Protocol Full Title prospective observational trial:

A prospective non-randomised control study to evaluate the efficacy of a physical activity promotion program on the experience of physical activity in patients with stage III and IV non-small cell lung cancer (NSCLC) with objective response after initial treatment

Protocol Acronym/short title:

Monitoring and telecoaching of physical activity in patients with stage III and IV non-small cell lung cancer

Version and date of final protocol:

Version 5 amendment (15-03-2019).

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1. Study Synopsis

Title of clinical trial	A prospective non-randomised control study to evaluate the efficacy of a physical activity promotion program on the experience of physical activity in patients with stage III and IV non-small cell lung cancer (NSCLC) with documented disease control (stable disease, partial response or complete response defined by RECIST V1.1) after initial treatment
Protocol Short Title/Acronym	Monitoring and telecoaching of physical activity in patients with stage III and IV non-small cell lung cancer
Sponsor name	UZ Leuven
Principal Investigator	Prof. Dr. Wim Janssens
Medical condition or disease under investigation	Patients with stage III and IV NSCLC with documented disease control (stable disease, partial or complete response defined by RECIST V1.1) at least 6 months after start of first line treatment.
Purpose of clinical trial	The objective of this pilot study is to investigate if physical activity can be improved by telecoaching in patients with advanced stages of lung cancer in remission. The physical activity telecoaching promotion program is a personalized, coaching program using a direct measurement of physical activity to facilitate the semi-automated coaching.

Primary objective	To assess the impact of a telecoaching program on physical activity in patients with stage III and IV NSCLC in addition to usual care. This will be measured by the Dynaport movemonitor (Dynaport®), as the change in average daily number of steps at baseline (1 week preceding V3) and at the end (1 week preceding V4) in the intervention and the control group.
Secondary objective (s)	The secondary objectives are to assess: Change from baseline to 8 weeks in the coaching program and the control group in: • Change in health status assessed by QLQ-C30 (Cancer quality of life questionnaire) • Change in exercise capacity by 6 minutes walking distance Exploratory outcomes: Change from baseline to 8 weeks in the coaching program and control group. • Comparison of change between coaching and control group in number of daily steps, in health status assessed by QLQ-C30 and in 6 MWT • Time spent in at least moderate intense physical activity • Walking time and intensity of moving during walking • Symptoms and difficulties perceived during exercise (Pro Active questionnaire) • Health related quality of life as measured by SGRQ.
Trial Design	A prospective non-randomised control study
Endpoints	The amount of steps per day objectively measured with Dynaport Movemonitor after 8 weeks

Sample Size	32 patients
Summary of eligibility criteria	Inclusion criteria: 1. Patients diagnosed with stage III or stage IV NSCLC who have a documented disease control (stable disease, partial or complete response defined by RECIST V1.1) at least 6 months after start of first line treatment. Stage III patients can only be included, if first line treatment consisted of concurrent chemoradiotherapy and a consolidation immunotherapy if indicated (if PDL1 > 1% and no potential contraindications for immunotherapy). Stage IV patients, should have received only immunotherapy (PDL1 > 50%) or a treatment of at least 4 cycles of a platinum based chemotherapy. Maintenance therapy with chemotherapy and/or immunotherapy and administration of local radiotherapy is allowed. Patients with documented disease control can be included in the study until 2 years after starting up initial treatment. 2. > 18 years 3. Patients who are able to engage in a remote coaching program through the use of a smartphone Exclusion criteria: 1. Patients actively participating in a pulmonary rehabilitation program 2. Patients with sequential chemoradiotherapy for stadium III non-small cell lung cancer 3. The presence of orthopedic problems not allowing an increase in PA levels
Maximum duration of treatment of a Subject	8 weeks
Version and date of final protocol	Version 5 (15-03-2019)

Version and date of protocol amendments	Version 5 amendment 15-03-2019)

2. Background and rationale

Lung cancer has one of the highest mortality rates in both man and woman.[1]The most common type is non-small cell lung cancer (NSCLC).[2,3] When diagnosed, most of the patients have an advanced stage of lung cancer, which are not eligible for a curative intervention and can only be treated by chemotherapy or biologicals.[3,4]

A vast majority of patients with advanced lung cancer experiences various impairments resulting from symptoms of the disease (like dyspnoea, coughing, fatigue, appetite loss) and side effects from the treatment affecting their quality of life.[5,6] Today, long-term remission in advanced lung cancer is more frequently reached by the new targeted tumor therapies, often at the cost of a pronounced inactive lifestyle. Physical inactivity negatively influences the symptom burden, quality of life and likely prognosis, and should therefore be considered as an individual therapeutic goal.[7,8,9,10] Factors contributing to the level of physical activity in lung cancer include patient-level factors, such as symptoms, comorbidities, sedentary lifestyle, mood and fear, and environmental factors.[11]

For patients with lung cancer, exercise can be of contributory value. It increases strength and endurance and reduces fatigue. It may also help to decrease emotional issues following the diagnosis lung cancer and to better tolerate symptoms of the disease and its treatments.[9,12,13,14] Whether a physical activity promotion program is effective in improving daily physical activity and whether this improvement leads to changes in quality is not yet demonstrated.

Stimulating home-based, low-intensity exercise monitored with a pedometer including behaviour strategies (goal setting, contracting, feedback, consequences and/or cues) has shown promising results to improve physical activity.[15,16] Tele coaching interventions are attractive tools in this regard allowing remote communication and individual feedback through electronic devices like a smartphone and improving quality of life by treating patients in their own home environment and providing patients with independence by having them play an active role in their own treatment.[27,17,18,19,20] Furthermore it is less time consuming and a cost-effective solution compared to usual care.[20,21,22]

A few studies have been done to investigate the effectiveness of tele coaching in patients with cancer or cancer survivors. These studies showed that tele coaching is significantly more effective in increasing and maintaining moderate physical activity compared to usual care in cancer

survivors.[23,24,25,26] As far as we know, there are no studies that focussed on tele coaching for improving physical activity in patients with lung cancer in particular. As most of these patients are also suffering from COPD , in which these interventions have been proven extremely effective , there is an obvious need to develop such programs.

The telecoaching program uses a previously developed coaching program, developed and validated by our research group in COPD patients.[27] Briefly, the coaching will be facilitated by using a telecoaching system. Patients will be equipped with a step counter, which connects to a smartphone equipped with the needed coaching application.

Data from the stepcounter collected on the smartphone device will be shared using 'health care integrating information technology'.

3. Trial objectives and Design

3.1 Trial objectives

The objective of this pilot study is to investigate if physical activity can be improved by telecoaching in patients with advanced stages of lung cancer in remission. We hypothesize that a smartphone application, designed for a population with respiratory symptoms, will increase daily physical activity, which translates into significant improvements on quality of life. This uncontrolled pilot study will therefore address if a 8-week PA promotion telecoaching program in addition to usual care has the potential to improve physical activity and quality of life in patients with lung cancer for a limited burden and at low cost. If so, a randomized controlled trial in a larger patient group can be envisaged.

3.2 Primary endpoints

To assess the impact of a telecoaching program on physical activity in patients with stage III and IV NSCLC with objective response (partial response or complete response defined by RECIST V 1.1) after initial treatment. This will be measured by the activity tracker (Dynaport movemonitor), as the change in average daily number of steps at baseline (1 week preceding V3) and at the end of the study (1 week preceding V4).

3.3 Secondary endpoints

1. Change in health status assessed by QLQ-C30 (*Cancer quality of life questionnaire)*
2. Change in exercise capacity by 6 minutes walking distance

3.4 Exploratory endpoints

1. The time in at least moderate intense physical activity
2. Walking time
3. Intensity of moving during walking

4. Symptoms and difficulties perceived during exercise (clinical version of the PROactive tool, C-PPAC)Active)
5. Health related quality of life as measured by SGRQ (St. George's respiratory questionnaire)
6. Change from baseline to 8 weeks between the telecoaching program and the control group in average daily number of steps, QLQ-C30 and 6 MWT.

Activity monitor (Dynaport movemonitor)

The Dynaport® is the activity monitor that will be used in this study. It will be carried one week prior to visit 3 and one week prior to visit 4. It is an electronic device that is used to measure the patient's physical activity level (number of steps/day). The activity monitor provides valuable information of different aspects (i.e. different output parameters: time spent in at least moderate physical activity (MVPA), walking time, intensity of moving during walking, …) on physical activity, directly from the wearer, in real time and in real life. This monitor will be worn during the time patients are awake, and must not be worn during bathing or water sports activities. Mean daily step count has been chosen as primary outcome.

Clinical version of the PROactive questionnaire (C-PPAC)

The PROactive questionnaire investigates relevant dimensions of physical activity and is a PRO (patient reported outcome) tool that is developed for the measurement of physical activity in the daily life of COPD patients. The tool has 2 domain scores (difficulties experienced and experiences amount of PA) and a total score. We will use the clinical version of the PROactive tool, in which the responses are intended to reflect the patients experience over the preceding 7 days. Patients will complete the web-based version of this questionnaire on visit 3 and visit 4.

QLQ-C30 (*Cancer quality of life questionnaire)*

The QLQ-C30 is an internationally validated 30-item questionnaire assessing cancer-specific QOL. This widely used questionnaire comprises five functional scales (physical, social, role, cognitive and emotional functioning), 3 symptom scales (fatigue, pain, nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impacts of the disease. Each linear converted scale score ranges from 0 to 100. High scores for functional scales and for the global health status/QOL indicate better functioning, whilst high scores for symptom scales represent a higher level of symptom burden.

The test takes about 10 minutes. A copy of the English version is attached in Appendix 1.

SGRQ (St. George's respiratory questionnaire)

The SGRQ is a 50-item questionnaire developed to measure health status (quality of life) in patients with diseases of airway obstruction. Score are calculated for three domains: symptoms, activity and impacts (psycho-social) as well as a total score. A minimum change in score of 4 units was established as clinically relevant after patient and clinician testing. The SGRQ has been used in a range of disease groups including asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis.

The test takes about 25 minutes. A copy of the English version is attached in Appendix 1.

Six minute walking test (6MWT) and Borg CR10

All patients will undergo the Six minute walking test (6MWT). It is a reliable, valid and responsive outcome measure in patients with COPD and cancer patients. Patients will be asked to cover as much distance as possible in 6 minutes. The test will be carried out in accordance with ATS guidelines in a quiet corridor of at least 30 meters in length. Before and at the end of the test; heart rate, oxygen saturation and symptoms of dyspnea and fatigue (Borg scale CR 10) will be recorded. The result will be recorded and expressed as meters covered and as percentage of the predicted normal value. Patients will perform 2 six minute walking tests and the best of 2 tests will be retrieved.

3.5 Patient characterizing and safety measures

Patient characterizing:

1. Baseline demographic data
   (date of birth and gender, medical/surgical history, COPD history (if applicable), smoking history, current medication, height and weight.)
2. Lung function (Post bronchodilator spirometry, body plethysmography and diffusion capacity)
3. Medical history including oncological stage, type and treatment.
4. Co-morbidities based on self-report.

Safety measures:

Patients are asked to report any hospitalization and major medical events during the trial period.

Lung function

All lung function tests will be carried out according to ATS/ERS guidelines (Miller et al 2005) and post bronchodilator values will be recorded.

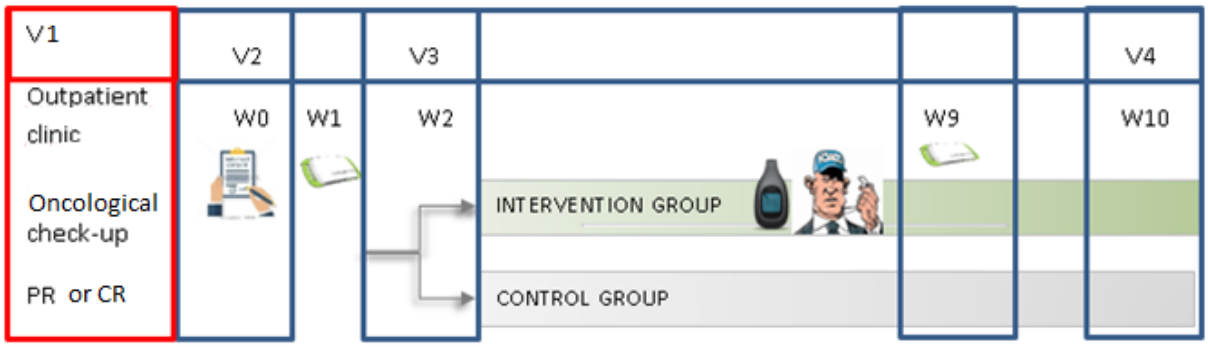
3.6 Trial Design

It will be a prospective non-randomised control study in which patients are evenly divided into the telecoaching group or usual care group according to owning a smartphone and their affinity with it. It is not possible to fully blind the investigator and patients. The trial will consist of 4 visits. An outpatient clinic visit (V1), a screenings visit (V2), a third visit (V3) at which the intervention will start and where the patients will be divided into the control or the intervention group and a final visit (V4) 8 weeks after starting up the intervention (V4).

Patients in both groups will receive a brochure during V3 explaining the importance of physical activity with recommendations to improve it. This brochure will be discussed together with the patients.

In the intervention group patients will receive the usual care in combination with the telecoaching intervention consisting of the following components: 1: motivational interview with the investigator during V3 discussing motivation, barriers, favourite activities and strategies to become more active; 2: a pedometer giving direct feedback on the amount of steps; 3: the coaching application linked to the step counter, which will be installed on the patient's smartphone. 4: telephone contact when a patient is non-compliant with either the use of the coaching intervention or with achieving the PA goals for 2 consecutive weeks.

3.7 Study diagram



3.8 Trial Flowchart

	Visit 1 Outpatient clinic	Visit 2	Visit 3	Visit 4
Oncological check-up (CT/labo/…) demonstrating PR after initial treatment	**X**			
Informed consent		X		
Baseline demographic data		X		
Medical history including oncological stage and type, co-morbidities		X		
Lung function	**X**			
Instruction of the importance of PA (+ explanation on the intervention)			X	
PA measurement by Dynaport movemonitor (measurement for 7 consecutive days)			X	X
Clinic version of the proactive questionnaire			X	X
QLQ-C30			X	X
6MWT			X	X
SGRQ			X	X

Legend:

X routine clinical practice

X Additional (study protocol)

X Indicate which tests are clinical routine in context of follow up after lung cancer treatment. All other tests are in context of study protocol and will be obtained by research staff.

4. Trial intervention

4.1 Investigational Medicinal product and dosing regimen

Telecoaching intervention:
The intervention group receives a step counter together with a coaching application installed on their smartphone. This application is a renewed version of the program used in a previous coaching trial, conducted by our research group (Demeyer 2017) and is based on the basic principles of behavioral change and contains four major domains.

Motivational interviewing:
A semi-structured interview is conducted to address barriers and enables to increase physical activity. Motivation and self-efficacy scores are asked to the patient.

Step counter:
The step counter gives direct feedback, expressed as amount of steps taken. Patient is instructed to wear this step counter every day, around the waist or wrist, as preferred.

The coaching application:
The coaching application, installed on the patient's smartphone, shows a daily goal (expressed as amount of steps per day) to the patient. This start goal is individual and based on the physical activity level at the beginning of the coaching intervention. This goal is weekly revised and patients themselves are able to increase the goal every week with +500 of +1000 steps per day.
Every evening, they are able to check the daily feedback platform, which gives them insights in their physical activity pattern of the day and previous weeks. Hereby they are able to evaluate their progression. At a regular basis, 'tip of the day' messages appear as a pop-up, to keep patients motivated. The last page of the application contains an action plan with activities discussed during the motivational interview in case there are difficulties to increase or maintain the physical activity levels.

4.2 Drug accountability
Not applicable.

4.3 Subject compliance
Not applicable.

4.4 Concomitant medication (non-IMP)

Not applicable.

5. Selection and withdrawal of subjects

5.1 Inclusion criteria

1. Patients diagnosed with stage III or stage IV NSCLC who have a documented disease control (stable disease, partial or complete response defined by RECIST V1.1) at least 6 months after start of first line treatment. Stage III patients can only be included, if first line treatment consisted of concurrent chemoradiotherapy and a consolidation immunotherapy if indicated (if PDL1 > 1% and no potential contraindications for immunotherapy). Stage IV patients, should have received only immunotherapy (PDL1 > 50%) or a treatment of at least 4 cycles of a platinum based chemotherapy . Maintenance therapy with chemotherapy and/or immunotherapy is allowed. Administration of local radiotherapy is allowed.
   Patients with documented disease control can be included in the study until 2 years after starting up initial treatment.
2. > 18 years
3. Patients who are able to engage in a remote coaching program through the use of a smartphone

3.1 Exclusion criteria

1. Patients actively participating in a pulmonary rehabilitation program
2. Patients with sequential chemoradiotherapy for stadium III non-small cell lung cancer
3. The presence of orthopedic problems not allowing an increase in PA levels

5.3 Selection of participants

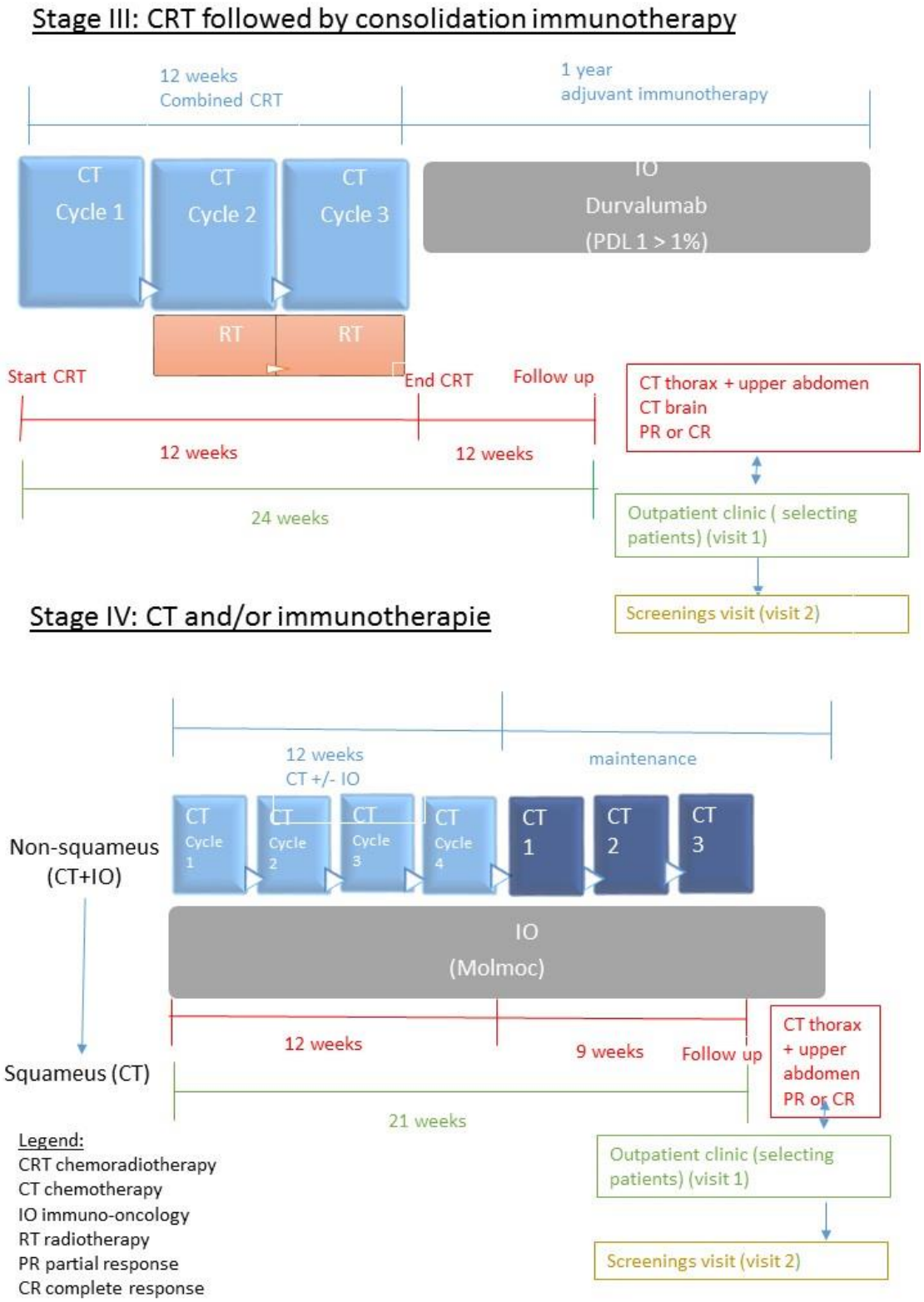
Patients will be screened for inclusion in the study during follow up visits in the outpatient lung cancer clinic at visit 1 (outpatient clinic).

Patients with stage III or stage IV NSCLC are included in the study if they have a documented objective partial or complete response (defined by RECIST V 1.1) around 6 months after start of first line treatment.

Stage III patients can only be included, if first line treatment consisted of concurrent chemoradiotherapy and a consolidation immunotherapy if indicated (if PDL1 > 1% and no potential contraindications for immunotherapy).

Stage IV patients, should have received only immunotherapy (PDL1 > 50%) or a treatment of at least 4 cycles of a platinum based chemotherapy. Maintenance therapy with chemotherapy or immunotherapy is allowed. The indication to start immunotherapy or chemotherapy will be discussed case by case based on a multidisciplinary discussion (Molmoc). (cfr figure 1)

Figure 1:


Stage III: CRT followed by consolidation immunotherapy
12 weeks
Combined CRT
1 year
adjuvant immunotherapy
CT Cycle 1
CT Cycle 2
CT Cycle 3
IO
Durvalumab
(PDL 1 > 1%)
RT
RT
Start CRT
End CRT
Follow up
CT thorax + upper abdomen
CT brain
PR or CR
12 weeks
12 weeks
24 weeks
Outpatient clinic (selecting patients) (visit 1)
Screenings visit (visit 2)
Stage IV: CT and/or immunotherapie
12 weeks
CT +/- IO
maintenance
Non-squameus (CT+IO)
CT Cycle 1
CT Cycle 2
CT Cycle 3
CT Cycle 4
CT 1
CT 2
CT 3
IO
(Molmoc)
12 weeks
9 weeks
Follow up
CT thorax + upper abdomen PR or CR
Squameus (CT)
21 weeks
Outpatient clinic (selecting patients) (visit 1)
Screenings visit (visit 2)
Legend:
CRT chemoradiotherapy
CT chemotherapy
IO immuno-oncology
RT radiotherapy
PR partial response
CR complete response

5.4 Expected duration of trial

Patients will be coached for 8 weeks. A screening period of 1-2 weeks before makes a trial duration of maximum 10 weeks for this pilot study. We expect to start January 2019.

1. Trial Procedures

6.1 By visit

Describe the sequence of procedures to be performed at each visit as detailed in the time/event flowchart in section 3.6.

Visit 1 (outpatient clinic)

Patients will be screened for inclusion in the study during follow up visits in the outpatient lung cancer clinic. If oncological check-up after starting initial lung cancer treatment(with CT thorax upper abdomen, CT-brain, …) demonstrates documented disease control (stable, partial or complete response defined by RECIST V1.1) the patient is asked to join the study. If the patient wants to join the study a screening visit (V2) will be planned. Patients with documented disease control can be included in the study until 2 years after starting up initial treatment.

Visit 2 (screening visit (run-in))

During visit 2 (run-in) all eligible patients who have signed the informed consent will enter the run in epoch of 1 to 2 weeks.

Patients are asked about their medical history (baseline demographic data) and their previous respiratory treatment including their oncological stage and type. Co-morbidities will also be assessed and a basic lung function will be performed.

On visit 2 patient will receive a Dynaport movemonitor to wear one week before visit 3. For patients where the run in period is more than one week, they will receive a telephone reminder to wear PROactive monitors. Patients are instructed to wear the device during waking hours. A measurement of more than 8 hours of wearing time will be defined as a 'valid day). The tri-axial accelerometer will captured steps waked per day, movement intensity and time spent in sitting, lying walking and high-intense activities.

Visit 3 (baseline, allocation)

Patients will complete the web-based version of the clinical visit of the PROactive questionnaire. Two six-minutes walk tests will be performed and the patient will complete the quality of life questionnaires. During visit 3, the patients are divided into either control (usual care) or telecoaching group based on personal preferences and the abilities of using and having a smartphone.

All patients will be equipped with the Dynaport movemonitor one week before visit 4 and will be instructed to wear the monitor for 7 consecutive days.

Visit 4 (end of the study, 8 weeks post allocation)

Visit 4 is the end of the study. All assessments performed on visit 3 will be repeated during this study visit.

6.2 Laboratory tests

Not applicable.

5.3 Other investigations

Not applicable.

7 Assessment of efficacy

The efficacy of the intervention will primary be assessed with an activity monitor worn for one week at baseline and after 8 weeks of intervention.

8 Assessment of Safety

8.1 Specification, timing and recording of safety parameters

If problems occur during the trial period, patients are asked to contact the investigator to discuss the possible adverse events. If necessary, an extra visit or consultation with a physician will be scheduled.

8.2 Procedures for recording and reporting adverse events (AE)

8.2.1 Definitions in Law of May 7, 2004 concerning experiments on the human person

Adverse reaction (AR): all untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered;

Adverse event (AE): any untoward medical occurrence in a patient or subject of the treated group during an experiment, and which does not necessarily have a causal relationship with this treatment;

Unexpected adverse reaction (UAR): an adverse reaction, the nature or severity of which is not consistent with the information on the experiment, and, when a clinical trial is concerned, with the applicable product information (e.g. investigator's brochure for an unauthorized investigational

product or the patient leaflet joined to the summary of product characteristics for an authorized product);

Serious adverse event (SAE) or serious adverse reaction (SAR): any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect, and this, when it is a clinical trial, at any dose;

Suspected unexpected serious adverse reaction (SUSAR): is an AR that is serious and unexpected (meaning that nature or severity of the AR is not consistent with the Investigational Medicinal Product reference safety information, which is the Investigator's Brochure) and is judged by either the investigator or the sponsor as having a reasonable suspected causal relationship with the investigational medicinal product.

8.2.2 Notification of adverse events

The investigator shall report all serious adverse events immediately, after first knowledge, to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers.
For reported deaths of a subject, the investigator shall supply the sponsor and the accredited ethics committee with any additional information requested.
The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the minister if the experiment is being conducted in Belgium, if he so requests.

8.2.3 Notification of serious adverse reactions

The sponsor shall ensure that all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the minister, to the competent authorities in all the Member States concerned in the case of a trial, and to the competent ethics committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected unexpected serious adverse reactions shall be reported to the minister, to the competent authorities of all Member States concerned in the case of a clinical trial and to the ethics committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

The sponsor shall also inform the other investigators.
Once a year throughout the experiment, the sponsor shall provide the minister and the ethics committee in Belgium and those of the member States in whose territory the trial is conducted in the case of a multicentre trial, with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.
Regarding those adverse events and serious adverse reactions the Principal Investigator will take all reasonable measures, in consultation with Sponsor, to protect subjects at risk following the occurrence of such events.

8.3 Treatment stopping rules
Not applicable.

9 Statistics

9.1 Sample size
We will include 16 patients motivated for a coaching program and compare them with a matched control group of 16 patients receiving usual care. As this pilot study is underpowered to detect between group differences at the end of the intervention, we will base our primary analysis on the within group difference of the intervention group. Based on an anticipated pre-post difference of 1500 steps/day and a SD of 2000 steps/day, we need 16 individuals for a power of 80% using an α level of 0.05 (two-sided, paired T test). The control group will be used to address the repeatability of the activity measures. Both groups will be needed for a power calculation of the subsequent randomized trial.

9.2 Analysis
Within group comparison of the primary and secondary outcome parameters will be analyzed by paired T-test statistics for parametric distributions and Wilcoxon signed-rank test test for non-parametric distributions. Linear and logistic regression will be used to address determinants of treatment response. Ancova analyses will be used to compare between group differences at 8 weeks, adjusted for baseline differences and possible confounders. Data will be presented as mean ± SD. Statistical significance will be set at $p<0.05$ for all the analyses.

10 Quality assurance
The study team performs the tests in a standardized way, according to the guidelines. The research group is familiar with the telecoaching intervention and motivational interviewing due to internal courses and previous studies.

11 Direct access to source data and documents
It will be specified, (or reference is made to another written agreement) that the investigator(s) and the institution(s) will permit trial-related monitoring, audits, EC review, and regulatory inspections

(where appropriate) by providing direct access to source data and other documents (ie patients' case sheets, blood test reports, X-ray reports, histology reports etc).

12 Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to Ethics Committee and to the Federal Agency for medicinal products for Clinical Trial Authorisation.

The Study can and will be conducted only on the basis of prior informed consent by the Subjects, or their legal representatives, to participate in the Study. The Participating Site shall obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (the patients' rights are guaranteed by the European Data Protection Regulation (GDPR), by the Belgian legislation on the protection of natural persons with regard to the processing of personal data and by the Law of 22 August 2002 on patient rights).

Data are **anonymous** if no one, not even the researcher, can connect the data to the individual who provided it. No identifying information is collected from the individual.
When data are **coded**, there continues to be a link between the data and the individual who provided it. The research team is obligated to protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers should be stored separately from their research data and replaced with a unique code to create a new identity for the subject. Note that coded data are not anonymous.
The present study will use coded data after giving a unique study identifier to each included subject.

13 Data Handling

Data will be coded and collected in a excel database, and will be saved on the KU Leuven server.

14 Data Management

Data will be collected on paper and electronically in an excel database. This will be saved on the KU Leuven server.

15 Translational research

Not applicable.

16 Publication Policy

Not applicable.

17 Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance.

18 Financial Aspects

All tests related to the study will be performed by the study team and covered by the budget of the research group. There will be no compensation for patients who decide to enter the study. Every patients receives a free parking ticket per visit.

19 References

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Appendix 1

1.1 Clinical version of the PROactive questionnaire (C-PPAC)

PROactive VRAGENLIJST

Patiënten met een chronische longaandoening, zoals u, vermelden vaak dat zij problemen hebben tijdens lichamelijke activiteiten. Met lichamelijke activiteiten bedoelen we alle activiteiten waarbij u uw lichaam moet bewegen. Voorbeelden zijn huishoudelijke activiteiten, wandelen, naar uw werk gaan, of zich aankleden. Denk hierbij aan alle activiteiten die u doet en niet alleen aan deze voorbeelden.

We zouden graag willen weten hoe u uw lichamelijke activiteiten hebt ervaren IN DE AFGELOPEN 7 DAGEN.

Gelieve het antwoord te kiezen dat het meest van toepassing is op u IN DE AFGELOPEN 7 DAGEN.
Er zijn geen foute antwoorden.

1) In de afgelopen 7 dagen, hoeveel hebt u buitenshuis gewandeld?

- ☐ Helemaal niet
- ☐ Een beetje (ongeveer 10 minuten per dag)
- ☐ Wel wat (ongeveer 30 minuten per dag)
- ☐ Veel (ongeveer 1 uur per dag)
- ☐ Heel veel (meer dan 1 uur per dag)

2) In de afgelopen 7 dagen, hoeveel taken hebt u buitenshuis uitgevoerd? Enkele voorbeelden zijn tuinieren, vuilnis buiten zetten, of kleine boodschappen doen.

- ☐ Helemaal geen
- ☐ Weinig
- ☐ Wel wat
- ☐ Veel
- ☐ Heel veel

3) In de afgelopen 7 dagen, hoeveel moeilijkheden hebt u ondervonden bij het aankleden?

- ☐ Helemaal geen
- ☐ Een beetje
- ☐ Middelmatig
- ☐ Veel
- ☐ Heel veel

4) In de afgelopen 7 dagen, hoeveel moeilijkheden hebt u ondervonden om ergens naartoe te gaan?

- ☐ Helemaal geen
- ☐ Een beetje
- ☐ Middelmatig
- ☐ Veel
- ☐ Heel veel

5) In de afgelopen 7 dagen, hoe vaak hebt u vermeden om activiteiten te doen als gevolg van uw longproblemen?

- ☐ Helemaal niet
- ☐ Nauwelijks
- ☐ Soms
- ☐ Vaak
- ☐ De hele tijd

6) In de afgelopen 7 dagen, hoe kortademig was u in het algemeen tijdens uw activiteiten?

- ☐ Helemaal niet
- ☐ Een beetje
- ☐ Middelmatig
- ☐ Erg
- ☐ Extreem

7) In de afgelopen 7 dagen, hoe vaak hebt u een gebrek aan lichamelijke kracht ervaren om dingen te doen als gevolg van uw longproblemen?

- ☐ Helemaal niet
- ☐ Nauwelijks
- ☐ Soms
- ☐ Vaak
- ☐ De hele tijd

8) In de afgelopen 7 dagen, hoe moe was u in het algemeen tijdens uw activiteiten?

- ☐ Helemaal niet
- ☐ Een beetje
- ☐ Middelmatig
- ☐ Erg
- ☐ Extreem

9) In de afgelopen 7 dagen, hoe vaak hebt u pauzes moeten inlassen tijdens uw lichamelijke activiteiten?

- ☐ Helemaal niet
- ☐ Nauwelijks
- ☐ Soms
- ☐ Vaak
- ☐ De hele tijd

10) In de afgelopen 7 dagen, hoe kortademig was u bij het wandelen op een vlakke ondergrond binnen- en buitenshuis?

- ☐ Helemaal niet
- ☐ Een beetje
- ☐ Middelmatig
- ☐ Erg
- ☐ Extreem

1.2 QLQ-C30 (*Cancer quality of life questionnaire)*

EORTC QLQ-C30 (version 3)

Wij zijn geïnteresseerd in bepaalde dingen over u en uw gezondheid. Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is. Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

Naam: Geb.dat.: Datum:

	Helemaal niet	Een beetje	Nogal	Heel erg
1.Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?	1	2	3	4
2. Heeft u moeite met het maken van een lange wandeling?	1	2	3	4
3. Heeft u moeite met het maken van een korte wandeling buitenshuis?	1	2	3	4
4. Moet u overdag in bed of op een stoel blijven?	1	2	3	4
5. Heeft u hulp nodig met eten, aankleden, uzelf wassen of naar het toilet gaan?	1	2	3	4

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
6. Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?	1	2	3	4
7. Was u beperkt in het uitoefenen van uw hobby's of bij andere bezigheden die u in uw vrije tijd doet?	1	2	3	4
8. Was u kortademig?	1	2	3	4
9. Heeft u pijn gehad?	1	2	3	4
10. Had u behoefte om te rusten?	1	2	3	4
11. Heeft u moeite met slapen gehad?	1	2	3	4
12. Heeft u zich slap gevoeld?	1	2	3	4
13. Heeft u gebrek aan eetlust gehad?	1	2	3	4

1.3

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
14. Heeft u zich misselijk gevoeld?	1	2	3	4
15. Heeft u overgegeven?	1	2	3	4
16. Had u last van obstipatie? (was u verstopt?)	1	2	3	4
17. Had u diarree?	1	2	3	4
18. Was u moe?	1	2	3	4
19. Heeft pijn u gehinderd in uw dagelijkse bezigheden?	1	2	3	4
20. Heeft u moeite gehad met het concentreren op dingen, zoals een krant lezen of televisie kijken?	1	2	3	4
21. Voelde u zich gespannen?	1	2	3	4
22. Maakte u zich zorgen?	1	2	3	4
23. Voelde u zich prikkelbaar?	1	2	3	4
24. Voelde u zich neerslachtig?	1	2	3	4
25. Heeft u moeite gehad met het herinneren van dingen?	1	2	3	4
26. Heeft uw lichamelijke toestand of medische behandeling uw familieleven in de weg gestaan?	1	2	3	4
27. Heeft uw lichamelijke toestand of medische behandeling u belemmerd in uw sociale bezigheden?	1	2	3	4
28. Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?	1	2	3	4

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is

29. Hoe zou u uw algehele gezondheid gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

30. Hoe zou u uw algehele "kwaliteit van het leven" gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

SGRQ (St. George's respiratory questionnaire)

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
DUTCH FOR BELGIUM VERSION

DE ADEMHALINGSVRAGENLIJST VAN HET ST. GEORGE-ZIEKENHUIS (SGRQ)

Deze vragenlijst is ontworpen om ons te helpen meer inzicht te krijgen in uw ademhalingsproblemen en hoe deze uw leven beïnvloeden. Door middel van deze vragenlijst willen we te weten komen welke aspecten van uw ziekte u de meeste problemen geven, in plaats van wat de artsen en verpleegkundigen denken dat uw problemen zijn.

Gelieve de instructies zorgvuldig te lezen en indien u iets niet begrijpt, kan u dit altijd vragen. Denk niet te lang na over uw antwoorden.

Vóór u de rest van de vragenlijst invult :

Gelieve 1 vakje aan te kruisen om aan te duiden hoe u uw huidige gezondheid zou omschrijven :

Zeer goed	Goed	Redelijk	Slecht	Zeer slecht
☐	☐	☐	☐	☐

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Vervolg op de volgende pagina

De ademhalingsvragenlijst van het St. George-ziekenhuis
DEEL 1

Vragen over hoeveel ademhalingsproblemen u hebt gehad gedurende de afgelopen 4 weken.

Gelieve *bij elke vraag één vakje* aan te kruisen :

	de meeste dagen van de week	meerdere dagen van de week	een paar dagen van de maand	alleen bij een lucht-weginfectie	helemaal niet
1. De afgelopen 4 weken heb ik gehoest :	☐	☐	☐	☐	☐
2. De afgelopen 4 weken heb ik slijm opgehoest :	☐	☐	☐	☐	☐
3. De afgelopen 4 weken was ik kortademig :	☐	☐	☐	☐	☐
4. De afgelopen 4 weken heb ik aanvallen van piepende ademhaling gehad :	☐	☐	☐	☐	☐

5. Hoeveel keer is uw ademhaling, gedurende de afgelopen 4 weken, verstoord door zware of zeer onaangename aanvallen :

Gelieve *één vakje* aan te kruisen :

- Meer dan 3 keer ☐
- 3 keer ☐
- 2 keer ☐
- 1 keer ☐
- Nooit ☐

6. Hoelang duurde de ergste aanval ? *(Ga naar vraag 7 wanneer u geen zware aanval hebt gehad)*

Gelieve *één vakje* aan te kruisen :

- 1 week of langer ☐
- 3 of meer dagen ☐
- 1 of 2 dagen ☐
- minder dan 1 dag ☐

7. Gedurende de afgelopen 4 weken, hoeveel goede dagen (met weinig last van ademhalingsproblemen) hebt u in een gewone week gehad ?

Gelieve *één vakje* aan te kruisen :

- Geen goede dagen ☐
- 1 of 2 goede dagen ☐
- 3 of 4 goede dagen ☐
- Bijna elke dag was goed ☐
- Elke dag was goed ☐

8. Indien u piepend ademhaalt, is dit dan 's morgens het ergst ?

Gelieve *één vakje* aan te kruisen :

- Nee ☐
- Ja ☐

De ademhalingsvragenlijst van het St. George-ziekenhuis
DEEL 2

Sectie 1

Hoe zou u uw ademhalingsproblemen beschrijven ?

Gelieve *één vakje* aan te kruisen :

- Het meest belangrijke probleem dat ik heb ☐
- Het geeft mij nogal wat problemen ☐
- Het geeft mij weinig problemen ☐
- Het geeft mij geen problemen ☐

Indien u ooit betaald werk hebt gehad.

Gelieve *één vakje* aan te kruisen :

- Mijn ademhalingsproblemen waren er de oorzaak van dat ik volledig stopte met werken ☐
- Mijn ademhalingsproblemen belemmeren mij in mijn werk of hebben mij van werk doen veranderen ☐
- Mijn ademhalingsproblemen beïnvloeden mijn werk niet ☐

Sectie 2

Vragen over welke activiteiten u gewoonlijk kortademig maken <u>de laatste dagen (vandaag inbegrepen)</u>.

Gelieve *elk vakje* dat op u van toepassing is ***de laatste dagen (vandaag inbegrepen)*** aan te kruisen :

	Waar	Niet Waar
Stil zitten of stil liggen	☐	☐
Zich wassen of aankleden	☐	☐
Thuis rondlopen	☐	☐
Buiten wandelen op vlak terrein	☐	☐
De trap opgaan	☐	☐
Een helling oplopen	☐	☐
Bij sport of fysieke spelen	☐	☐

De ademhalingsvragenlijst van het St. George-ziekenhuis

Hieronder ziet u een lijst van activiteiten die u vanwege uw ademhalingsproblemen misschien niet kan doen (deze hoeft u niet aan te kruisen; het zijn voorbeelden die u helpen bedenken op welke manier uw kortademigheid u kan beïnvloeden) :

Een wandeling maken of de hond uitlaten

Dingen thuis of in de tuin doen

Geslachtsgemeenschap hebben

Naar de kerk, café, club of plaats van amusement gaan

Bij slecht weer naar buiten gaan of in rokerige ruimten verblijven

Familie of vrienden bezoeken of met kinderen spelen

Gelieve hieronder voorbeelden te geven van andere belangrijke activiteiten die u ten gevolge van uw ademhalingsproblemen niet kan doen :

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Gelieve nu het vakje (slechts één) aan te kruisen dat volgens u het best omschrijft hoe uw ademhalingsproblemen u beïnvloeden :

Het weerhoudt mij er niet van iets te doen dat ik graag zou willen doen ☐

Het weerhoudt mij ervan één of twee dingen te doen die ik graag zou willen doen ☐

Het weerhoudt mij ervan de meeste dingen te doen die ik graag zou willen doen ☐

Het weerhoudt mij ervan alles te doen wat ik graag zou willen doen ☐

Hartelijk dank voor het invullen van deze vragenlijst. Gelieve na te gaan of u alle vragen beantwoord heeft alvorens deze vragenlijst in te dienen.