuing legitimate interests of the controller or a third party, provided it does not override the fundamental rights and freedoms of the data subject. The choice of the basis to rely on should consider the type and sensitivity level of the data to be processed.

In VOCORDER explicit consent will serve as a legal basis for processing. As a result, the overview of it should take place beforehand, in the present Deliverable. As stipulated in Articles 6(1)(a) ,9(2)(a) and 89(1) GDPR, the consent plays a crucial role in data processing. A differentiation should proceed between the consent for participation in a clinical study demanded by the relevant legislation and consent as a legal basis for personal data processing. According to GDPR standards, valid consent must be freely given, specific, informed, unambiguous, and explicit. When considering consent for processing sensitive data in research, controllers should adhere to the WP29 Guidelines on consent and ensure compliance with all conditions set in the document.

Since relying solely on individual consent as a legal basis presents challenges throughout medical, alternative pathways should be identified, such as public interest or legitimate interests of the controller.

Processing personal data may be deemed necessary for tasks conducted in the public interest if clinical studies align with the responsibilities conferred upon a public or private entity by national law. The pertinent medical partner should evaluate this in accordance with their respective national legislation.

Last but not least, in its guidelines, EDPB recommended the use of legitimate interest as the legal basis for processing sensitive data in the context of general medical research. Consequently, processing can happen for scientific purposes based on EU or national if the principle of proportionality and the protection of human rights are guaranteed.

In VOCORDER, MITERA shall identify a suitable legal justification according to both EU and national regulations. They must ensure that there is a lawful basis for processing the data collected and that any subsequent processing within VOCORDER aligns with its initial purpose. Processing must be necessary for the intended purpose to be considered lawful and should be strictly limited to what the legal basis permits. If consent is chosen as the legal basis, the processing must allow for easy withdrawal of consent, comparable to the ease of giving consent. Failure to provide such easy withdrawal means any consent obtained is not considered valid. Although explicit consent serves as an adequate legal basis for VOCORDER, it would be beneficial for the partners to identify in the applicable national legislation, namely the Greek one, additional legal bases for processing personal data. In Law 4624/2019, it is stated that processing is deemed lawful when conducted for the purposes of [...] medical diagnosis, [...] or pursuant to a contract with a health professional or other people who is subject to a duty of professional secrecy or supervised by him/her; or for reasons of public interest in the area of public health, such as [...] ensuring high standards of quality and safety of health care and of medicinal products or medical devices (Article 22 (b) and (c)). These provisions should be assessed as alternative means of achieving VOCORDER's goal, designing a novel breath analysis and health status monitoring apparatus. If there is a valid change in the legal basis for processing, the ongoing processing must be adjusted accordingly to align with the new legal grounds. If the legal basis no longer applies, the processing must cease accordingly. The responsibility to ensure compliance with these requirements lies with the controller of the data, MITERA.

Fairness

Fairness plays a crucial role in data processing activities. Controllers should inform both data subjects and the broader public about their intention to process data in a manner that is lawful and transparent. They must also be prepared to actively demonstrate the compliance of their processing activities with the GDPR. The rights of the data subjects should be addressed and respected throughout research endeavors. The subjects should be made aware of any potential risks associated with the processing of their data

and be allowed to communicate with the controller of their data, while any discriminatory or exploitative practices must be excluded from the very beginning.

In VOCORDER, special measures will be taken to avoid unfair practices. Prior to their participation, data subjects will receive contact details of the responsible partner to whom they can reach out. Potential risks will be communicated to them, while the consortium will follow the guidelines prescribed in this document to avoid violations of fundamental rights and freedoms, discrimination against or exploitation of the data subjects.

Transparency

To fulfill the requirement of transparency, controllers should be capable of informing data subjects in a clear, concise, and easily understandable manner about the use of their data. The controller's identity and the purposes of data processing, the risks and the safeguards at hand, but also the rights of the data subjects and the ways to exercise them properly are among the information that should be enclosed to them. It becomes obvious that transparency is closely linked to the right to information enshrined in Articles 13 and 14 of the GDPR, which is going to be developed below.

In VOCORDER, the information about the project, its scope and methodology is included in the information sheet, which is part of the consent form that will be distributed to the participants. The details included are presented in clear and straightforward language, ensuring it is concise and understandable to the intended audience. It will be translated into Greek since more participants are anticipated to be speakers of the Greek Language. Apart from the written statement, an oral presentation will be conducted by the competent medical staff to ensure the effectiveness of information spread after the guidelines they will receive from the institutional DPO, but also the guidance provided for by this Deliverable.

B)	**Purpose Limitation** (Article 5(1)(b) GDPR): Personal data shall be collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes; further processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes shall, in accordance with Article 89(1), not be considered to be incompatible with the initial purposes ('purpose limitation')

The principle of purpose limitation mandates that a clear, explicit, and lawful purpose must be identified before any data processing commences. This purpose/ these purposes should be specific, clearly outlining why personal data is being processed, and

oriented towards guiding the processing design and setting boundaries. The necessity of processing for the intended purposes should also be reviewed from time to time. The processing has to align with the intended purpose. Further processing for reasons other than the ones mentioned at start is permissible for specific purposes, provided that appropriate technical and organisational safeguards are in place.

In VOCORDER, the principle of purpose limitation will be adopted and respected throughout the clinical study. Nevertheless, in case data is used for a different purpose to the one it was initially collected for implications might arise. However, as mentioned above for purposes like archiving, public interest, or scientific research processing of data can continue without requiring a new legal basis as long as attention to data protection obligations is paid.

C) Data Minimisation (Article 5(1)(c) GDPR): Personal data shall be adequate, relevant, and limited to what is necessary in relation to the purposes for which they are processed ('data minimisation')

The principle of data minimisation aims to reduce the amount of data processed to only what is adequate, relevant, and strictly necessary for the intended purpose. This principle aligns with the concept of necessity, underlining that data should not be collected or retained beyond what is required. It also aims at limiting the degree of identification of a data subject. Whenever identification is not necessary, efforts should be made to de-personalise the data as much as possible. De-personalisation techniques already noted serve for the implementation of this important principle. When it is no longer necessary for the intended purpose, in accordance with the principle of limitation, the collected data should be deleted.

Adhering to the principles of relevance, necessity, and limitation, only the necessary data will be collected, while anonymisation and pseudonymisation techniques will be explored to minimise the risk of the identification of the participating individuals in the context of VOCORDER.

D) Accuracy (Article 5(1)(d) GDPR): Personal data shall be accurate and, where necessary, kept up to date; every reasonable step must be taken to ensure that personal data that are inaccurate, regarding to the purposes for which they are processed, are erased, or rectified without delay ('accuracy')

To uphold data reliability, it is imperative to maintain accuracy across all data sources. Each piece of personal data should possess sufficient accuracy to fulfil its intended

purpose effectively. Wrong outcomes if not fully avoided should be diminished. Mitigating errors that accrue throughout the processing chain is vital to prevent the exacerbation of inaccuracies. So, inaccurate data should be removed and monitoring should be constant, with updates conducted as needed to preserve data relevance.

The personal data collected and processed within VOCORDER serves solely to assist within the device development. No diagnoses will be communicated to the data subjects. However, ensuring the accuracy of data is vital to validate compliance with the rules governing the project. The contact details of the responsible person should be furnished to the participants to whom they can refer for any rectification of their collected data. These requests should be addressed effectively and in due time to achieve accuracy in the data and in the results based upon them.

E)	**Storage Limitation** (Article 5(1)(e) GDPR): Personal data shall be kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the personal data are processed; personal data may be stored for longer periods insofar as the personal data will be processed solely for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes in accordance with Article 89(1), subject to implementation of the appropriate technical and organisational measures required by this regulation in order to safeguard the rights and freedoms of the data subject (‘storage limitation’)

Personal data should be stored only in the form of essential data elements required for specific purposes, with strict adherence to retention policies to avoid unnecessary data collection. Anonymisation or deletion should be promptly applied to or at least considered for personal data that is no longer usable or necessary for the purposes collected. Controllers should transparently disclose their data processing rationale and exercise caution in temporarily storing personal data.

As highlighted above, in VOCORDER all collected will be stored anonymously in the project’s database repository, adhering to all privacy and security measures for data protection. The storage period will be decided and communicated to the participants beforehand, but it will not exceed the duration of the project. Adequate state-of-the-art technologies for secure storage will be employed.

F) Integrity and Confidentiality (Article 5(1)(f) GDPR): Personal data shall be processed in a manner that ensures appropriate security of the personal data, including protection against unauthorised or unlawful processing and against accidental loss, destruction, or damage, using appropriate technical or organisational measures ('integrity and confidentiality')

Confidentiality safeguards data from unauthorised access or disclosure, whereas integrity protects against unauthorised modifications. Personal data confidentiality is directly connected to processing security. Once security is assured, personal data will be kept confidential. The overarching goal of these principles is to prevent data breaches and facilitate seamless data processing while upholding data protection principles and rights. To achieve these goals, security measures should be put into effect.

Under VOCORDER premises, regular security reviews are recommended to evaluate the effectiveness of implemented measures, both technological and managerial ones. Only the authorised personnel will have access to the data. Secure storage practices, including anonymisation or deletion of personal data when no longer necessary will be employed. A security incident response management protocols to detect, handle, report, and learn from data breaches is suggested. Moreover, procedures for handling personal data breaches, including notification to supervisory authorities and affected individuals, must be agreed upon between the consortium partners.

G) Accountability (Article 5(2) GDPR): The controller shall be responsible for, and be able to demonstrate compliance with, paragraph 1 ('accountability').

The VOCORDER partners handling personal data must actively comply with GDPR regulations not only for the data subjects involved in the clinical study but also for the supervisory authorities. MITERA, as the data controller, is the partner anticipated to enact internal measures to ensure adherence to data protection laws. Each partner involved in VOCORDER will appoint a DPO or designate a contact person responsible for addressing legal and ethical concerns related to the project's research activities.

H) Data protection by design and by default (Article 25 GDPR): 1.Taking into account the state of the art, the cost of implementation and the nature, scope, context and purposes of processing as well as the risks of varying likelihood and severity for rights and freedoms of natural persons posed by the processing, the controller shall, both at the time of the determination of the

> means for processing and at the time of the processing itself, implement appropriate technical and organisational measures, such as pseudonymisation, which are designed to implement data-protection principles, such as data minimisation, in an effective manner and to integrate the necessary safeguards into the processing in order to meet the requirements of this Regulation and protect the rights of data subjects. 2. The controller shall implement appropriate technical and organisational measures for ensuring that, by default, only personal data which are necessary for each specific purpose of the processing are processed. That obligation applies to the amount of personal data collected, the extent of their processing, the period of their storage and their accessibility. In particular, such measures shall ensure that by default personal data are not made accessible without the individual's intervention to an indefinite number of natural persons. 3. An approved certification mechanism pursuant to Article 42 may be used as an element to demonstrate compliance with the requirements set out in paragraphs 1 and 2 of this Article.

The principles of data protection by design and by default necessitate that controllers embed data protection principles and data subject rights into the design and default settings of systems and services. Data protection by design requires implementing safeguards and measures at the outset of processing activities or services to effectively uphold data protection principles. Controllers must continually assess the effectiveness of these measures throughout processing to pre-emptively mitigate risks. Data protection by default mandates processing only the necessary personal data for each specific purpose in compliance with the law and transparently informing concerned individuals.

Those principles should navigate the clinical study and it will be ensured that all technical and organisational measures that can fulfill these requirements are established, provided they are suitable for effectively implementing data protection principles and proportionately addressing potential risks.

Data Subjects Rights in Vocorder

A) **Right to information** (Articles 13,14 GDPR)

The right to information can be found in Articles 13 and 14 of the GDPR, with Article 13 focusing on scenarios where personal data is directly obtained from the data subject, while Article 14 pertains to situations where data originates from other sources.

Disclosure of information to data subjects regarding processing activities is crucial for ensuring fair and transparent processing and enabling individuals to exercise their data subject rights. At the point of data collection, controllers must furnish data subjects with essential processing details: (a) the identity and the contact details of the controller and, where applicable, of the controller's representative; (b) the contact details of the data protection officer, where applicable; (c) the purposes of the processing for which the personal data are intended as well as the legal basis for the processing; (d) where the processing is based on point (f) of Article 6(1), the legitimate interests pursued by the controller or by a third party; (e) the recipients or categories of recipients of the personal data, if any; (f) where applicable, the fact that the controller intends to transfer personal data to a third country or international organisation and the existence or absence of an adequacy decision by the Commission, or in the case of transfers referred to in Article 46 or 47, or the second subparagraph of Article 49(1), reference to the appropriate or suitable safeguards and the means by which to obtain a copy of them or where they have been made available.

Any additional necessary information should be provided for transparent and fair processing including: (a) the period for which the personal data will be stored, or if that is not possible, the criteria used to determine that period; (b) the existence of the right to request from the controller access to and rectification or erasure of personal data or restriction of processing concerning the data subject or to object to processing as well as the right to data portability; (c) where the processing is based on point (a) of Article 6(1) or point (a) of Article 9(2), the existence of the right to withdraw consent at any time, without affecting the lawfulness of processing based on consent before its withdrawal; (d) the right to lodge a complaint with a supervisory authority; (e) whether the provision of personal data is a statutory or contractual requirement, or a requirement necessary to enter into a contract, as well as whether the data subject is obliged to provide the personal data, and of the possible consequences of failure to provide such data; (f) the existence of automated decision-making, including profiling, referred to in Article 22(1) and (4) and, at least in those cases, meaningful information about the logic.

For the exercise of the right of information of the participants, an information sheet for the VOCODER project has been drafted (ANNEX 8) and will be circulated among the participants containing all the information characterised as necessary in the GDPR. Contact points will be communicated to the data subjects in order to pose questions on

stages after the data collection. Any other purpose or additional information on the data processing will be made available to the participants beforehand.

B) Right to access (Article 15 GDRP)

Article 15 of the GDPR grants individuals the right of access, aiming to enable them to verify the lawfulness of processing their personal data. Similar to the right to information, the right of access serves as a tool for exercising other data subject rights. Pursuant to this right, data subjects are entitled to specific information, including: (a) the purposes of the processing; (b) the categories of personal data concerned; (c) the recipients or categories of recipient to whom the personal data have been or will be disclosed, in particular recipients in third countries or international organisations; (d) where possible, the envisaged period for which the personal data will be stored, or, if not possible, the criteria used to determine that period; (e) the existence of the right to request from the controller rectification or erasure of personal data or restriction of processing of personal data concerning the data subject or to object to such processing; (f) the right to lodge a complaint with a supervisory authority; (g) where the personal data are not collected from the data subject, any available information as to their source; (h)the existence of automated decision-making, including profiling, referred to in Article 22(1) and (4) and, at least in those cases, meaningful information about the logic involved, as well as the significance and the envisaged consequences of such processing for the data subject. However, this right is subject to limitations to safeguard the rights and freedoms of others or if a request by a data subject is deemed manifestly unfounded or excessive.

In VOCORDER, participants will be able to have access to the information surrounding the processing of their personal data. A copy of the personal data undergoing processing, if requested will be provided by MITERA, the responsible partner. A policy for recording details of the received requests is also advisable.

C) Right to rectification (Article 16 GDRP)

The right to data rectification is provided for in Article 16 of the GDPR and typically involves substituting inaccurate data with accurate information. This process may also entail completing an incomplete dataset by incorporating the necessary information. The request to rectify personal data may be given in writing or verbally. Under certain circumstances a request for rectification can be refused.

The exercise of the right to rectification will be offered to the data subjects taking part in the VOCORDER research. Relevant requests will be handled following the procedures already envisaged for the right to access to personal data.

D) Right to erasure (to be forgotten) (Article 17 GDRP)

The GDPR, in Article 17, enshrines the right to erasure, also known as the right to be forgotten. This empowers individuals to request the deletion of their personal data from controllers under specific circumstances: (a) the personal data are no longer necessary in relation to the purposes for which they were collected or otherwise processed; (b) the data subject withdraws consent on which the processing is based according to point (a) of Article 6(1), or point (a) of Article 9(2), and where there is no other legal ground for the processing; (c) the data subject objects to the processing pursuant to Article 21(1) and there are no overriding legitimate grounds for the processing, or the data subject objects to the processing pursuant to Article 21(2); (d) the personal data have been unlawfully processed; (e) the personal data have to be erased for compliance with a legal obligation in Union or Member State law to which the controller is subject; (f) the personal data have been collected in relation to the offer of information society services referred to in Article 8(1). This right is not absolute, and exceptions are outlined in Article 17(3), particularly regarding scientific research. In such cases, the right may be restricted if its exercise would impede research goals. This limitation applies to unlawfully processed or unnecessary data, or when consent is withdrawn.

MITERA is the only partner retaining the ability to re-identify data subjects whose data is stored or the VOCORDER research in the hospital's repository. As a result, upon deletion of the participants' personal data from it, any pseudonymised information involved in the VOCORDER procedure by the end of the project should be turned anonymous. Any request for the erasure of the personal data will be evaluated and be accepted only as long as it does not hinder the project's research activities.

E) Right to restriction of processing (Article 18 GDRP)

In accordance with Article 18 of the GDPR, individuals have the right to request the restriction of processing from the controller. While 'restriction' is not explicitly defined in the GDPR, it is regarded to limit the controller's ability to process personal data. This may occur under specific circumstances: (a) the accuracy of the personal data is contested by the data subject, for a period enabling the controller to verify the accuracy of the personal data; (b) the processing is unlawful and the data subject opposes the

erasure of the personal data and requests the restriction of their use instead; (c) the controller no longer needs the personal data for the purposes of the processing, but they are required by the data subject for the establishment, exercise or defence of legal claims; (d) the data subject has objected to processing pursuant to Article 21(1) pending the verification whether the legitimate grounds of the controller override those of the data subject.

Measures that may facilitate this right include, among others, temporarily transferring data to another system, restricting access to certain personal data, or temporarily removing published data from an openly accessible space. Those can be adopted by the VOCORDER data controller, MITERA, in case of any restriction of the processing request arises. The restriction should be, furthermore, communicated to any other involved partners.

F) Right to data portability (Article 20 GDRP)

Article 20 of the GDPR establishes the right to data portability, allowing individuals to receive their personal data from a controller in a structured, commonly used, and machine-readable format, and to transmit this data to another controller without obstruction. This right applies when data processing is based on consent or a contract and is carried out using automated means.

Since in VOCORDER the collected data will be stored as pseudonymised, their portability might meet more difficulties. One of them is surely the maintenance of pseudonymity and the avoidance of re-identification during the data transmission. Although the right should remain available to the data subject, it should be executed with the utmost carefulness and with security measures enacted.

G) Right to object (Article 21GDRP)

The right to object is laid down in Article 21 of the GDPR. The right to object grants data subjects the authority to refuse, at any time, the processing of their personal data based on public interests or legitimate interests, provided it relates to their specific circumstances. Data subjects do not possess a universal right to object to data processing, but in cases of conflicting interests, the burden of proof lies with the controller. The controller must demonstrate compelling and legitimate reasons for continuing the data processing. If the interests of the data subject outweigh those of the controller, exercising the right to object compels the controller to cease processing the personal data.

It should be reminded that MITERA retains its status as individual controller for the personal data housed at its premises, thereby bearing full responsibility for upholding the rights of data subjects in accordance with EU and national regulations.

Data Protection Impact Assessment

Undoubtedly, not at all instances of processing personal data a Data Protection Impact Assessment (DPIA) is needed. Article 35 of the GDPR outlines specific conditions under which a DPIA becomes mandatory, with them depending on a type of processing in particular when using new technologies, and taking into account the nature, scope, context and purposes of the processing, or whether it is likely to result in a high risk to the rights and freedoms of natural persons.

The initial step in determining the need for a DPIA is to assess whether the processing activity is likely to pose a high risk. If it is not likely, a DPIA is not required. Amidst, if the risk is deemed high, the next consideration is whether the processing falls within the exceptions outlined in Article 35(5) and (10). If it does, no DPIA needs to be drafted; otherwise, a DPIA is essential.

Article 35(3) of the GDPR offers examples of processing activities likely to result in high risks, namely: (a) a systematic and extensive evaluation of personal aspects relating to natural persons which is based on automated processing, including profiling, and on which decisions are based that produce legal effects concerning the natural person or similarly significantly affect the natural person; (b) processing on a large scale of special categories of data referred to in Article 9(1), or of personal data relating to criminal convictions and offences referred to in Article 10; or (c) a systematic monitoring of a publicly accessible area on a large scale.

Additional criteria for assessing high-risk processing include evaluation or scoring of individuals, automated decision-making with significant legal effects, systematic monitoring, processing of sensitive data, large-scale data processing, combined datasets, data concerning vulnerable individuals, innovative or technological solutions, cross-border data transfers, and processing that limits individuals' rights or access to services.

DPIAs are not required in certain circumstances when the processing does not pose a high risk to individuals' rights and freedoms, when it resembles previously assessed activities, and their DPIA results are applicable, when EU or Member State laws provide a legal basis for the processing and have already undergone DPIA as part of their

establishment or when the supervisory authority's optional list exempts specific processing operations from DPIA requirements.

Based on the data processing operations anticipated for the VOCORDER project, which involves the processing of sensitive (health) data, the potential implementation of a DPIA will be considered by the consortium partners prior to the usage of the medical device.

International Data Transfers

Article 45 of the GDPR governs the process of transferring data to third countries outside the European Economic Area (EEA). The European Commission holds the authority to issue the adequacy decisions to determine if a third country provides an adequate level of data protection. When such a decision is in effect, controllers are not required to implement additional measures for data transfer, as long as they comply with all other aspects of the GDPR. Nevertheless, it's important to note that adequacy decisions do not prevent data subjects from lodging complaints against controllers, nor do they prevent supervisory authorities from challenging the validity of decisions. In VOCORDER no international transfer, outside the EU will take place, so no specific rules governing international data transfers should be included in the present section.

ANNEX 6: INFORMED CONSENT FORM FOR VOCORDER

vocorder

MITERA
Responsibility for life
MEMBER OF HHG GROUP

Informed Consent Form for VOCORDER

[Informed Consent form for VOCORDER participants]
This informed consent form is written for patients suffering from lung cancer, gastric and colon cancer, breast cancer, kidney insufficiency or infections - pneumonia (community-acquired and hospital-acquired) and for healthy controls of both sexes, aged between 20 to 75 years, who do not suffer from these diseases.

Name of Principal Investigator: Kontopidou Flora
Name of Organization: MITERA Hospital
Name of Project: VOCORDER - HORIZON-EIC-2022-PATHFINDERCHALLENGES-01-04

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

You are cordially invited to participate in the clinical study conducted within the project VOCORDER. Prior to making your decision regarding participation in the project's clinical study, it is essential that you comprehend the project's nature and your role within it. Kindly take the time to thoroughly review the following information. If you decide to participate in our study, we would like to thank you in advance. However, you are totally free to decline our invitation to take part in the project.

VOCORDER is a European funded project with duration of 3 years and 6 months, which was initiated in October 2023. The clinical study will take place under the premises of the MITERA hospital and run by MITERA research team. It will be decomposed into a baseline and a validation phase. This clinical study is going to address the correlation analysis between breath VOCs profiles as detected by the VOCORDER breath analyser and electronic medical data as collected by medical professionals.

Purpose of the clinical study

The objectives of the study could be summarised as follows:

- providing a solution for easy-to-use breath analysis able to monitor the health of any individual at any setting and offering life-long health status monitoring and elements of predictive medicine with methodologies grounded in existing scientific evidence;
- developing a health monitoring apparatus people can easily integrate into their everyday life, paying attention to minimising false positives that can occur in the real world and ensuring a clinically acceptable

solution amendable to successful evaluation under common Health Technology Assessment (HTA) methodologies;

- developing and demonstrating the beyond state-of-the-art technologies needed to implement the breath analysis apparatus;
- prioritising the development of AI-enhanced predictive models that address specific conditions in the continuum of a patient and enabling AI-breath analysis for identification of health conditions.

Type of Study Intervention

You will be asked to fill in a questionnaire with demographic and medical-history data. Moreover, an interview will be conducted with the responsible personnel. Afterwards, at least 2-3 breath samples are expected to be obtained by you on different days at the same time of day and further analysed.

Participant selection

Patients suffering from lung cancer, gastric and colon cancer, breast cancer, kidney insufficiency or infections - pneumonia (community-acquired and hospital-acquired) and healthy controls of both sexes, aged between 20 to 75 years, who do not suffer from these diseases are invited to participate in the clinical study.

Voluntary Participation

Your involvement is entirely voluntary. It is entirely your choice whether to participate or not. You are free to withdraw your participation at any time, without providing reasoning and without further consequences.

Duration

The clinical study will be conducted in two phases:

- 1st Phase: Baseline phase (June-December 2024)
- 2nd Phase: Validation phase – VOCORDED technology validation (May-December 2026).

Depending on the phase of the clinical study you will take part in and during that time, it will be necessary for you to come to the hospital 2 days at the same time for each day.

Side Effects

No side effects are anticipated from this clinical study.

Risks and Benefits

This clinical study is not interventional so there has been no reasonably foreseeable risk, discomfort or disadvantages identified in the context of your participation in the clinical study of VOCORDER. On the contrary, the method applied in VOCORDER for sample breath collection is one of the least intrusive. The benefits stemming from the results which may reasonably be expected from the research output include the provision of an easy-to-use breath analysis, enabling each individual to monitor their health at any setting. The obtained results are expected to have importance for tailoring the technology of breath analysis in the VOCORDER breath analyser toward the early detection of diseases of interest timely.

Reimbursements

No reimbursement is provided by the clinical study.

Data collected and analysed

In order to perform the clinical study, personal information will be collected upon the consent of the individuals. The collected data according to their purpose within the project, will consist of:

a) Name and surname
b) Age
c) Gender
d) Contact details (address, phone number, email address)

e) Medical data (medical history, medical record and questionnaire to be filled by the participant)
f) Personal details (Race/Ethnicity, Income, Education Level, Occupation, Marital Status, Geographic Location)

Processing and Storage of Data

Your data will be processed in accordance with the General Data Protection Regulation (GDPR), Clinical Trials Regulation (CTR) and the applicable national legislation. The data will be collected by the MITERA project team and stored in a computerised working folder within the hospital. The folder is only accessible to the MITERA project team. The patient-related data is then anonymised and entered into a specially developed database that is shared with the other partners - authorised users. All information will be kept strictly confidential. By March 2027, at the conclusion of the project, your personal data will be either deleted or destroyed. Processed data, however, may persist beyond the project's duration as it could be incorporated into scientific publications and other dissemination activities, as outlined below. The sole purpose of storing your data is for project activities.

Data Protection, Confidentiality and Privacy

All the necessary measures have been adopted for ensuring data protection, confidentiality and privacy in VOCORDER. More specifically, Data protection and privacy concerns have been addressed and compliance with the requirements posed by the relevant legislation has been achieved. Specific guidelines have been communicated to the involved beneficiaries. Confidentiality obligations have been agreed between the partners as well.

Dissemination of the Results

The stored data will be used for research purposes, which encompass, among others, publications, intellectual property management and further types of sharing of information and relevant events. It is important to note that in all instances, the data will be presented in an anonymised manner. The results will not be shared with the participants since the VOCORDER breath analysis method will till the end of the project remain an experimental one.

Incidental Findings

Any incidental findings will be deleted. If the findings render necessary for the purposes of immediately referred to MITERA, the project's responsible partner for the clinical trials and only if necessary to the Advisory Board members and the Internal Ethics Committee will assess their ethical ramifications and proceed to the appropriate course of action.

Data Sharing and Re-use

Your data will be not sent to third parties or to countries outside of the European Union. The stored data will be utilised for activities only associated with VOCORDER, including their processing for research purposes and dissemination activities. Rest assured that your data will not be sold or be freely provided to any third party under any circumstances.

Data Breach

In the event of a data breach, each partner will promptly notify the Project Coordinator (MITERA). They will together take all the essential measures to mitigate any potential adverse effects. Since your contact information is included in the collected data, you will receive a notification as soon as possible regarding the nature of the data breach, the information compromised, and the steps being implemented to prevent or reduce any possible harm.

Data Subjects' Rights

You have the right to request the correction and/or deletion of your data, as well as to restrict the processing of your data, as outlined in Articles 15-21 of the GDPR. In addition, you maintain the right to withdraw your consent at any time, in accordance with Article 6(1) and Article 9(2) of the GDPR, without facing any adverse

consequences, by simply sending an email at gdpr2@hygeia.gr. If needed, your local supervisory authority will furnish you with information on how to exercise your rights, as prescribed in Article 57(e) of the GDPR. To assert your rights or to address any further inquiries concerning the exercise of your data subject rights, you can reach out to MITERA, the project's coordinator, at gdpr2@hygeia.gr. Please be aware that you have the option to lodge a complaint within your national data protection authority regarding the handling of your personal data, or with another competent supervisory authority as per the GDPR.

Who to Contact

Each beneficiary of VOCORDER adheres to its respective ethical guidelines, in compliance with the national legislation of the country they reside at. If you have any specific inquiries concerning the research activities conducted within VOCORDER and/ or your rights, please direct your question to the project's Coordinator, MITERA, at zzacharouli@mitera.gr.

This proposal has been reviewed and approved by the Scientific Council of MITERA, which is a committee whose task is, among others, to verify the compliance of the study with ethical principles and legal obligations.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

PART II: Consent Form

Thank you for your interest in taking part in the clinical study of the VOCORDER project. Before you agree in participating, the medical personnel organising the study and gathering your information is obliged to provide an explanation of the project to you. At any case, please review the VOCORDER Information Sheet for further details. If anything is not clear to you, please refer to the personnel for further inquiries. Based on the information provided and after reviewing the VOCORDER Information Sheet and being offered the explanations by the research team,

☐ **I confirm that I comprehend the nature of the project. I have also been afforded the opportunity to pose questions, and they have been addressed and answered to my satisfaction.**

☐ **I understand that my participation is voluntary and that I am free to withdraw my consent at any time, without providing reasoning and without further consequences.**

☐ **I have been informed that my data will be stored in a secure manner and for a duration not exceeding the length of the project.**

☐ **I understand that my information will be treated as strictly confidential and handled in accordance with the provisions prescribed in the applicable EU legislation, mainly in General Data Protection Regulation and Clinical Trials Regulation.**

I consent to voluntarily participate as a participant in this clinical study and to the processing of my personal data for the assessment the purposes of VOCORDER.

Print Name of Participant_____

Signature of Participant _____

Date _____
Day/month/year

If illiterate
I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____
Day/month/year

Statement by the researcher/person taking consent
I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. The participants will fill in a questionnaire and breath samples will be collected by them.
2. The data provided will be securely stored, anonymised and used for the purposes of VOCORDER till the finalisation of the project.
3. No result or incidental finding will be communicated to the participants.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Consent Form has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____
Day/month/year