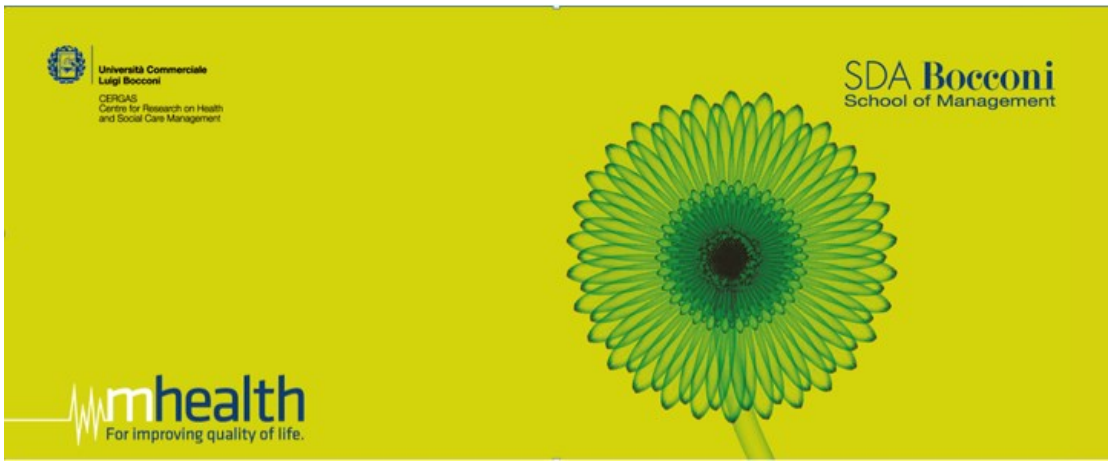

A mobile supportive care app for patients with metastatic lung cancer: a pilot randomized controlled trial

The **Lu**ng **C**ancer **App** (**LuCApp**) study

Version 1.0

Date 3 November 2017

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Signature of Coordinating Investigator Date

Paolo Pedrazzoli 6 November 2017

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Investigator Statement

By my signature, I agree with the content of the clinical study and confirm the Clinical Investigation Plan in the latest version. I confirm to conduct the study in compliance with the approved protocol and will adhere to the GCP guidelines, and other regulatory requirements as amended.

Study Center *please print name*

(Principal) Investigator *please print name*

Signature of (Principal) Investigator Date

ABBREVIATIONS

CSUQ	Computer system usability questionnaire
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EQ5D	Euro Quality of Life 5 Dimensions
FACT-L	Functional Assessment of Cancer Therapy - Lung
HADS	Hospital Anxiety and Depression Scale
HRQOL	Health-related quality of life
LuCApp	Lung Cancer App
OS	Overall survival
PROMs	Patient reported outcome measures
QALY	Quality-adjusted life year
SCNS-SF	Supportive Care Needs Survey Short Form
ZBI	Zarit Burden Interview

INTRODUCTION

Background and objectives

The substantial progress made in the treatment and diagnosis of cancer has entailed it can be managed as other chronic disease, where greater long-term active surveillance is needed. To enhance patients' quality of life new models of care thus need to be thought through and the paternalistic view according to which patients are sited in the role of patient recipients and should just follow what they are told by providers needs to be overcome (1).

To this end, self-management (SM) interventions can help patients and their families care for themselves along the cancer care continuum. SM is here defined as "the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent in living with a chronic condition" (2). With respect to cancer care, patient involvement can aim at enhancing symptom management. Although recent advances in cancer therapies have led to better clinical outcomes (3), treatment-related side effects still carry a great weight in affecting patients' quality of life.

This new need for self-care activities has coupled with the unsustainability of current healthcare spending thus leading to the need to acknowledge solutions that are disruptive, yet capable of controlling costs without diminishing quality of service and quality of life.

This scenario has witnessed the rapid and ongoing growth in mobile technologies, including mobile health (mHealth), defined as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices" (4).

As a booming technology, mHealth can be instrumental in supporting decision-making and strengthening the data generation process, by integrating data from several different sources.

For such reasons, the case of mHealth represents a highly significant one, since mobile devices can greatly enhance the connection between the main stakeholders in the health process and provide validated, yet innovative, approaches for economic evaluation. On the other hand, however, mHealth also poses new and unexplored regulatory, organizational and technological challenges that need to be better tackled in order to ensure that such technologies are put to best use.

This recent hype has led to the development of mHealth applications in all major therapeutic areas: in 2016, there were over 259,000 mHealth applications (apps) with over 3 billion downloads, reflecting a growth rate of over 35% in 2015 (5, 6). However, the development and subsequent download process has by far outpaced the evaluation phase: whether mHealth leads to better overall health outcomes and reduced disease burden is still unknown and overall scientific evidence is scant.

mHealth, here intended as a stand-alone technology, can also be incorporated in broader health care programs that aim at enhancing overall patient empowerment by providing him with greater continuity of care and centrality along the whole care continuum.

mHealth applications are being developed and evaluated in a variety of chronic care domains, including diabetes (7), asthma (8), obesity (9), smoking cessation (10), stress management (11) and depression treatment (12). However, although oncology is among the therapeutic areas where mHealth could have a more disruptive impact on, fewer interventions are aimed at cancer patients, with some notable exceptions. Basch et al. tested symptom self-reporting during routine cancer treatment via STAR (Symptom Tracking and Reporting) against usual care (13), while Denis et al. compared an e-follow-up application (e-FAP) for detecting lung cancer relapse with standard surveillance, showing improved overall survival (OS) for the experimental compared with the control arm (median OS: 19.0 vs 12.5 months) (14). In 2016, instead, the University of Surrey launched the eSMART study, a 5-year RCT conducted across five countries that aims at testing the impact of the Advanced Symptom Management System (ASyMS), a system that enables the real-time monitoring of patients-reported outcome measures (PROMs) (15).

A similar remote monitoring system available to manage therapy-induced side effects is LuCApp (Lung Cancer App), an application developed by researchers and lung cancer clinicians and specifically tailored to lung cancer patients' needs. LuCApp allows to gather symptom data in real time and to share it with healthcare professionals. Whilst focusing on a specific type of cancer, LuCApp adapts to all potential therapies for its treatment and not only to chemotherapy. The evaluation of LuCApp will be tested against the current standard of care, where symptom management during chemotherapy and other therapies is mostly up to clinicians and therapeutic professional teams with little technology support. The primary objective will be to determine whether, by enhancing self-monitoring of therapy-induced side effects, this application can lead to increased health-related quality of life (HRQoL) and therefore

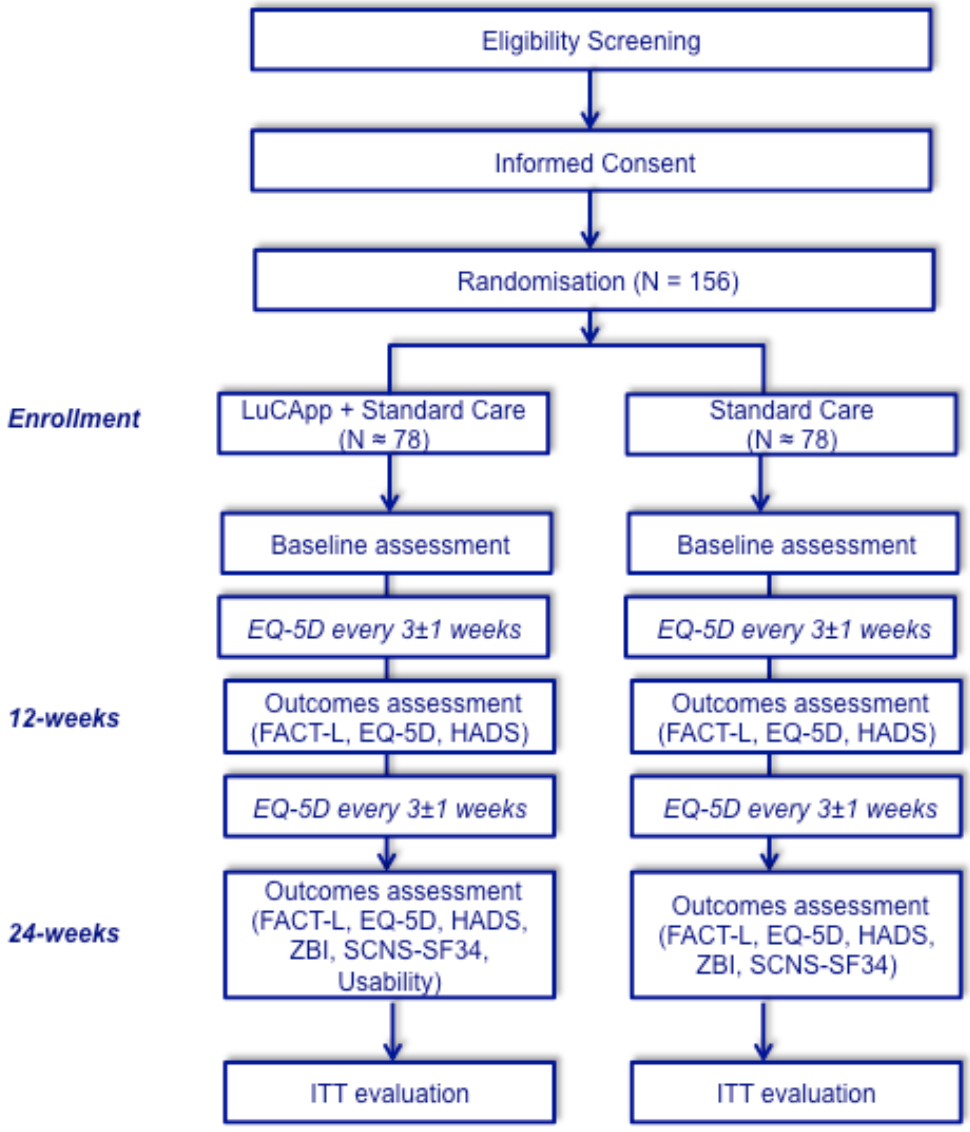
generate value from a patient and public health perspective. The study summary is available in both English and Italian as an attachment.

METHODS

Trial design

This is a 24-week, two-arm, multicenter feasibility parallel randomized controlled trial designed to evaluate the usability and effectiveness of LuCApp to improve self-management of symptoms and quality of life in lung cancer patients. The protocol has been developed in accordance with the CONSORT-EHEALTH checklist (16). The flow diagram for recruitment and randomization is shown in Figure 1.

Figure 1 - Flow diagram for recruitment, randomization and data collection



Participants

Adults of both sexes with lung cancer (small and non-small cell) will be assessed for eligibility at participating sites. Study inclusion criteria will be (

Table 1):

- over 18 years of age individuals of both sexes;
- diagnosed with small or non-small cell lung cancer;
- patients eligible for chemotherapy, immunotherapy or biological therapy;
- patients diagnosed with non-resectable tumor and eligible for neoadjuvant therapies;
- life expectancy of six months or more;
- a performance status between 0 (asymptomatic) and 2 (symptomatic, <50% in bed during the day) according to the Eastern Cooperative Oncology Group (ECOG) score;
- patients fluently speaking Italian;
- patients able to provide informed consent to participate in the study;
- patients who own a smartphone that can access either the iOS or the Android platform.

Although internet literacy was not defined as an explicit eligibility criterion in this study, it works as a *de facto* selection criterion since only individuals that personally own a smartphone can be enrolled in the study. It was assumed that, if individuals owned a smartphone, they would be able to use it.

Patients will be excluded if they: i) are unable to provide written informed consent, ii) are unable to use the app and all other materials (i.e. blind), iii) have received, are receiving or plan to receive radiotherapy or surgical resection as their management will likely be different from patients undergoing pharmacological therapy. Furthermore, patients that are already included or about to join other clinical trials and individuals who are already using another smartphone application to self-manage cancer will not be considered eligible for the trial.

Table 1 - Summary of inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• over 18 years of age individuals of both sexes; • diagnosed with small or non-small cell lung cancer; • patients eligible for chemotherapy, immunotherapy or biological therapy; • patients diagnosed with non-resectable tumor and eligible for neoadjuvant therapies; • life expectancy of six months or more; • a performance status between 0 (asymptomatic) and 2 (symptomatic, <50% in bed during the day) according to the Eastern Cooperative Oncology Group (ECOG) score; • patients fluently speaking Italian; • patients able to provide informed consent to participate in the study; • patients who own a smartphone that can access either the iOS or the Android platform.	• individuals unable to provide written informed consent; • individuals unable to see the App and all other materials (i.e. are blind); • patients receiving or that plan to receive radiotherapy or surgical resection; • patients already included or about to join other clinical trials; • patients already using other smartphone applications to self-manage cancer symptoms.

Once eligibility has been established, patients will be asked to join the study by the medical oncologists after diagnosis and a face-to-face assessment at the participating centers. Patients will receive an invitation letter, the study leaflet and the informed consent form. This will not be a purely web-based trial, since face-to-face components will still be present: data will be collected through questionnaires via the app for the intervention patients, while standard-of-care patients will complete paper questionnaires during clinic visits, or at home (having received paper questionnaires during the previous visit) or via telephonic interviews with the research team. Outcomes will be self-assessed through Patient Reported Outcome Measures (PROMs) (for further information, please look at the "Outcomes" section) at different points in time. Patients assigned to the intervention arm will be trained to use LuCApp (study staff will provide them with a 15-minute presentation on how to use the App) and will be assisted during the whole study period by a "helpdesk".

University and participating centers affiliations will be displayed on the invitation letter to obtain participants' trust but no bias is expected to result from the display of such information.

Intervention (LuCApp)

BIOMEdical Research Informatics Solutions (BIOMERIS), a laboratory accredited as an academic spin-off by University of Pavia, in collaboration with the oncologists of the cancer center "Fondazione IRCCS Istituto Nazionale dei Tumori" (Milan, Italy) initially developed a web-based intervention. The original application was specifically tailored to the needs of head and neck cancer patients. Cancer type later switched to lung cancer and CRO Advice Pharma Group was commissioned the adjustment of the app to the new pathology and to the iOS platform. LuCApp was first made available on Playstore (Android online store) and on iTunes (Apple online store) in November, 2017.

The original App (HeNeA) was developed in direct collaboration with the oncologists of the cancer center "Fondazione IRCCS Istituto Nazionale dei Tumori" (Milan, Italy) and was pilot-tested with a small number of clinicians of the same institute. The structure and the flow chart were later refined in accordance with present legislation and in collaboration with the clinical teams of the three participating centers. Satisfaction with LuCApp was further tested with healthcare professionals from recruiting sites and a small group of oncologists and specialists in palliative care from other Italian centers before the launch of the randomized control trial. The information gathered was used to further improve the App. After several revisions and updates the App is now at its 5th version and is released on the main apps stores (see above). We do not anticipate any updating on LuCApp during the evaluation process, hence the technology content will be frozen once the trial begins. It is projected that there will be no further revisions or updating of either the intervention or the comparator during the study period.

With respect to data quality and accuracy, the system allows to collect data and to perform checks by using automated range and consistency checks set during the setup phase. The user will be lead throughout the compilation phase by alerts and notifications that will ensure completeness and consistency of data captured.

The study was developed in close cooperation with an Advisory Board, composed of the Scientific Directors and some healthcare professionals of all participating centers, the researchers at Università Bocconi and representatives of the CRO. Healthcare professionals will be trained on several aspects of the study protocol and on the use of LuCApp before the study begins. A research coordinator from each center will be identified.

Data will be collected through an electronic data capture (EDC), ICE (Integrated Clinical Trial Environment) owned by Advice Pharma Group. This system is compliant with Title 21, Part 11 of the Code of Federal Regulations and with the EU GMP Annex 11 about electronic records for patients. Figure 2 and
Figure 3 show the ICE data collection mask and the mobile app ("LuCApp") data collection mask respectively. Data will be anonymized and stored in a secure database for the study.

Figure 2 - Integrated Clinical Trial Environment mask

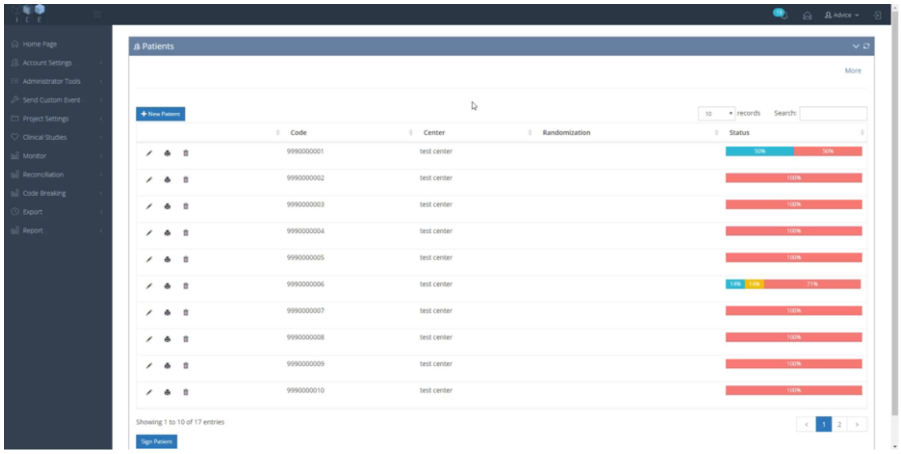
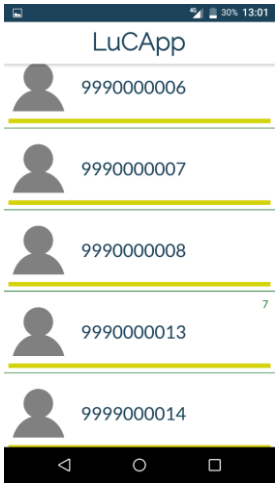


Figure 3 - LuCApp interface



After informed consent and randomization, happening in hospital setting before the start of medical therapy for lung cancer, clinicians will access a secured web-based platform where they will register patients and their credentials. Clinicians will use a hospital PC or their own mobile device connected to internet. Upon activation of a

personal account, patients, with the help of the team, will download the app on their mobiles and log in by inserting their e-mail address and a self-chosen password. For the duration of the trial, the interaction with LuCApp will thus occur via the patient's own mobile and rely on the usual network connectivity. Patients will be required to log in whenever they access the application: this will guarantee that validated data are included in the eCRF and that only patients can access to sensitive data. Patients will not be paid any cash or in-kind amount nor will they be asked to disburse any amount, as LuCApp will be free to download for them.

The intervention presents several different and unique functionalities and components that were designed to aid symptom self-reporting and management. The intervention content is organized as follows:

1) "How do I feel today?" – This component of the app allows participants to fill in a questionnaire every day to report their current situation with respect to 22 side effects that are commonly experienced during therapies for lung cancer and were identified from the literature. Symptoms will be rated on a scale from 0 to 4 (where 0 is symptom not present, 4 is maximum degree of severity). Questions were adapted for patient use from the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (final list is available as an attachment "4.2_LuCApp_Annex 2_Adverse event list") (17). LuCApp will trigger alerts to healthcare professionals whenever a symptom of level 3 or above is inserted. Although the compilation is possible multiple times per day at will, patients will receive a reminder (as a mobile banner or email) to fill in this questionnaire every three days. Up to three different reminders will be sent at noon, 6 p.m. and 9 p.m. to encourage patients to self-report their symptoms using a recall period of the past 24 hours. Symptom reports are available for clinicians only.

   In order to identify this comprehensive list of symptoms, first, a rapid review of the literature was conducted. References considered included:

   a. The Edmonton Symptom Assessment System (ESAS): 9 most common symptoms in cancer patients (first 9 symptoms) (25);
   b. Symptoms identified from a systematic review of studies in adults with lung cancer (26), another review the common symptoms in advanced NSCLC (27), and a third review of symptoms at initial evaluation of lung cancer patient (28).

This activity resulted in a list of 68 symptoms. From this list, lung cancer specialists who are investigators in this trial checked those symptoms that they consider relevant for the patient population under investigation. A second team of experts was then asked whether those symptoms not selected by the experts but identified in the literature would also be worth including. These included: anorexia, weight loss (clinical parameter), constipation, weakness, insomnia, dry mouth, remembering, and peripheral neuropathy. A final list was then circulated and validated amongst all experts and is available as an attachment to this protocol.

2) "Temperature" and "Weight" – Patients in the intervention arm will be asked to enter their body temperature everyday and to report their weight once per week (again via mobile banners or emails). Whenever body temperature exceeds the 38 degree Celsius threshold or a 5-percentage point reduction in body weight in the previous two weeks is reported, specific alerts will be generated to inform the clinical team in charge.

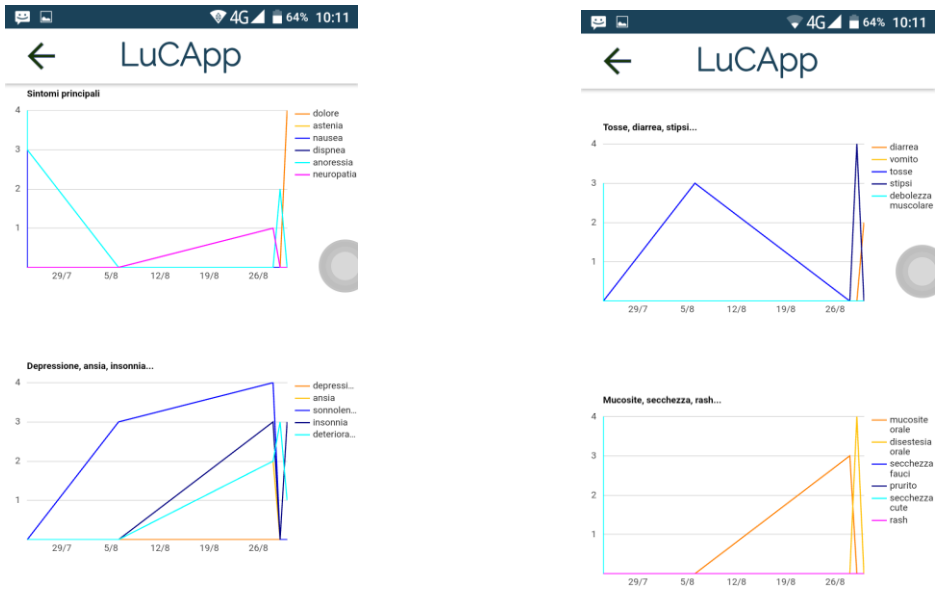
3) "Tip of the day" – Whenever a patient logs into the app, this feature of the app shows a daily tip, a short suggestion to better manage the side effects of the therapies. The tip is selected randomly among those related to the therapy the patient is undergoing. Tips were drawn from clinical practice guidelines and discussed by a consensus group of experts including medical oncologists, radiation oncologists, surgeons, nutritionists, speech language pathologists, infectious disease specialists, dentists and nurses (18, 19). All tips were later validated with the healthcare professionals from the three sites participating in the trial (final list is available as an attachment "4.1_LuCApp_Annex 1_Tips of the day").

4) "Questionnaires" – A final section allows patients to fill-in several PROMs about their HRQoL and experience with supportive care needs and LuCApp: EuroQol 5D, Functional Assessment of Cancer Therapy (Lung), Hospital Anxiety and Depression scale, supportive care needs survey, usability and satisfaction with the app (see next section on outcomes). Data will be collected at several points in time, depending on the type of questionnaire considered (see next section on outcomes). Questionnaire completion is instrumental in evaluating several end-points and in determining whether LuCApp can improve patient-relevant outcomes compared to

the standard of care. To enable the comparison, patients in the standard of care arm will fill out the same questionnaires via paper at clinic visits or follow up.

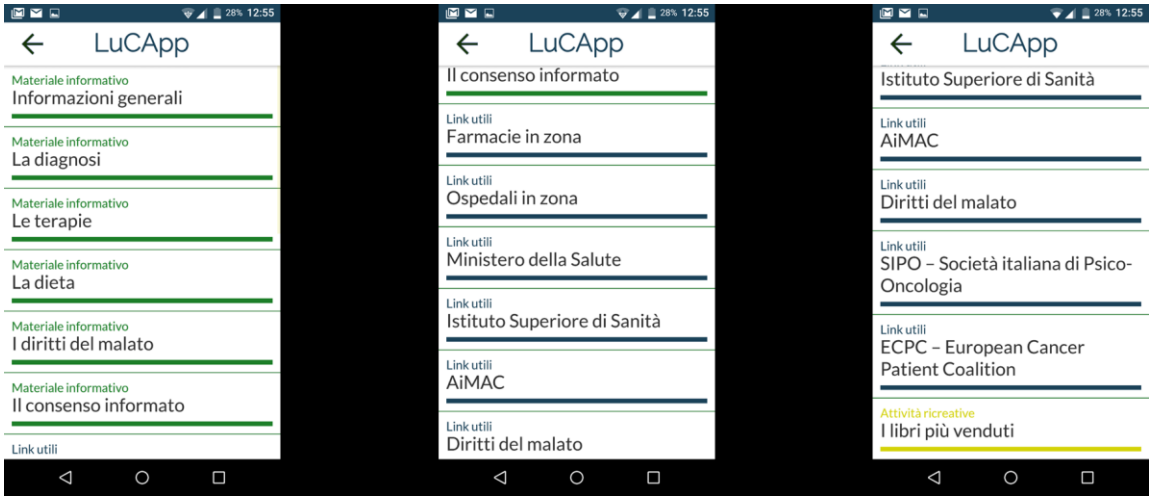
5) "Trend" – In the Trend component, available in the healthcare professional App only, clinicians can access the longitudinal trend of their patients' clinical parameters. Side effects, temperature and weight are displayed in charts, and it is possible to select a specific timeframe. Clinicians can access the same graphs remotely and analyze the progress of each patient's clinical parameters and side effects over time (Figure 4).

Figure 4 - An example of how trends for different symptoms and parameters are visualized in the app



6) "Info" – In this final section, in order to increase the overall awareness of the disease and its potential treatments, the most relevant educational material is collected. This section includes some general information on lung cancer, therapies, patients' rights, up to a series of institutional useful links (such as nearest pharmacy, hospital contacts) that patients can browse if needed (Figure 5).

Figure 5 - An example of how information is visualized in the app



Continuity in the utilization of the application will be strongly recommended. Participants will be advised to access the App daily to receive their daily tip and enter their temperature information. Questionnaires and other clinical parameters will have to be entered according to the schedule, but additional information can be added at discretion and alerts will activate whenever necessary. Patients will be advised to enter their daily body temperature at similar times each day and to use the same scale to measure their weight. To facilitate a greater use of the application, LuCApp provides for several rounds of banner reminders (better detailed above) scheduled on days when the input of a specific information is due according to study protocol.

Patients in the standard of care will follow the routine procedures and will be assisted by a clinical team at their site. Such professionals will still provide frequent assistance related to the trial since they will administer questionnaires when due and will update the CRF for the standard of care patients. On the other hand, in order to deal with the intervention arm, healthcare professionals will be trained through dedicated sessions prior to the launch of the patient recruitment phase. Contact details of LuCApp developers and technicians will be provided for assistance. However, if the technology does not function properly and the clinician believes an action is urgently needed for a patient, the research team is advised that standard of care applies to the intervention arm, too. During weekends it is possible that clinicians will not be reachable or will not reply promptly to alerts. Also in this case patients are advised to use the standard of care approach (e.g. out-of-hours service doctor, emergency department). The clinical teams that will take care of the intervention patients will be different from the standard

of care arm ones, to ensure that behaviors and results will not be influenced. The research teams are also advised not to share feedback or comments for the duration of the trial in order to reduce performance bias as much as possible. Clinicians will receive alerts on their dedicated LuCApp device and will be responsible for managing them in a timely way. A single alert will be generated for each patient and clinical parameter monitored (i.e. temperature, weight, side effects). Healthcare professionals will then be able to gain more information on the symptoms that triggered the alert and to monitor the longitudinal trend of side effects both on their device and on the LuCApp website from a PC or laptop. Professionals will be able to access all other patient information on the secure LuCApp website, only. In response to an alert triggered for a specific patient, clinicians will be requested to act within 24 hours and to document the type of intervention performed among a list of possible alternatives derived from the literature: referral to the ER/hospital, telephone counselling about symptom management, dose modification, supportive medication initiation/change, visit anticipation (13).

To guarantee a greater use of the application automated reminders will be sent to participants both via email and via push notification. Participants will be prompted, via an automated message to update their body temperature and their weight and to fill out the side effects questionnaires. Three rounds of alerts will be generated at 12, 6 and 9 p.m. on the dates when the input of the relative data is scheduled (daily for body temperature, weekly for weight and every three days for the side effects questionnaire, see above).

Both groups will have access to treatment as usual. However, additional training will be provided to intervention arm participants right after enrolment: LuCApp features will be better detailed and training sessions will be scheduled accordingly. Furthermore, during the trial, a support center ("helpdesk") will be available to help participants with any technical issues that may occur.

Standard of care

Usual care will consist of standard procedures currently available at participating centers for monitoring and documenting symptoms. These therapeutical procedures are based on the guidelines developed by the National Comprehensive Cancer Network (NCCN) and the Associazione Italiana di Oncologia Medica (AIOM) (20). Symptoms for control arm patients will be discussed and registered during scheduled clinical visits

with the oncologists. Standard-of-care patients will fill out their PROMs following the same schedule identified for LuCApp patients with paper questionnaires during clinic visits, or at home (having received paper questionnaires during the previous visit) or via telephonic interviews with the research team. Patients are usually allowed to contact their relative sites for concerning symptoms that occur between scheduled visits or advised to see the out-of-hour doctor or the emergency department if needed. This option is also recommended for the intervention arm during weekends.

Outcomes

As discussed above, the overarching research question of this study is to explore and pilot the impact of using LuCApp on relevant outcomes in patients with lung cancer. LuCApp has several functionalities and this pilot explores whether these functionalities impact on the patients' health-related quality of lives (HRQoL) and needs in cancer supportive care. It also aims to assess whether it improves the burden on caregivers and the satisfaction with the use of the app. Finally, the cost-effectiveness of LuCApp will be explored, based on the improvement in HRQoL and the resources being used to manage the disease throughout the study period.

A number of outcome measures have been identified to allow the assessment of the above trial objectives. LuCApp will be evaluated in terms of: (1) impact on HRQoL, (2) impact on cancer supportive care needs, (3) impact on the burden for caregivers, (4) resource use, (5) usability and satisfaction with LuCApp. The rationale for selecting these measures and their characteristics are summarized in the next sections.

(1) HRQoL

The impact on HRQoL of using LuCApp will be measured with existing valid and reliable patient-reported outcome measures (PROMs). Their selection was based on the availability of a validated Italian version, for self-report use, that can be administered both on paper and via smartphones or tablets, and commonly used in lung cancer patients.

Symptoms are subjective experiences self-reported by the patient, and are a subset of patient perceptions of health status and HRQoL (21). HRQoL is a multidimensional construct of diverse functional scales (e.g. physical function, psychological function, social role function) and symptom scales (e.g. disease-related or treatment-related symptoms) (21).

Three questionnaires were selected and are described in the next paragraphs.

a) EQ-5D-5L

The EQ-5D-5L is a generic preference-based measure of health status, which is the most commonly used tool used to derive utility values that can be utilized within an economic evaluation model (22). This tool is also commonly used in lung cancer trials (23). It includes questions covering five domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. For each domain, 5-level questions are posed. Additionally, patients are asked to fill in how they feel today on a vertical visual analogue scale (VAS). Validated versions are available for paper-based and via smartphones and tablet administration.

The questionnaire will be administered at baseline, every 3 ± 1 weeks to take into account that visit intervals may vary between patients and across therapies (in this way the completion of the questionnaire will happen approximately 1 day before each cycle of treatment for chemotherapy patients), and at the end of the study period. This frequency of administration is in line with other trials involving lung cancer patients that administered the EQ-5D (24, 25).

b) FACT-L (lung cancer module):

The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire is a disease-specific measure capturing multidimensional aspects of lung cancer patients' quality of lives (26). The symptoms covered are shortness of breath, weight loss, consciousness, cough, hair loss, appetite, tightness in chest, breathing. FACT-L is the result of the combination of FACT-G (general module and core instrument), which is a general quality of life questionnaire for use in a variety of chronic illness conditions, with a Lung Cancer subscale. It is validated in the Italian version. These questionnaires are extensively used in clinical research, health care delivery studies, symptom management studies, psychological intervention studies, and other treatment evaluations. Studied in various subgroups of lung cancer patients receiving different courses of treatment. The administration mode could be interviews (in-person or telephone), self-administration (in the clinic or by mail) or computer administered questionnaire. Available data suggest that while there are small differences in the way people respond based on mode of administration, these alternate formats are essentially

equivalent, particularly when reporting data at the group level (27). The questionnaire will be administered at baseline, at 12 weeks, and at the end of the study period.

c) Hospital Anxiety and Depression scale (HADS)

HADS is a self-assessment scale developed to detect states of depression, anxiety and emotional distress amongst patients treated for a variety of problems in the setting of out-patient clinics (28). It is composed of two 7-item scales for depression and anxiety respectively. All symptoms relating to physical disorders (e.g. dizziness, headaches) were excluded to avoid interference with other diagnoses (29). HADS was identified as one of the most commonly used PROMs in advanced-staged lung cancer clinical trials of pharmaceutical agents (30), and has been used to measure HRQoL in NSCLC patients (31).

The Italian version of the HADS showed to be valid and reliable, similarly to those results obtained in other languages (32). Specifically, there was a high internal consistency of both anxiety and depression scales. Factor analysis confirmed the bi-dimensionality of the HADS model. Results showed that the two scales are not sufficient to detect distinct cases of anxiety and depression, which is supported by other studies. This is likely because patients with one or the other disorder are likely to have a common area of emotional disturbance, which is not differentiated by the HADS. The use of the total scale has shown high internal consistency. HADS has been used in various clinical settings, in cross-section and longitudinal studies as an outcome measure. Results show that the scales and total scale are sensitive to change, but may be less likely to the smaller changes.

Another study conducted an updated literature review to assesses the validity of HADS (29). They highlight that HADS is administrated mainly in patients with cancer or other somatic illnesses. They looked at the number of factors in HADS identified by factor analysis, the correlation between the subscales of HADS, and the internal consistency of the subscales (Cronbach's alpha). They confirm the two-dimensionality of the model, as well as the fact that although depression and anxiety are very different, it is difficult to distinguish these constructs empirically. The reliability of this self-report instrument was confirmed in all translations (based on Cronbach's alpha). Results also show that the HADS is a good tool to identify patient with emotional disorders. Its concurrent validity with other scales ranged between good and very good. The

questionnaire will be administered at baseline, at 12 weeks, and at the end of the study period.

(2) Cancer supportive care needs

LuCApp is to be used in the context of cancer supportive care. Given its functionalities in terms of monitoring and providing support and information, it may be that some of the unmet needs of cancer patients surrounding their supportive care may be met. Lung cancer patients have greater unmet supportive care needs than other cancer patients (33).

The supportive care needs survey, short form (SCNS-SF34) is a needs assessment questionnaire in cancer supportive care measuring the gap between patients' experience and their expectations (34, 35). It consists of 31 items covering four domains: psychological needs, health system and information needs, physical and daily living needs, and patient care and support needs. For each question, patients are asked to provide an indication of their level of need on a 5-point Likert scale (1: not applicable; 2: satisfied; 3: low need; 4: moderate need; 5: high need) (36). It is applicable to research, clinical settings (36) and routine care (37). It is commonly used to identify priorities for action, to assess the adequacy of current practice in order to identify areas for improvement, and as an intervention tool to reduce patients' perceived needs.

The SCNS-SF34 has been translated and culturally validated (38), and more recently validated in a multicenter study led by Dr Paolo Leombruni. Its construct validity and internal reliability have been demonstrated (36). Its administration as pen-and-paper has been successfully psychometrically tested. It has also been adapted for electronic administration (via touchscreen computer), where the data collected was shown to be equivalent to the data collected from the pen-and-paper version (39).

The SCNS-SF34 will be administered at the end of study, to assess whether some of the supportive care needs were fulfilled in the different study arms. There is still not evidence that the SCNC-SF34 is responsive to change over time, however this is currently being tested in an ongoing longitudinal study assessing how perceived needs change over time over the course of the cancer journey (newly diagnosed cancer patients are being administered the survey four times over the first five years after diagnosis) (36).

(3) Burden on caregivers

The Zarit Burden Interview (ZBI) is a 22-item self-administered scale measuring caregiver burden in health, psychological well-being, finances, social life, and relationship with patient. Each item is measured on a 5-point Likert scale (0=never to 4=nearly always). The total burden is obtained by adding the scores across all 22 items: the higher the score, the higher the burden. Shorter versions have been developed with 18 and 12 items.

The ZBI was selected on the basis that it has been used in cancer patients (40) and is one of the most widely referenced scales in studies measuring caregiver burden (41). The ZBI was developed for nervous system disorders and mental disorders, but has also been applied to cancer patients (42-45). In one study, the authors explore if caregiver burden was in agreement with patient ratings. Patients had different forms of advanced cancer and their carer's Zarit scores were relatively low. They conclude that Zarit may not capture some important aspects of burden in cancer, given that it was initially developed for dementia patients (42). A second study used the ZBI to assess the impact of breathlessness in lung cancer patients on their caregivers, and found high levels of unmet needs and burden particularly in the more severe cases (43).

Assessment timing of the ZBI will be at the end of the study, and will be administered in paper format. Its criterion validity, construct validity and internal consistency have been demonstrated (40). The Italian version of the questionnaire is valid, reliable and useful for use in clinical contexts and in future studies (46).

(4) Usability and satisfaction of LuCApp

At the end of the study, patients in the intervention arm will have an opportunity to provide feedback on strengths and shortcomings of the application, including unintended/unexpected effects. This session will be of interest also for those who did not use the application as intended by the developers. Use and adoption metrics are important process outcomes to understand the mechanism of action of such intervention. The mHealth application contains a tracking system. Frequency and duration of logins and the activity will be recorded and evaluated. To test user satisfaction with the App, a modified computer system usability questionnaire (CSUQ) will be utilized at the end of the study and will be administered to both patients and clinicians using LuCApp. The CSUQ is an overall satisfaction questionnaire that was developed together with other subjective usability measures at IBM in the nineties (47). The CSUQ is identical to the Post-Study System Usability Questionnaire (PSSUQ),

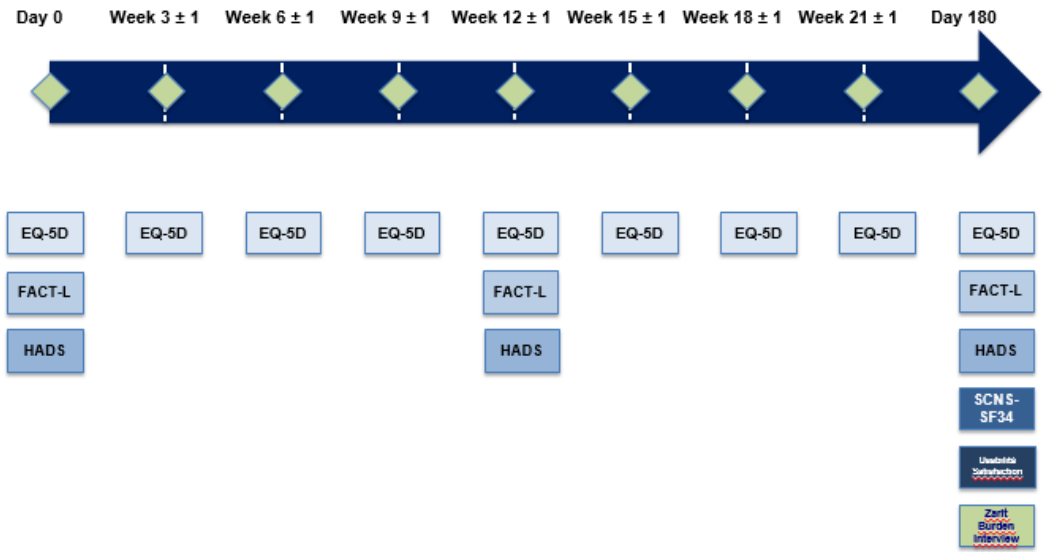
except that the wording of the items does not refer to a usability-testing situation but is rather appropriate for a field-testing situation. The CSUQ was later adapted for mobile apps usability testing to elicit participant satisfaction with the PAediatric Risk Assessment (PARA) app, a mHealth tool developed to help health care professionals in resource-limited settings detect patients at high risk of both in-hospital and post-discharge mortality (48). Based on this revised version, the questionnaire was further elaborated upon: the final version consists of 12 items evaluated on a Likert scale ranging from 1 ("Strongly agree") to 7 ("Strongly Disagree"). In addition, three qualitative questions were added to draw further information on the application and on the generalizability of LuCApp in the current and other clinical contexts: 1) "What do you like the most about the App?"; 2) "What do you like the least about the App"; 3) "How could the App be changed to make it easier to use?". No validated Italian version of the CSUQ was available, so the authors, in cooperation with healthcare professionals of the participating sites, developed the current version. The questionnaire will be administered at the end of the study.

(5) Resource use

The perspective taken for the evaluation of resource consumption will be that of the National Healthcare System. In order not to overload patients and the App design with additional modules, resource use will be captured through patients reports of symptoms and clinicians actions in response to those symptoms (e.g. prescriptions, hospitalization, change in therapy). Moreover, additional information will be obtained for both control and treatment group patients via a form administered by the physician during the clinics. Unitary costs will be expressed as euros 2018. Drug unitary costs will be derived from national price listings, laboratory and instrumental tests will be valued according to the outpatient procedures formulary in accordance with the ongoing policies of Lombardy Region as well as eventual hospitalizations.

Figure 6 summarizes the data collection process throughout the study.

Figure 6 - Time-points of outcomes assessment



Sample size

As described above, the FACT-L v.4 contains four general and one lung cancer symptom-specific subscales. General subscales include: Physical Well-Being (PWB), Social/family Well-Being (SWB), Emotional Well-Being (EWB), and Functional Well-Being (FWB).(49) The Lung Cancer Subscale (LCS) assesses symptoms commonly reported by lung cancer patients (e.g., shortness of breath; loss of weight; tightness in chest). The Trial Outcome Index (TOI) is derived by adding scores on the PWB and FWB subscales to the LCS. Because they contain the most relevant questions about symptoms and physical functioning, the LCS and TOI were selected as the primary focus of this analysis. All FACT-L questions are rated on five-point Likert-type scales ranging from 0 ("not at all") to 4 ("very much"). Therefore, because the seven-items PWB, FWB, and LCS subscales scores range from 0–28 for each subscale, TOI scores range from 0–84. Higher scores represent better QoL or fewer symptoms.

The primary outcome is the change in the score on the TOI from baseline to 12 weeks. We estimated that with 120 patients (Figure 7), the study would have 80% power with a two-sided α of 0.05 to detect a significant between-group difference of 6 points in the change in the TOI score from baseline to 12 weeks, given a pooled standard deviation of 11.54 and change in the reference group score of 53.(50) After accounting for 30% attrition rate, the expected number of enrolled patients is 156 allocated 1:1 between LuCApp and usual care groups. This sample size will also allow the detection with 80% power with a two-sided α of 0.05 of 2-points difference in the LCS subscale, assuming

a pooled standard deviation of 4.15 and change in the reference group score of 19.3 (50) (Figure 8). The clinically meaningful changes on the TOI and LCS subscales of FACT-L were derived from Cella et al.(51)

The FACT-L questionnaire will be administered electronically (via LuCApp) or via paper in the control group at baseline, 12 weeks and 24 weeks, with an understanding that in the routine care setting, lung cancer therapies administration intervals vary between patients.

Figure 7 - Sample size estimation: 5 to 10 -point difference in change in TOI score at 12 weeks

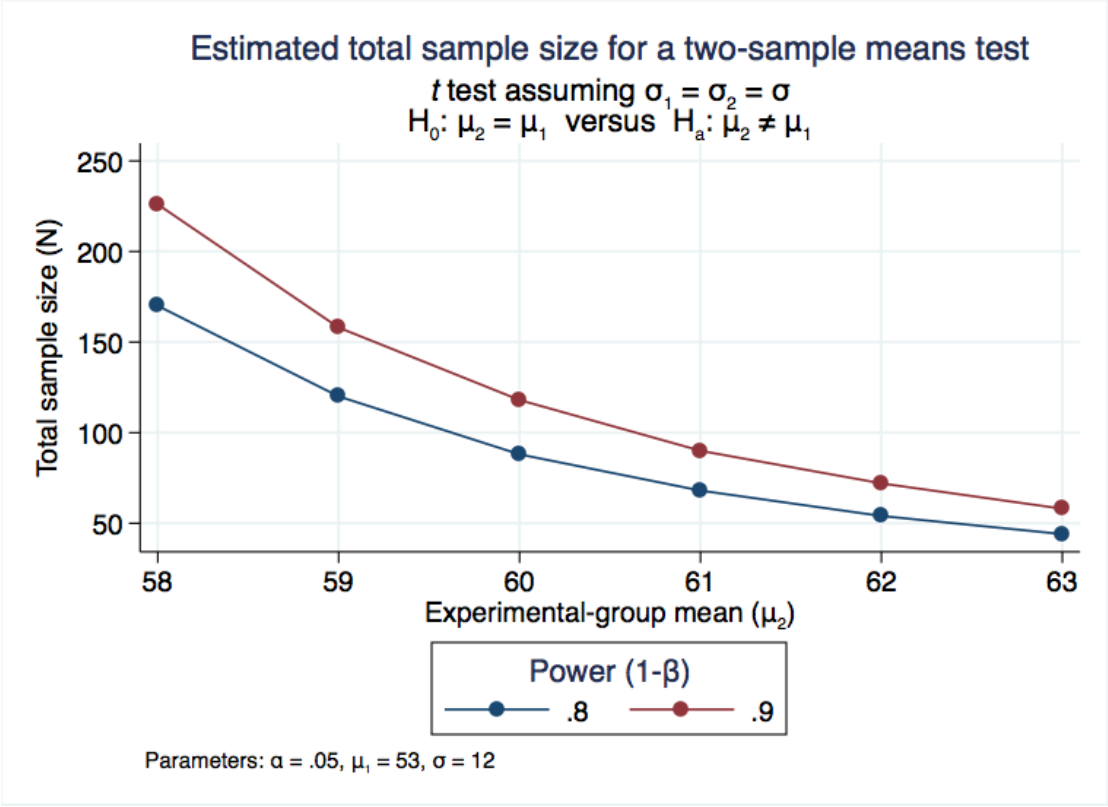
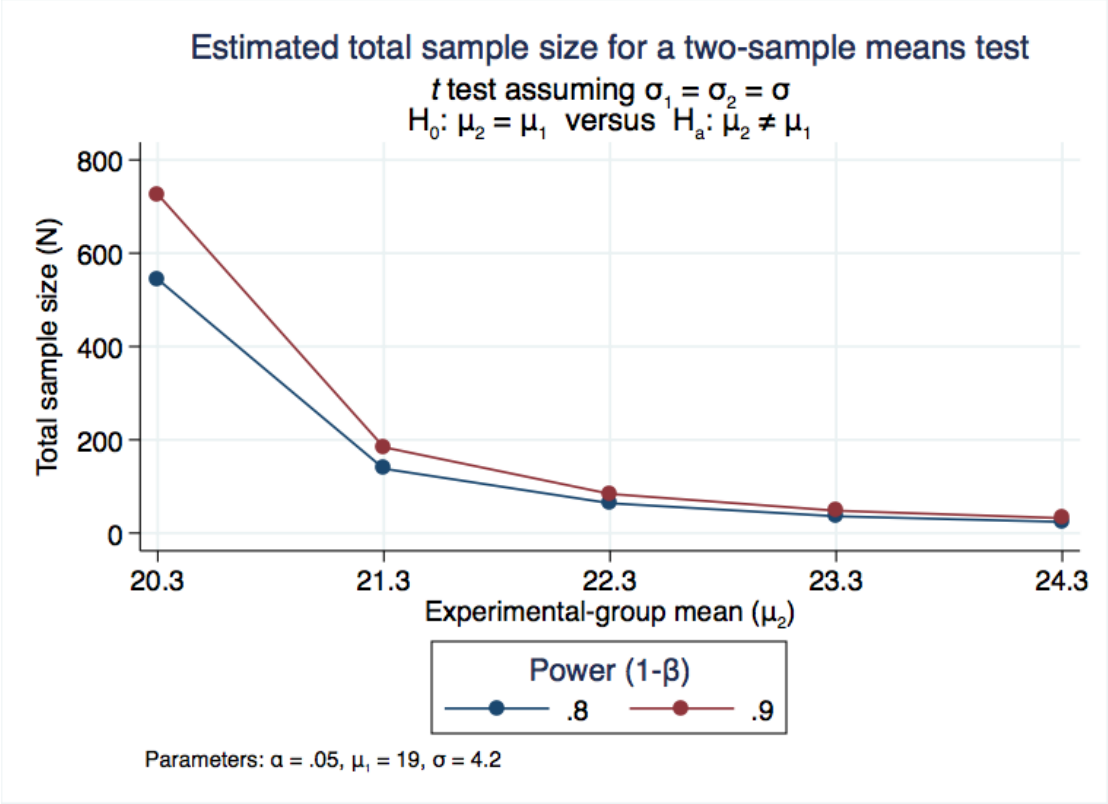


Figure 8 - Sample size estimation: 1 to 5-point difference in change in LCS score at 12 weeks



Assuming a constant recruitment rate of 6 patients per week (2 patients per centre) the study is planned to recruit consecutively for 26 weeks (Figure 9).

Figure 9 - Planned recruitment process

Randomization

Randomization services will be provided by AdvicePharma via a computer system using randomly permutated blocks and stratified by trial centers and therapy (i.e.

chemotherapy, immunotherapy and biological therapy). Nurses or physicians involved in the study will take care of the enrollment phase. After signature of informed consent, a randomization code will be generated electronically and assigned to the patient. During the informed consent procedure, the team will go carefully through the different aspects of the study design and will present LuCApp as well as the usual care alternative. During this phase the patient will have an opportunity to discuss her level of experience with mobile technology.

The study is nonblinded, in fact it is not possible to blind the participants when this type of intervention and these outcomes are under investigation.

Participants will remain on study until discontinuation of cancer treatment, voluntary withdrawal, study termination or death.

Statistical methods

The baseline differences between the intervention and control groups will be assessed using the chi-square (χ^2) test for binary demographic data and the independent sample t-test for continuous variables. We will summarize graphically and numerically the distributions of symptoms, outcomes as well as covariates.

For the primary quality of life endpoint, two groups t-test will be used to compare changes from baseline in FACT-L in the experimental group and the control group 12 weeks after randomization. A multivariable linear regression model, with change score as the dependent variable, adjusted for covariates will be fitted. The proportion of patients in each arm who experienced improved, unchanged, or worsened scores from baseline will be compared using χ^2 or Fisher's exact test. This analysis will be run for both any change and clinically meaningful changes for specific subscales (51). The analyses will be repeated at 24 weeks after randomization.

For all other questionnaires, changes from baseline in the LuCApp group and the control group at 12 and 24 weeks after randomization will be computed using t-test comparison. The SCNS-SF34, usability and ZBI data results will be summarized graphically and numerically.

As a secondary analysis, adjusting for possible confounding factors of demographic variables and clustering in centers, the repeated measures multivariate analysis of covariance will be conducted to determine whether LuCApp affects HRQoL and symptoms as measured via EQ-5D-5L, FACT-L and HADS at different time points of

data collection. Additionally, mixed-effects models will be used to analyze the same subject-specific continuous outcomes with incorporation of terms for intervention, time, centers, and any identified covariates.

Analysis of missing data will first determine how common a problem this is and whether it can be assumed to be missing at random or not missing at random. Multiple sensitivity imputation analyses will be conducted, including last observation carried forward, minimum observation values carried forward, average observation values carried forward, and multiple imputation. EQ-5D value will be set to zero if death occurs before 6 months. Survival time will be calculated from the date of enrollment to the date of death or censoring those alive at the last follow-up with the use of the Kaplan–Meier method. A Cox proportional-hazards model will be fitted to assess the effect of LuCApp on survival, with adjustment for demographic characteristics and baseline performance status.

By combining EQ-5D derived utilities and survival quality-adjusted life years (QALY) for participants in both arms will be computed and compared using two group t-tests between LuCApp and standard care arm. A multivariable linear regression model with QALY as dependent variable will be used to adjust for other covariates. Resource consumption and related costs will be calculated and reported for each treatment group and compared by means of parametric and non-parametric tests (52).

Two-sided P values of less than .05 were considered to indicate statistical significance. All statistical analyses will be performed using STATA® 14.2, StataCorp, Texas.

Ethics & Informed Consent

All procedures involved in the study were consistent with generally accepted standards of ethical practice. The protocol is submitted for ethical clearance to the ethical committees at the three sites involved in the RCT (full list of participating centers is available as an attachment).

Patients will be informed about the study by their clinician during the enrollment visit. The oncologist will provide patients with a brief introduction of the trial content and will hand them over a leaflet where all relevant information is gathered. This will enable patients to make an informed decision about whether to take part in the study. The leaflet will better explain the App's "terms and conditions", will assure the confidentiality of the data collected and outline users' rights and responsibilities.

Safety, privacy and legality are guaranteed using a unique username with an associated password, firewalls, secured sites and the transfer of confidential information: whenever one of the previous is missing, the brochure will explain which procedures to follow during an emergency. Furthermore, a statement on how data will be stored and when they will be destroyed is included in the form.

To further support patients during the trial and increase security, an email "helpdesk" will be activated to help participants manage any kind of unexpected trouble.

Participant signature is required for informed consent. After signing it, patients will send the consent form both to the research team and to their clinician.

DISCUSSION

The electronic and mobile health revolution holds great potentials for improving symptom management strategies in chronic conditions. With spending review reforms under way, using web- and mobile-based technology to develop low cost and pragmatic patient-centered intervention is the key to lessening the health care cost and advancing the science of symptom management. In parallel with the development of new strategies and products, the evaluation of such interventions becomes important in order to bring to patients and to healthcare systems effective and cost-effective solutions. This clinical trial focuses on primary outcomes of health related quality of life and usability to test preliminarily the impact of LuCApp as a technology to improve self-reporting and self-management of symptoms in patients with lung cancer. The trial was designed with a pragmatic "attitude", eligibility criteria were intentionally set wide to capture the lung cancer population seen in real practice. However, this trial is to be intended as a pilot one in order to understand the usability and feasibility of introducing a new mobile technology in the management of symptoms and side effects of patients undergoing pharmaceutical treatments for lung cancer in three centers in Northern Italy.

Dissemination and impact

The protocol will be registered on a public repository and possibly published on a peer reviewed journal. Once the study will be completed and the analyses will be performed, a report will be produced and shared with all participating centers for interpretation. A manuscript will be drafted by the team and submitted for publication at conferences and in scientific journals.

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