ETERNALS

Early detection of clinical deterioration using an integrated remote monitoring system in lung cancer patients receiving cytotoxic chemotherapy.

Protocol

Version number: version 2

Version date: 6th of March 2024

STUDY REFERENCE NUMBERS

Clinical trials.gov: XXXClinicalTrails.govNumber

SPONSOR: Ziekenhuis Oost-Limburg

Study reference number Z2023080

EudraCT: B3712024000013

1. DOCUMENT HISTORY

Version no	Version date	Author	Reason for change
06DEC2023	V1	Julie Vranken	Initial draft of the study protocol
06MAR2024	V2	Julie Vranken	Adjustment based on the comments of the Ethical Committee

2. PROTOCOL SIGNATURE PAGE

I agree to conduct this study in accordance with the design and specific provisions of this protocol.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects.

I agree to personally conduct or supervise this study and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study in accordance with the protocol, Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical experimentation and the protection of patients.

I will ensure that the requirements relating to Ethics Committee review and approval are met.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements including the provision of direct access to data and source documents.

I agree to promptly report to the Ethics Committee any changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without Ethics Committee approval, except where necessary to ensure the safety of study participants.

Name of the Principal Investigator	Site name	Signature	Date
Dr. Maarten Criel	**Ziekenhuis Oost-Limburg**		

3. PROTOCOL SUMMARY

Full title	*Early detection of clinical deterioration using an integrated remote monitoring system in lung cancer patients receiving cytotoxic chemotherapy.*
Protocol number	*Z-2023080*
Short title/acronym	*ETERNALS*
Study duration	*16 months*
Rationale	*Lung cancer is a highly prevalent malignant tumour with 5.563 new cases in Belgium in 2020. Up to 70% of patients present with locally advanced or metastatic disease at diagnosis. Most of these patients require systemic therapy including cytotoxic chemotherapy as part of their treatment plan. The mortality rate in this patient population remains high due to the aggressive nature of the disease, but also due to treatment related toxicities such as dehydration, infection, and anaemia, resulting in emergency department (ED) visits and rehospitalizations. Routine administration of highly effective anti-emetics and the use of granulocyte colony-stimulating growth factors greatly reduced the complication rate in these patients. Also, remote symptom monitoring using a web-based tool to which patients can self-report their toxicities (i.e., patient-reported outcomes; PROs) had a marked impact on reducing ED visits and increasing overall survival in the PRO group. Despite these successes there is still a large proportion of lung cancer patients for whom weekly self-reports are not feasible. More specific: low socio-economic status, elderly patients and social isolation are associated with low compliance. The latter lung cancer patient subgroup is at the highest risk of under-detection when presenting with treatment- or disease-related toxicity. We hypothesize that implementation of an integrated remote monitoring system tracking heart rate, heart rate variability, body temperature, respiration rate, nocturnal oxygen saturation, sleep tracking and daily activity level via an unobtrusive wearable device is more performant and less burdensome compared to other self-reporting methods (e.g., PROs). The primary aim of this project is to set up and implement an integrated remote monitoring system in the routine care of lung cancer patients receiving cytotoxic chemotherapy, in which the remote monitoring is enabled via an unobtrusive wearable device. Via this innovative implementation we believe that patient care can be drastically improved due to the earlier detection of deterioration (i.e., less rehospitalizations and ED visits), especially for those high-risk frail patients.*
Objectives	*The primary objective of this project is to determine the feasibility of an integrated remote monitoring system in the routine care of lung cancer patients receiving cytotoxic chemotherapy.*
Study design	*Monocentre prospective interventional feasibility study*
Study population	*Stage IV lung cancer patients treated with cytotoxic chemotherapy, older than 18 years of age.*
Main study endpoints	• Determining the time interval between clinical deterioration detected by the integrated remote monitoring system and the first contact with the care team (i.e., in current clinical practice the patient suffering from chemotherapy-associated symptoms self-reports at the ED) • Patient compliance in using the integrated remote monitoring system
Chief investigator/ project leader	*Dr. Maarten Criel*

Sponsor	Ziekenhuis Oost-Limburg A.V. Synaps Park 1 3600 Genk - BELGIUM

4. TABLE OF CONTENTS

5. LIST OF ABBREVIATIONS

The following table presents the abbreviations and acronyms used in this document.

AE	Adverse Event
ADE	Adverse Device Effect
AR	Adverse Reaction
eCRF	Electronic Case Report Form
EC	Ethics Committee
ED	Emergency Department
EMR	Electronic Medical Record
EOS	End Of Study
GDPR	General Data Protection Regulation
HRV	Heart rate variability
MAUQ	mHealth Usability questionnaire
ICF	Informed Consent Form
MDR	Medical Device Regulation
PI	Principal Investigator
PROs	Patient reported outcomes
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAR	Serious Adverse Reaction
SUS	System Usability questionnaire
SUSAR	Suspected Unexpected Serious Adverse Reaction
USADE	Unanticipated Serious Adverse Device Effect

6. BACKGROUND AND RATIONALE

Lung cancer is a highly prevalent malignant tumor with 5.563 new cases in Belgium in 2020[1]. Up to 70% of patients present with locally advanced or metastatic disease at diagnosis [1]. Most of these patients require systemic therapy including cytotoxic chemotherapy as part of their treatment plan. The mortality rate in this patient population remains high due to the aggressive nature of the disease, but also due to treatment related toxicities such as dehydration, infection, and anemia, resulting in emergency department (ED) visits and rehospitalizations. Routine administration of highly effective anti-emetics and the use of granulocyte colony-stimulating growth factors greatly reduced the complication rate in these patients [2, 3]. Also, remote symptom monitoring using a web-based tool to which patients can self-report their toxicities (i.e., patient-reported outcomes; PROs) had a marked impact on reducing ED visits and increasing overall survival in the PRO group [4-6]. Despite these successes there is still a large proportion of lung cancer patients for whom weekly self-reports are not feasible. More specific: low socio-economic status, elderly patients and social isolation are associated with low compliance [7, 8]. The latter lung cancer patient subgroup is at the highest risk of under-detection when presenting with treatment- or disease-related toxicity. We hypothesize that implementation of an integrated remote monitoring system tracking heart rate, heart rate variability, body temperature, respiration rate, nocturnal oxygen saturation, sleep tracking and daily activity level via an unobtrusive wearable device is more performant and less burdensome compared to other self-reporting methods (e.g., PROs). The primary aim of this project is to set up and implement an integrated remote monitoring system in the routine care of lung cancer patients receiving cytotoxic chemotherapy, in which the remote monitoring is enabled via an unobtrusive wearable device. Via this innovative implementation we believe that patient care can be drastically improved due to the earlier detection of deterioration (i.e., less rehospitalizations and ED visits), especially for those high-risk frail patients.

7. OBJECTIVES AND OUTCOME MEASURES

The primary objective of this project is to determine the feasibility of an integrated remote monitoring system in the routine care of lung cancer patients receiving cytotoxic chemotherapy.

7.1 Primary Objective

- Determining the time interval between clinical deterioration detected by the integrated remote monitoring system and the first contact with the care team (i.e., in current clinical practice the patient suffering from chemotherapy-associated symptoms self-reports at the ED)
- Patient compliance in using the integrated remote monitoring system

7.2 Secondary Objectives

- Acceptability and usability of the integrated remote monitoring system by both the patient and the healthcare specialists
- Determine the number of ED visits retrospectively, including the disease- and therapy related/induced complications (retrospective sub-study, see Paragraph 8 STUDY DESIGN).

7.3 Endpoints

Primary objective

- Number of days prior to the ED visit the remote monitoring system detects changes in vital parameters (time interval expressed in days, description of the changes in trends of the vital parameters, theoretical impact of the remote monitoring system on early intervention expressed in days)
- Compliance rate to the remote monitoring system (expressed in %)

Secondary objective

- Acceptability and usability (expressed in %)
- Retrospective sub-study has the following endpoints: (see Paragraph 8 STUDY DESIGN)
    - Demographical phenotyping of Stage IV lung cancer patients (age, gender, comorbidities, smoking status/history, caregiver support, etc.)
    - Number of disease-related and therapy-induced complications
    - Tumor-specific/related information (metastasis, blood analyses, imaging, pulmonary functioning testings, etc.)
    - Treatment-related information (type of treatment and medication, time-to-treatment from diagnosis, number of hospitalizations, number of presentations to the ED department)
    - Outcomes and mortality (3, 6 and 12 months)

8. STUDY DESIGN

The ETERNALS project consists of two parts, a retrospective sub-study and the main, monocenter, prospective, single-arm interventional study (Figure 1).

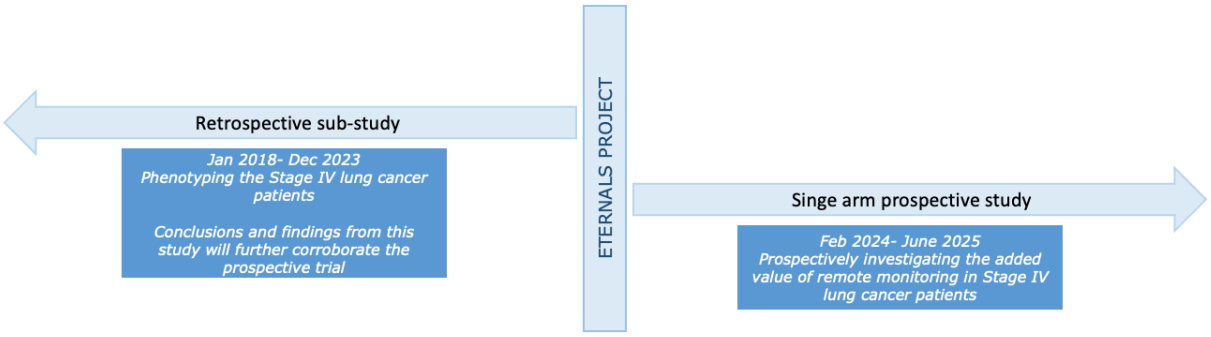


Figure 1. Overview of the presented studies within the ETERNALS project.

8.1 Retrospective sub-study: Phenotyping the Stage IV lung cancer patients

From Jan 2018-Dec 2023 data will be collected from the electronic medical record of Ziekenhuis Oost-Limburg, with the main objective to identify and phenotype patients diagnosed with Stage IV lung cancer. Conclusions and findings from this data will be compared to the prospective study, e.g., the number of ED visits to estimate a possible (theoretical) impact of the remote monitoring system on the time-to-ED-visit. In addition, this can also be incorporated in the estimation of the remote monitoring reduced complication rate and mortality. Moreover, this data is also important for the insights of the compliance rates in the prospective trial (e.g., number of comorbidities, age, the presence of an informal caregiver, severity of disease, etc.). The specific endpoints are described in Paragraph 7.3 Endpoints.

Data that will be collected during this retrospective study consists of, but is not limited to:

- Age
- Gender
- Smoking status and history
- Imaging results (PET, CT, etc.)
- Current and previous treatment in relation to the cancer diagnosis
- Mortality
- Time in between diagnosis, treatment and death/recovery
- Number of ED visits, and associated complications, treatment and hospital duration
- Number of rehospitalizations
- Medication profile
- Comorbidities (diabetes, heart failure, hypertension, etc.)
- Treatment-induced complications, toxicity
- Family history of cancer
- Tumor-specific information (metastasis, etiology, etc.)

8.2 Prospective single-arm monocenter interventional feasibility study:

This is a single-arm, unblinded, interventional feasibility study in which the integrated remote monitoring system using a wearable device will serve to follow-up lung cancer patients receiving cytotoxic chemotherapy. Patients will be included after receiving the diagnosis of lung cancer with indication to treat with cytotoxic chemotherapy. After signing the informed consent patients receive the wearable device to monitor their vital parameters at home, awaiting their first round of chemo (baseline). Next, patients will keep wearing the wearable device daily, which enables the remote monitoring with the care team until they have finalized their entire chemotherapy cycle (4 rounds, in which each round is followed by 3 weeks of recuperation). This implies the total project duration per patient corresponds to 15 weeks of remote monitoring (Figure 2).

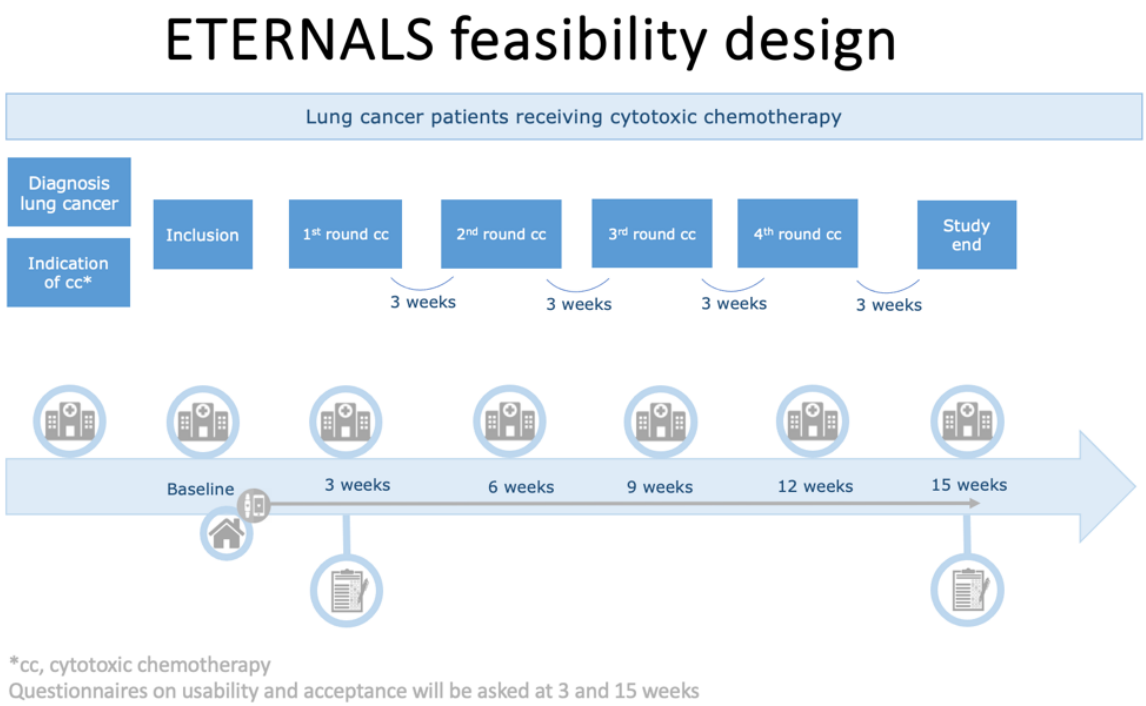


Figure 2. Overview of the ETERNALS prospective single-arm study timeline.

8.2.1 Wearable device – Oura ring

The wearable device patients receive is an Oura ring (Figure 3), which has the capacity to measure vital signs in a very unobtrusive manner. The vital signs that will be measured are: heart rate, heart rate variability (HRV), oxygen saturation, level of activity, sleep (incl sleep stages), sleep quality, early illness detection (shifts in temperature and HRV), temperature and stress (based on temperature, HRV and sleep).

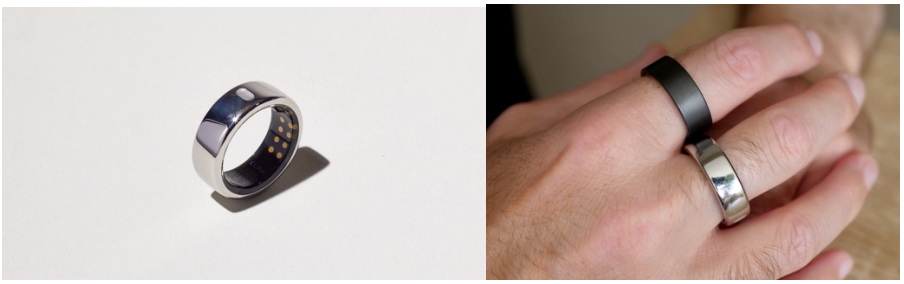


Figure 3. The Oura ring, which consists of several sensors to measure vital signs. The Oura ring is sized to the desired finger.

The choice for this wearable is based on its unobtrusiveness, its wide range of parameters it can measure and the battery life, which lasts up to 7 days. The ring can be worn on the finger of choice, of which the size is determined via the sizing kit. The Oura ring is a fitness device (CE marked, see Appendix 'Declaration of conformity Oura Ring and charger'), and is not classified as a medical device, nor will it be used in safety or performance testing, and therefore, it does not fall under the classification of the medical device regulation (MDR).

8.2.1.1 GDPR compliance of Oura ring servers

Oura uses technical and organizational safeguards to keep the data safe and secure. Where appropriate, these safeguards include measures such as anonymization or pseudonymization of personal data, strict access control, and the use of encryption to protect the data they process. They also ensure their staff receives adequate training to guarantee personal data is processed only in accordance with their internal policies, consistent with their obligations under applicable law, i.e., GDPR. Oura does not sell or rent the patient's personal information and only shares the personal data with certain trusted service providers after consent. They also require these service providers to protect the personal information to at least the same standards that they do.

Oura upholds the security measures by routinely testing their services, systems, and other assets for possible security vulnerabilities. They update the Oura App and the ring firmware regularly. They recommend to always having the latest app and firmware versions installed to maximize the protection of your data. Oura's data privacy practices are maintained in compliance with the California Consumer Privacy Act of 2018 (CCPA) and the General Data Protection Regulation (GDPR).

Data is transferred once every 24 hours to the server automatically. The patients connect the Oura ring to the Oura App via Bluetooth on their smartphone. For this study, data will be pseudonymized, meaning a study email and ID will be used to generate an account for the patient. Therefore, the data is also already pseudonomized on the Oura servers.

Oura stores personal data primarily within the geographic region where it is collected (EU server based).

9. STUDY POPULATION

The study population will only be described for the prospective feasibility study.

The study will enroll a total of 50 subjects over a period of 12 months. They will be recruited in 1 center located in Belgium, Ziekenhuis Oost-Limburg. Patients that receive the diagnosis of Stage IV lung cancer, are proposed therapy via cytotoxic chemotherapy and are compliant to the inclusion criteria are eligible to participate to the study. Eligible patients will be screened by the principal investigator (PI), after which they will receive information concerning the study. All screened patients will be entered into the Screening Log. The patients will receive enough time to review the informed consent and provided information and they will have time to ask questions to the PI (in accordance with the Declaration of Helsinki and GDPR). After signing the informed consent, the patient will be enrolled in the study as described in the paragraph 'STUDY PROCEDURES AND ASSESSMENTS'.

9.1 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria;

Provide signed and dated informed consent

Inclusion criteria:

- Patient must be in the possession of a smartphone
- Diagnosis of Stage IV lung cancer patients treated with cytotoxic chemotherapy
- Older than 18 years of age

An inherent consequence of remote monitoring is the exclusion of patients that not have a smartphone. However, recent literature suggests that 92% of the Belgian population has access to a smartphone [9].

9.2 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Life expectancy of less than 6 weeks
- Not able to understand the Dutch language

9.3 Subject withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study.

10. STUDY INTERVENTION

10.1 Description of the study intervention

Eligible patients are screened (i.e., Stage IV lung cancer and being treated with cytotoxic chemotherapy) and provided with the necessary information. No randomization is done, as this is a single-arm study design. Patients are approached in-hospital during their routine visits and consultations with their treating physicians. Patients can also be approached when hospitalized (only when they have not initiated their chemotherapy yet). In other words, patients do not need to plan an additional, unplanned visit to the hospital to be enrolled. After signing the informed consent and prior to the patients' first round of cytotoxic chemotherapy they will be equipped with the Oura ring.

First, the patient will be asked to test the sizing kit and communicate his/her finger of preference to wear the Oura ring. The sizing kit will help to identify the ring size that suits best to the diameter of the preferred finger of the patient, and that guarantees the best contact to the finger to have the best measuring capabilities. Once the size is determined, the patient will receive the Oura ring (i.e., the sizing kits offers a variety of sizes, of which we have all rings directly available). **The patient is asked to wear the ring on the same finger during the entire study and to only take the ring off when charging.** In other words, the patient is asked to wear the ring throughout the entire day. The study team will provide the patient with an e-mail address (e.g., eternals001@mobilehealthunit.org) that will be used to create an account on Oura Web and app. At the site the deidentifying key will be kept in a secure folder in 'Teams'. The patient will be asked to download the Oura App on his/her smartphone. Next, the study team will help the patient in logging into the Oura App and Web and connecting the Oura ring with Bluetooth to the patient's smartphone. Once all the connections are set in place, the patient starts wearing the Oura ring and the study starts. The data will be checked twice a week, to check for compliance or to identify possible technical issues. Patients will be made attentive that when they experience any distress, clinical deterioration, etc. they need to present themselves to the ED. The patient will be made attentive this remote monitoring system is not an alarm system/ being reviewed 24/7, nor that any interventions based on the study data will be made. The patient will wear the Oura ring for approximately 15 weeks, after which he/she will return the ring to the hospitals in accordance with a routine visit. After the first and third round of chemotherapy, and at the end of the study a questionnaire will be asked to the patient (i.e., mHealth Usability questionnaire, MAUQ).

In addition, the healthcare practitioners (i.e., treating physician and nurse) will be asked to fill in the System Usability questionnaire (SUS) once after using the Oura Web platform to review the data. This will be done after a training session that will be provided by the study team. Important to note is that the nurse/treating physician will not act upon the study data and the standard-of-care is applied.

11. STUDY PROCEDURES AND ASSESSMENTS

No additional visits or procedures are required when for the patient when participating to the study. Once the informed consent is signed, data from the electronic medical record (EMR) will be recorded and updated if/when changed during the study*:

- Demographic data (age, gender, comorbidities, relevant medical history, smoking status/history)
- Imaging results* (PET, CT, etc.)
- Current and previous treatment in relation to the cancer diagnosis
- Mortality*
- Time in between diagnosis, treatment and death/recovery*
- Number of ED visits, and associated complications, treatment and hospital duration*
- Number of rehospitalizations*
- Medication profile*

- Comorbidities (diabetes, heart failure, hypertension, etc.)
- Treatment-induced complications, toxicity*
- Family history of cancer
- Tumor-specific information (metastasis, etiology, etc.)*

11.1 Schedule of events

The hereafter schedule of events only apply to the prospective feasibility study.

Table 1. Overview of the schedule of events. The study intervention does not include additional procedures, the data will be checked twice a week. Abbreviations: EMR, electronic medical record; AE, adverse events.

Visit	Screening	Baseline/inclusion	1	2	3	4	EOS
Study days		Day 0	Day 30	Day 51	Day 72	Day 93	Day 114
Window		7 days	7 days	7 days	7 days	7 days	7 days
Informed consent		X					
Review inclusion/exclusion criteria	X						
Demographics/medical history/etc. (see prior section), hereafter referred to as EMR information		X					
Standard-of-care performed procedure and examinations		X	X	X	X	X	X
Study intervention		X	X	X	X	X	X
EMR information updated				X	X		X
AE Evaluation		X		X	X		X
Questionnaires			X		X		X

11.2 Screening period

As mentioned in paragraph 'STUDY INTERVENTION' patients that are eligible will be screened, only if they comply to the inclusion criteria. Screening will be done using the Screening log (Appendix Screening log). Screening will be done after diagnosis of Stage IV lung cancer. Screening will be done by the PI, after which he communicates his findings to the study team.

11.3 Intervention

Upon inclusion and signing the informed consent the following steps will be taken (as described in the paragraph 'Description of the study intervention'):

- Determining the ring size
- Setting up the pseudonymized account (e.g., eternals001@mobilehealthunit.org)
- Setting up the technical steps (account, Bluetooth, etc.)

- Providing education on using and charging the ring
- Repeating the study protocol

11.4 Follow-up period

Before the first round of cytotoxic chemotherapy the patient is equipped with the Oura ring. Next, the patient is expected to wear the ring the next 15 weeks, up to a maximum of 3 weeks after his/her last round of chemotherapy. Approximately 18-22 weeks of remote monitoring is expected per patient (dependent on the time between inclusion and initiation of cytotoxic chemotherapy).

11.5 End of study visit

During a routine care visit the patient is asked to take the Oura ring with him/her to the hospital. The patient can leave the Oura ring at the designated boxes that will be foreseen at the departments.

11.6 Study procedures

11.6.1 Informed consent

All subjects, or their legally authorized representative(s), must sign and date the informed consent document that has been approved by the appropriate EC before any study-specific procedures are performed. If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to him/her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

The PI or his/her representative is responsible for explaining the nature of the study to the subject and answering all questions regarding the study. Moreover, the PI or his/her representative is responsible for ensuring that the participant fully understands the nature and purpose of the study. No subject should be obliged to participate in the study. The subject must understand that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the subject's subsequent care. The subject must be allowed sufficient time to decide whether they wish to participate. The subject must be made aware of and give consent to direct access to his/her source medical records by study monitors, auditors, the EC, and regulatory authorities. The subject should be informed that such access will not violate participant confidentiality or any applicable regulations. The subject should also be informed that he/she is authorizing such access by signing the ICF.

After signing the informed consent, the original signed informed consent is retained by the site and a copy of the informed consent is provided to the subject.

The process of obtaining informed consent should be documented in the patient's source documents.

11.6.2 Study specific information that will be collected

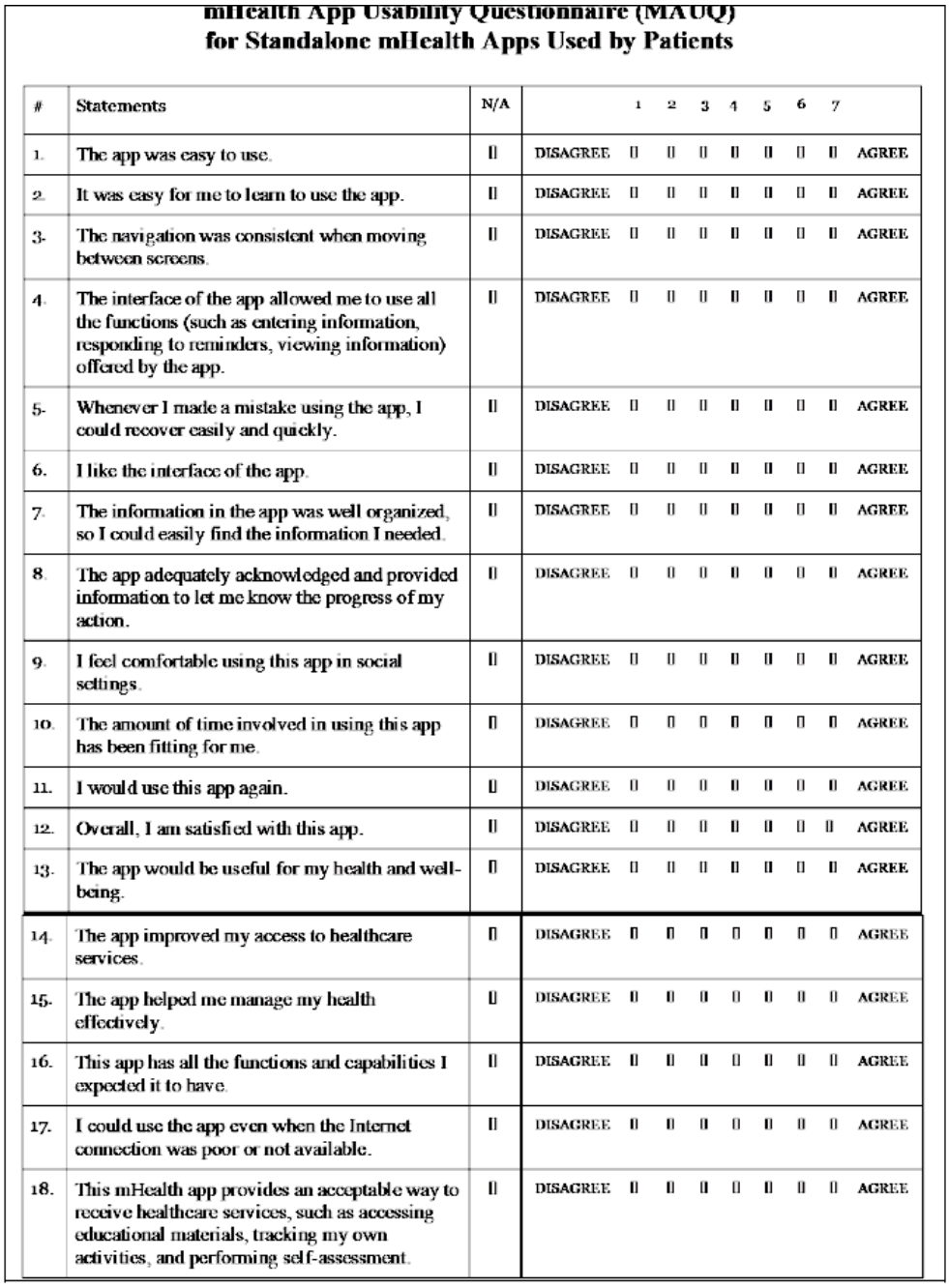
The following information will be collected at the start and during the study:

- Demographic data (age, gender, comorbidities, relevant medical history, smoking status/history)
- Imaging results* (PET, CT, etc.)
- Current and previous treatment in relation to the cancer diagnosis
- Mortality*
- Time in between diagnosis, treatment and death/recovery*

- Number of ED visits, and associated complications, treatment and hospital duration*
- Number of rehospitalizations*
- Medication profile*
- Comorbidities (diabetes, heart failure, hypertension, etc.)
- Treatment-induced complications, toxicity*
- Family history of cancer
- Tumor-specific information (metastasis, etiology, etc.)*

11.6.3 Questionnaires

All questionnaires used within this protocol are validated. Patients will be asked to fill in the MAUQ questionnaire (Figure 4) after the first and third round of chemotherapy and at the end of the study (i.e., when they return the Oura ring during a routine visit). The questionnaire will be translated to Dutch.



mHealth App Usability Questionnaire (MAUQ)
for Standalone mHealth Apps Used by Patients

#	Statements	N/A		1	2	3	4	5	6	7	
1.	The app was easy to use.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
2.	It was easy for me to learn to use the app.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
3.	The navigation was consistent when moving between screens.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
4.	The interface of the app allowed me to use all the functions (such as entering information, responding to reminders, viewing information) offered by the app.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
5.	Whenever I made a mistake using the app, I could recover easily and quickly.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
6.	I like the interface of the app.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
7.	The information in the app was well organized, so I could easily find the information I needed.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
8.	The app adequately acknowledged and provided information to let me know the progress of my action.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
9.	I feel comfortable using this app in social settings.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
10.	The amount of time involved in using this app has been fitting for me.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
11.	I would use this app again.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
12.	Overall, I am satisfied with this app.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
13.	The app would be useful for my health and well-being.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
14.	The app improved my access to healthcare services.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
15.	The app helped me manage my health effectively.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
16.	This app has all the functions and capabilities I expected it to have.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
17.	I could use the app even when the Internet connection was poor or not available.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE
18.	This mHealth app provides an acceptable way to receive healthcare services, such as accessing educational materials, tracking my own activities, and performing self-assessment.	☐	DISAGREE	☐	☐	☐	☐	☐	☐	☐	AGREE

Figure 4. mHealth Usability questionnaire is a validated questionnaire that will be used to assess the use of the Oura ring and app by the patient.

The healthcare practitioners (i.e., nurse and one treating physician) will be asked to fill in the SUS questionnaire after they received a training session from the study team. The questionnaire will also be translated to Dutch.

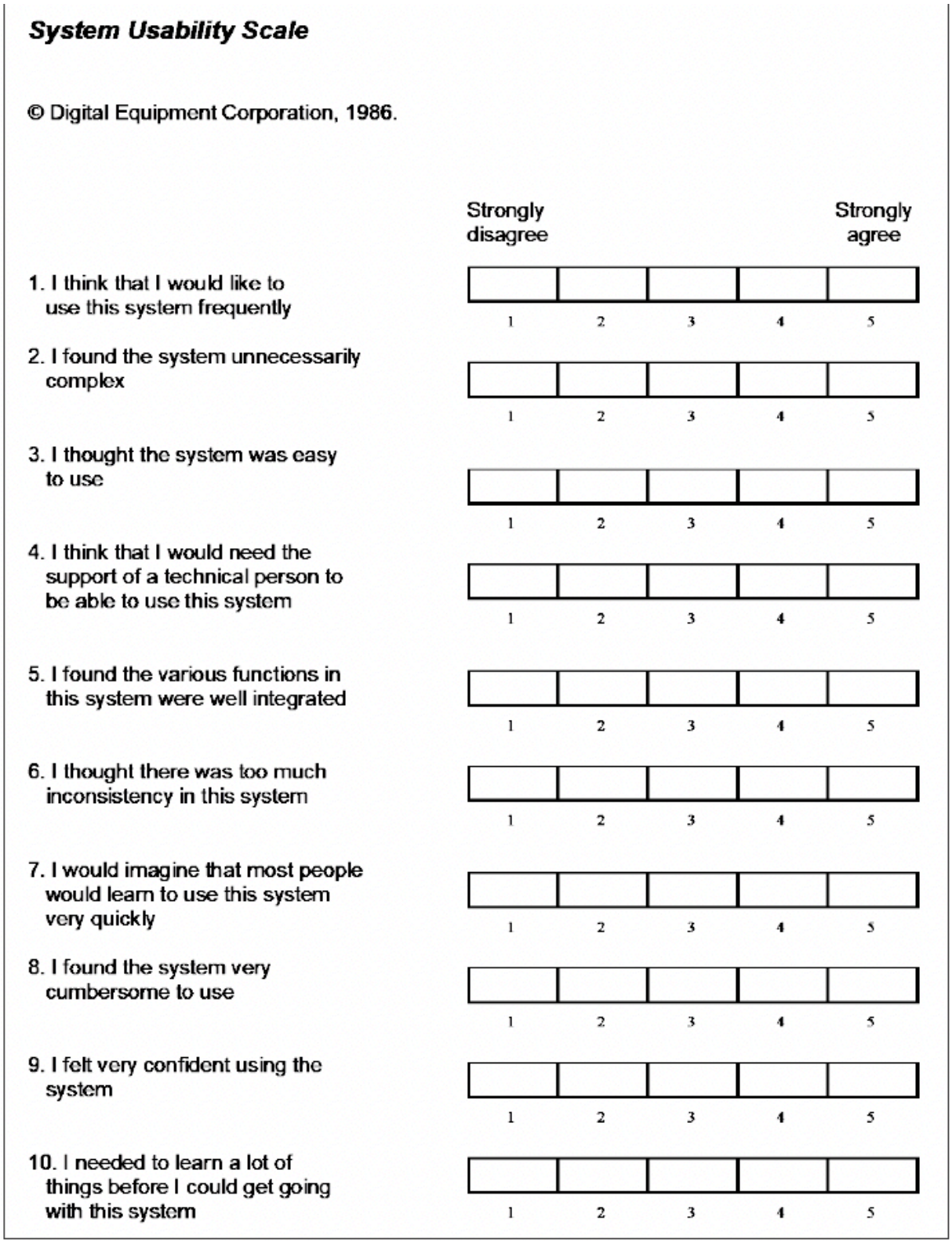


Figure 5. The system usability Scale questionnaire will be used to assess the potential of the Oura ring and its associated platform by the healthcare practitioners.

12. SAFETY REPORTING

12.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a subject during the study, related to the Oura ring.

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- Results in death (note that death is an outcome of an event; the event(s) causing death should be recorded); or
- Is life-threatening; or
- Requires inpatient hospitalization or prolongation of existing hospitalization; or
- Results in persistent or significant disability/incapacity; or
- Requires medical or surgical intervention to prevent life threatening illness; or
- Results in a congenital anomaly/birth defect

Note that a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.

A **Device Deficiency (DD)** is any inadequacy of an investigational device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

An **Adverse Device Effect (ADE)** is any adverse event related to the use of an investigational device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes as well any event that is a result of a use error or intentional abnormal use of the investigational medical device.

A **Serious Adverse Device Effect (SADE)** is any ADE that:

- Results in death (note that death is an outcome of an event; the event(s) causing death should be recorded); or
- Is life-threatening (at the time of the event); or
- Requires inpatient hospitalization or prolongation of existing hospitalization; or
- Results in persistent or significant disability/incapacity; or
- Requires medical or surgical intervention to prevent life threatening illness; or
- Results in a congenital anomaly/birth defect

An **Unanticipated Serious Adverse Device Effect (USADE**) is a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

The severity of an event refers to the extent to which it affects the participant's daily activities. This severity will be judged by the investigator based on his/her discretion and the definitions of severity as follows:

- Mild: The event doesn't affect the participant's daily activities.

- Moderate: The event interferes with the participant's daily activities and may or may not require medical intervention.
- Severe: The event prevents the participant to perform his/her daily activities and requires therapeutic intervention.

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors. The following guidelines are used to assess relationship of an event to study intervention:

- Related (Possible, Probable, Definite)
    - The event is known to occur with the study intervention.
    - There is a temporal relationship between the intervention and event onset.
    - The event abates when the intervention is discontinued.
    - The event reappears upon a re-challenge with the intervention.
- Not Related (Unlikely, Not Related)
    - There is no temporal relationship between the intervention and event onset.
    - An alternate etiology has been established.

12.2 Collection and reporting of Adverse Events

All subjects will be monitored for AEs during the study. All AEs will be recorded by the investigator from the time the subject signs informed consent until the end of study visit. Any significant finding that was present prior to administration of the study intervention will be considered as medical history.

All AEs and SAEs reported spontaneously by the subject or observed by the investigator or his/her staff will be recorded in the medical file of the patient. They will be reported to the sponsor without undue delay by entering them in the eCRF.

The investigator will report all SAEs within 24 hours of notice to the sponsor and, if requested by national law or regulation, to the appropriate EC.

The sponsor will report the fatal and life-threatening related SAEs to the EC upon the requirements of the EC.

13. RISK BENEFIT ANALYSIS

The risk benefit analysis will only be described for the prospective feasibility study.

Risks

No major risks are associated to participate to the study, as no interventions based on the study will be done and standard-of-care is still applied. The following possible risks are associated to the study;

- Patients will be able to see their data, which might cause concerns regarding their health. Patients will be made attentive that no interventions can occur based on the study data and that they should present themselves at the ED/general practitioner (GP) if they experience any clinical deterioration.

- Patients might lose interest in wearing the Oura ring, which will be picked up by the study team as they will review the data twice a week. In order to uphold the compliance rate, the study team will contact the patient in trying to motivate the patient into wearing the ring. The number of contacts will also be recorded to get a good estimation of the actual compliance rate.
- Data security: patient that might have concerns on who has access to their data will be mitigated because a pseudonymized email is used. Therefore, only the PI and study team will know the identity of the patient (and this information is of course not available to Oura).

Benefits

This study will provide no direct benefit to the participating patients, however it does create very valuable insights:

- The added value of in-home monitoring (i.e., remote monitoring system) of the vital signs can be investigated via changes in trends/vital signs
- Use of the remote monitoring system within this population will also be addressed (i.e., via the compliance rate and the number of contacts that have been made)
- A theoretical assumption can be made on the effect of the remote monitoring system on the number of ED visits and complications of the patient
- Phenotyping the patient will also provide valuable insights on where the remote monitoring system could play a supportive role
- The burden and advantages of the remote monitoring system can be assessed

14. STATISCIAL ANALYSIS

14.1 Statistical hypothesis

The main hypothesis is to investigate the insights the remote monitoring system can provide on vital signs and trends prior to an ED visit and/or clinical deterioration of the patient (i.e., time-to-ED-visit).

14.2 Sample size calculation

The sample size calculation is only described for the prospective feasibility study.

Currently patient-reported outcome measures are being used in the lung cancer patient population to assess their health remotely. However, applying a remote monitoring system using a wearable (i.e., Oura ring) has to our knowledge not been conducted (only for symptom management or to report PROMs). As this prospective feasibility study also does not imply an intervention based on the study data and the predefined objectives cannot be translated to means to determine the sample size, a sample size of 50 patients is determined.

14.3 Statistical analysis plan

Retrospective study

The retrospective study will mainly be descriptively described (means, %, standard deviations and interquartile ranges). Difference in phenotyping between groups will be done using the appropriate type of test, dependent on the distribution (t-test, Mann-Whitney-U test, etc.).

Prospective feasibility study

Mainly descriptive statistics will be used to describe the patient population and compliance rate.

15. ETHICAL CONSIDERATIONS

The study will be conducted according to the legal and regulatory requirements outlined in the guidelines for Good Clinical Practice (International Conference on Harmonization), the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) the EU GDPR 2016/679, the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights, the sponsor's applicable standard procedures, and other regulatory requirements as applicable.

15.1 Ethics Committee review and reports

Prior to the start of this study, this protocol and other related documents (e.g. ICF, questionnaires, etc.) will be submitted for review to the EC as well as to all ECs of the participating sites. The study will not start until approval has been obtained. Any subsequent protocol amendments will be submitted to the appropriate EC to seek approval.

Additionally, an Annual Progress Report on a yearly basis will be submitted to the EC and the EC will be notified of the end of study. In case the study would be ended prematurely, this will be notified to the EC and the notification will include the reasons for premature termination. After termination of the study a summary of the study results will be submitted to the EC.

15.2 Amendments

Unless for urgent reasons as specified in ICH-GCP E6(R2) section 4.5.4, substantial amendments will not be implemented prior to EC review and approval, as applicable.

A "substantial amendment" is defined as any change to any aspect of the clinical trial which is made and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

15.3 General Data Protection Regulation

The investigator and the participating site will treat all information and data relating to the study as confidential and will not disclose such information to any third parties or use such information for any purpose other than the performance of the study.

The identity of the participant will be kept confidential according to the GDPR of 27 April 2016 (in application on 25 May 2018), to the Belgian law of 30 July 2018 on the protection of natural persons with regard to the processing of personal data and the Belgian patient's right law (22 August 2002). Personal data will be coded. Participants will be assigned a unique identifier code. Participants will not be identified by name or in any other recognizable way in any of the records, results or publications related to the experiment. Any records or datasets that are transferred to the sponsor will contain the unique identifier only. Participant data should be kept in a secure location. Access to participant data will be limited to authorized study members only.

16. DATA MANAGEMENT

16.1 Data collection tools

Source data will be collected and recorded by the PI and his/her study team in the electronic and/or paper patient file of the subject. Patient reported outcomes will be collected via electronic questionnaires that will be filed in an electronic case report form.

The central database that will be used to collect study data is Castor. Access to this database will be granted to the investigator and appointed study members. CASTOR EDC complies with all applicable medical data privacy laws and regulations: GCP, 21 CRF Part 11, EU Annex 11, the European Data Protection Directive, ISO9001 and ISO27001/NEN7510.

16.2 Data handling

The PI and his/her study team (under supervision of the PI) are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Collected study data will be transcribed from the source documents into the eCRF by the PI or his/her study team. This will be done as soon as possible after the visit took place.

All data that will be provided to the sponsor will be pseudonymized. Every subject receives a unique study number upon enrolment in the study. This unique number can only be linked to the participant through a subject identification file, containing at least the subject's name, date of birth, hospital ID and unique study number. It is the responsibility of the PI to safeguard the subject identification file.

16.3 Data storage

Specify the length of time the PI has to retain all records pertaining to this study after study completion and how these records need to be stored during the study and after study completion. Indicate whether permission is required (and from whom) prior to destruction of records. The following sentences can be used to describe the data storage:

All source data needs to be retained by the PI for a minimum period of or 20 years after study completion. Both during the study and after study termination, source documents will be stored in a secured location with restricted access. No records may be destroyed during the retention period without written approval of the sponsor.

17. MONITORING, AUDIT AND INSPECTION

17.1 Monitoring

In accordance with ICH-GCP E6(R2) the Sponsor is responsible for monitoring the study to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the study procedures have been followed as shown in the approved protocol, and that relevant study data have been collected and reported in a manner that assures data integrity. Therefore, source data will be compared with the data recorded in the eCRF. Remote and on-site monitoring of the study will be performed by qualified individuals (independent from the site study staff) according to the monitoring plan. The PI/participating site will permit direct access to the study data and corresponding source data and to any other study related documents or materials to verify the accuracy and completeness of the data collected. More details about the monitoring strategy are described in the study specific monitoring plan.

The study monitoring plan has been developed on the trial risk assessment which will be done by exploring the study dataset and performing site visits.

17.2 Audit and inspection

The PI will permit direct access to study data and documents for the purpose of monitoring, audits and/or inspections by authorized entities such as but not limited to: the sponsor or its designees and competent regulatory or health authorities. As such eCRFs, source records and other study related documentation (e.g. the investigator site file, pharmacy records, etc.) must be kept current, complete, and accurate at all times.

18. PUBLICATION AND DATA SHARING POLICY

The sponsor will manage study publications with the goal of publishing findings from the data. Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria. Authors must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data; AND
- Drafting the article or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All investigators not listed as co-authors will be acknowledged as the “Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible. Any other contributors will be acknowledged by name with their specific contribution indicated. Based on the recruitment, site investigators might also be part of the Authorship.

Considering that ongoing research contributing to the completion of datasets must not be compromised by premature or opportunistic sharing and analysis of data, the sponsor will not release the data of this study until the primary study results have been published, unless authorized for release has been granted.

The sponsor follows the European FAIR principle (Findable – Accessible – Interoperable – Reusable) and acknowledges that data need to be open as possible and as closed as necessary.

19. INSURANCE

In accordance with the Belgian Law relating to experiments on human persons dated 07 MAY 2004, the sponsor will assume, even without fault, the responsibility of any damages incurred by a participant and linked directly or indirectly to the participation to the study and will provide compensation for the damages. The sponsor will therefore take out a no-fault insurance. The participating site will ensure appropriate insurance to meet the potential legal liability of the investigators/collaborators arising from harm to participants in the conduct of the study.

20. REFERENCES

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21. Appendix

21.1 Declaration of conformity Oura Ring and charger

EU Declaration of Conformity

Model name: Gen3 and Gen3 charger

Address: Ōura Health Oy, Elektroniikkatie 10, 90590 Oulu, Finland

This declaration of conformity is issued under the sole responsibility of the manufacturer. Object of the declaration, this is identification of the radio equipment allowing traceability;

The object of the declaration described above is in conformity with the relevant Community harmonisation:

- Directive2014/53/EU–RadioEquipment
- Directive2011/65/EU-RoHS
- Directive2012/19/EU–WEEE

The conformity with the essential requirements of the following directives has been demonstrated against the standards:

Standard reference	Article of Directive 2014/53/EU
EN 62368-1:2014 + AC:2015 + A11:2017 EN 62479:2010	3.1 (a): Health and Safety of the User
Draft ETSI EN 301 489-1 V2.2.3, EN 301 489-17 V3.2.4	

EN 55011:2016/A1:2017 EN 61000-6-1:2007 EN 61000-6- 3:2007/A1:2011/AC:2012 EN 62233:2008/AC:2008	3.1 (b): Electromagnetic Compatibility
ETSI EN 300 328 v2.2.2	3.2 : Effective use of spectrum allocated

The Notified Body (Dekra, 1909) has performed the documentation assessment of the product and issued the EU-Type Examination Certificate according to directive 2014/53/EU. Thus, CE is placed on the product. The Technical Documentation (TD) relevant to the product described above and which supports this Declaration of Conformity, is held at: Ōura Health Oy, Elektroniikkatie 10, 90590 Oulu, Finland. ŌURA is the company behind the Oura Ring — a wearable health platform that delivers personalized health data, insights and daily guidance. At ŌURA, our mission is to empower every person to own their inner potential. We believe health is a daily practice and, with insights and guidance, you can control the course of your health to live a more balanced life. The Oura Ring Gen3 is smarter and more comprehensive than ever. Your daily health guide for a balanced life, with 24/7 health tracking and personalized insights that translate your body's hidden messages and have the power to transform how you feel, day and night. Updated with our new, more accurate, state-of-the-art sleep staging algorithm, daytime and workout heart rate monitoring, blood oxygen (SpO2) sensing, Period Prediction, and so much more.

Signed for and on behalf of Ōura Health Oy, in San Francisco 10/11/2021

Michael Chapp

EU Declaration of Conformity

Model name: OURA and OURA charger

Address: Ōura Health Oy, Elektroniikkatie 10, 90590 Oulu, Finland

This declaration of conformity is issued under the sole responsibility of the manufacturer

Object of the declaration, this is identification of the radio equipment allowing traceability;

The object of the declaration described above is in conformity with the relevant Community harmonisation:

- Directive2014/53/EU–RadioEquipment
- Directive2011/65/EU-RoHS
- Directive2012/19/EU–WEEE

The conformity with the essential requirements of the following directives has been demonstrated against the standards:

Standard reference	Article of Directive 2014/53/EU
EN 60950-1:2006 + A11:2009 + A1:2010 + A12:2011 + AC:2011 + A2:2013 EN 62479:2010	3.1 (a): Health and Safety of the User
Draft ETSI EN 301 489-1 V2.2.0 (2017-03) Draft EN 301 489-17 V3.2.0 (2017-03) EN 55011:2016/A1:2017 EN 61000-6-1:2007	3.1 (b): Electromagnetic Compatibility

ETSI EN 300 328 v2.1.1 (2016-11)	3.2 : Effective use of spectrum allocated

The Notified Body (Dekra, 1909) has performed the documentation assessment of the product and issued the EU-Type Examination Certificate according to directive 2014/53/EU. Thus, CE is placed on the product. The Technical Documentation (TD) relevant to the product described above and which supports this Declaration of Conformity, is held at: Ōura Health Oy, Elektroniikkatie 10, 90590 Oulu, Finland. OURA is a revolutionary wellness ring and app, designed to help user to get more restful sleep and to perform better. It enables user to learn how the lifestyle choices affect user's sleep, and how the quality of the sleep affects user's ability to perform. The OURA ring can automatically tell when user is sleeping. When user goes to sleep, the OURA ring analyzes the quality of the rest and recovery by measuring the heart rate (optically), respiration rate, body temperature, and movement. While user is awake, it monitors the duration and intensity of the activities, and the time user spends sitting. The OURA app integrates and visualizes this data to identify patterns between the sleep quality and daily activities. By understanding how well user slept and recharged, it can determine the readiness to perform and help user adjust the intensity and duration of the day's activities. It can also uncover actionable insights for changes to the daily activities that can help user sleep better.

Signed for and on behalf of Ōura Health Oy, in Oulu 27/6/2018

Michael Chapp

EU Declaration of Conformity

We Oura Health Oy Elektroniikkatie 10 90590 Oulu Finland Declare under our sole responsibility that the following products Equipment: Wellness ring Brand name: Oura Model/type: LE1 is in conformity with the Directive 2014/53/EU (RED) Directive 2011/65/EU (RoHS) and the following standards and technical specifications have been applied:

RF spectrum use	EN 300 328 V2.2.2
EMC (article 3.1b)	EN 301 489-1 V2.2.3 EN 301 489-17 V3.2.4 EN 55011:2016/A11:2020 EN 61000-6-1:2017 EN 61000-6-3:2021
Health & Safety	EN 62368-1:2014 + AC:2015 + AC:2017 + A11:2017 EN 62479:2010

Signed for and on behalf of Ōura Health Oy, in Oulu 24.03.2022

Jyri Suokas

Senior Quality Specialist

EU Declaration of Conformity

We Oura Health Oy Elektroniikkatie 10 90590 Oulu Finland Declare under our sole responsibility that the following products Equipment: Inductive Charger Brand name: Oura Model/type: LE1 Charger

is in conformity with the Directive 2014/30/EU (EMC) Directive 2011/35/EU (LVD)

and the following standards and technical specifications have been applied:

	EN 55011 (2016)/ A11 (2020)
2014/30/EU (EMC)	EN 61000-6-1 (2017) EN 61000-6-3 (2021)
	EN 62368-1:2014 + AC: +2015
2011/35/EU (LVD)	AC:2017 + A11:2017 EN 62233 (2008)/ AC (2008)

Signed for and on behalf of Ōura Health Oy, in Oulu 24.03.2022

Jyri Suokas

Senior Quality Specialist

21.2 Screening log

Protocol info	
Title	ETERNALS
Number	Z2023080
Version	V1
Date	23NOV2023

Patient Name	Suffices to all inclusion criteria	Does not comply to any exclusion criterion	Date of screening (DDMMYY)	Investigator Name	Investigator signature
	☐ In possession of a smartphone ☐ Diagnosed with stage IV lung cancer and being(/planned to be) treated with cytotoxic chemotherapy ☐ Older than 18 years of Age	☐ Life expectancy of less than 6 weeks ☐ Not able to understand the Dutch Language			
	☐ Patient is in possession of a smartphone ☐ Diagnosed with stage IV lung cancer and being(/planned to be)	☐ Life expectancy of less than 6 weeks ☐ Not able to understand the Dutch Language			

	treated with cytotoxic chemotherapy ☐ Older than 18 years of Age				
	☐ Patient is in possession of a smartphone ☐ Diagnosed with stage IV lung cancer and being(/planned to be) treated with cytotoxic chemotherapy ☐ Older than 18 years of Age	☐ Life expectancy of less than 6 weeks ☐ Not able to understand the Dutch Language			

Protocol info	
Title	ETERNALS
Number	Z2023080
Version	V1
Date	23NOV2023

Patient Name	Suffices to all inclusion criteria	Does not comply to any exclusion criterion	Date of screening (DDMMYY)	Investigator Name	Investigator signature
	☐ In possession of a smartphone ☐ Diagnosed with stage IV lung cancer and being(/planned to be) treated with cytotoxic chemotherapy ☐ Older than 18 years of Age	☐ Life expectancy of less than 6 weeks ☐ Not able to understand the Dutch Language			
	☐ Patient is in possession of a smartphone ☐ Diagnosed with stage IV lung cancer and being(/planned to be) treated with cytotoxic chemotherapy	☐ Life expectancy of less than 6 weeks ☐ Not able to understand the Dutch Language			

	☐ Older than 18 years of Age				
	☐ Patient is in possession of a smartphone ☐ Diagnosed with stage IV lung cancer and being(/planned to be) treated with cytotoxic chemotherapy ☐ Older than 18 years of Age	☐ Life expectancy of less than 6 weeks ☐ Not able to understand the Dutch Language			