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Lung Cancer App (LuCApp) study protocol: a randomised controlled trial to evaluate a mobile supportive care app for patients with metastatic lung cancer

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ABSTRACT

Introduction Mobile health technologies may enhance patient empowerment and data integration along the whole care continuum. However, these interventions pose relatively new regulatory, organisational and technological challenges that limit appropriate evaluation. Lung Cancer App (LuCApp) is a mobile application developed by researchers and clinicians to promote real-time monitoring and management of patients' symptoms. This protocol illustrates a clinical trial designed to evaluate the usability, effectiveness and cost-effectiveness of LuCApp versus standard of care.

Methods and analysis This is a 24-week two-arm non-blinded multicentre parallel randomised controlled trial. A total of 120 adult patients diagnosed with small or non-small cell lung cancer and eligible for pharmaceutical treatments will be allocated 1:1 to receiving either standard care or LuCApp in addition to standard care at three oncology sites in Northern Italy. During the treatment period, LuCApp allows daily monitoring and grading of a list of symptoms, which trigger alerts to the physicians in case predefined severity thresholds are met. Patients will complete a baseline assessment and a set of valid and reliable patient-reported outcome measures every 3±1 weeks, and up to 24 weeks. The primary outcome is the change in the score of the Trial Outcome Index in the Functional Assessment of Cancer Therapy (Lung) questionnaire from baseline to 12 weeks. Secondary outcomes are the Lung Cancer Subscale, the EuroQoL 5D-5L questionnaire, the Hospital Anxiety and Depression Scale, the Supportive Care Needs Survey Short Form, the app usability questionnaire and the Zarit Burden Interview for the main caregiver.

Ethics and dissemination The trial received ethical approval from the three clinical sites. Trial results will be disseminated through peer-reviewed publications and conference presentations.

Conclusions This trial makes a timely contribution to test a mobile application designed to improve the quality of life and delivery of care for patients with lung cancer.

Trial registration number NCT03512015; Pre-results.

Strengths and limitations of this study

► Lung Cancer App (LuCApp) has been designed by a multidisciplinary team and developed through iterative sessions to improve patients' real-time monitoring of symptoms and side effects during pharmacological therapies for lung cancer.

► The impact of LuCApp on health-related quality of life, cancer supportive care needs, burden for caregivers and resource consumption will be tested in a parallel randomised controlled trial.

► Sources of bias may include the different levels of ease of participants when using mobile technologies, the impossibility to blind them and different modes of questionnaires administration (app-based vs paper/phone-based).

INTRODUCTION

The substantial progress made in the diagnosis and treatment of cancer entails it can be managed as other chronic diseases, where long-term active monitoring is needed. In order to enhance patients' quality of life, the traditional paternalistic model where the patient-provider relationship tends to be unilateral and the patient has little say in his/her care pathway might need to be outclassed by new models of care.[1]

To this end, self-management interventions can help patients and their families care for themselves along the cancer care continuum. Self-management 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 also aims at enhancing symptom management. Although recent advances in cancer therapies have led to better clinical outcomes,[3]

treatment-related side effects may be significant and consequently may have an impact on treatment adherence, frequency of hospitalisations and related costs as well as patients' and their carers' health-related quality of life (HRQoL).

This need for self-management systems together with the unsustainability of current healthcare spending 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 and other wireless devices'.[4] As a booming technology, mHealth can be instrumental in enhancing patient empowerment and patient centricity along the whole care continuum, in supporting clinical decision-making, in strengthening the data generation process by integrating data from several different sources and by connecting stakeholders in the healthcare pathway.

However, mHealth products also pose relatively new regulatory, organisational and technological challenges that need to be tackled in order to ensure appropriate evaluation and use.[5 6] While there were over 325 000 mHealth applications (apps) available in major app stores and over 3.6 billion downloads in 2017, reflecting a growth rate of over 12.5% from the year before,[7] overall scientific evidence about the effectiveness of mHealth apps in improving health-related outcomes is scant.

Few mHealth applications aimed at self-management of patients with cancer have been proposed and evaluated. Basch *et al* tested symptom self-reporting during routine cancer treatment via Symptom Tracking and Reporting against usual care,[8] showing a smaller decline in HRQoL in the intervention group than in the usual care and, in a post hoc analysis, a significant effect on overall survival (adjusted HR 0.83, 95% CI 0.70 to 0.99). Denis *et al* compared an e-follow-up application for detecting lung cancer relapse with standard surveillance, showing improved overall survival for the experimental compared with the control arm (HR 0.32, 95% CI 0.15 to 0.67).[9] In 2016, the University of Surrey launched the electronic Symptom Management using the Advanced Symptom Management System (ASyMS) Remote Technology study, a 5-year randomised controlled trial (RCT) conducted across five European countries to test the impact of ASyMS on patients to commence first-line chemotherapy for breast, colorectal or haematological cancer.[10]

In Italy, several oncologists at 'Fondazione IRCCS Istituto Nazionale dei Tumori' (Milan) together with researchers and software developers initially designed a web-based self-management system tailored to the needs of patients with cancer. Adjustments were incrementally made to refine the application by an extended clinical team of researchers at Bocconi University and Advice-Pharma in order to specifically target patients with lung cancer. Lung cancer is the most common oncological malignancy and cause of cancer deaths worldwide with a total of 1.71 million deaths in 2016.[11] The healthcare burden and costs attributed to lung cancer is substantial and its 5-year survival rate (17.8%) is still much lower than that of other leading cancers.[12] Because of the significant impact on HRQoL of lung cancer symptoms and the severity of side effects associated with the available pharmacological treatments for this condition, we believed this population was suitable to test an mHealth application for self-reporting and management of symptoms and treatment-related side effects.

Lung Cancer App (LuCApp) was first made available on Playstore (Android online store) and on iTunes (Apple online store) in April 2018.

LuCApp has been pilot-tested with a number of oncologists, healthcare professionals and specialists in palliative care from other specialised oncology centres as a mobile phone-based remote monitoring system to allow real-time gathering of patients' symptoms and patient-reported outcome measures (PROMs) to share with healthcare professionals during pharmacological therapies for lung cancer.

OBJECTIVES

The primary objective of the study will be to determine whether LuCApp, by enhancing self-monitoring of therapy-induced side effects compared with the current standard of care, can lead to increased HRQoL scores as measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire[13] from the start of the pharmacological treatment for lung cancer and up to 12 weeks (primary end point) and 24 weeks follow-up.

Other secondary objectives of the study will be to evaluate the impact of LuCApp during the pharmacological treatment for lung cancer and up to 12 weeks and 24 weeks follow-up from therapy start date on a number of outcomes. More specifically, the hypotheses made on the impact attainable through the app were:
1. Improved HRQoL as measured by a generic preference-based measure of health status, EuroQol-5-Dimensions-5 Level (EQ-5D-5L).[14]
2. Reduced anxiety and depression as measured by Hospital Anxiety and Depression Scale (HADS),[15] a self-assessment scale developed to detect states of depression, anxiety and emotional distress.
3. Positive impact on patients' cancer supportive care needs vis-à-vis their expectations, as expressed by the Supportive Care Needs Survey Short Form (SCNS-SF34).[16]
4. Positive impact on caregiver burden in health, psychological well-being, finances, social life and relationship with patient, as measured by the Zarit Burden Interview (ZBI).[17]
5. Acceptable cost-effectiveness profile of LuCApp versus standard care, based on resource use data collected throughout the study and quality-adjusted life-years (QALY) calculated through EQ-5D-5L on the patient population.
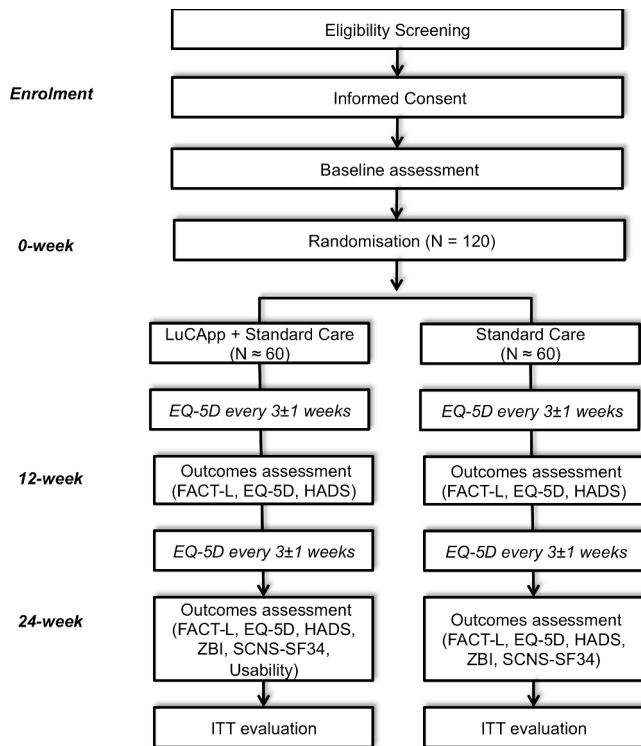
Figure 1 Flow diagram for screening, enrolment, randomisation, data collection and analysis. EQ-5D, EuroQoL 5 Dimensions; FACT-L, Functional Assessment of Cancer Therapy-Lung; HADS, Hospital Anxiety and Depression Scale; ITT, intention to treat; LuCApp, Lung Cancer App; SCNS-SF34, Supportive Care Needs Survey Short Form; ZBI, Zarit Burden Interview.

Table 1 Eligibility 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 targeted therapy. ▶ Patients diagnosed with non-resectable tumour. ▶ Life expectancy of 6 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 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 (ie, are blind). ▶ Patients receiving or that plan to receive radiotherapy or surgical resection as radical treatment for the primary disease. ▶ Patients already included or about to join other clinical trials. ▶ Patients already using other smartphone applications to self-manage cancer symptoms.

6. Good usability and user satisfaction with LuCApp, as assessed by a modified Computer System Usability Questionnaire (CSUQ) administered to the patients at the end of the study.

Study design

This is a 24-week two-arm multicentre parallel RCT designed to evaluate the effectiveness, cost-effectiveness and usability of LuCApp to improve symptoms and HRQoL in patients with lung cancer. The protocol has been developed in accordance with the Standard Protocol Items Recommendations for Interventional Trials Statement[18] and the Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and online Tele Health checklist.[19] The flow diagram for recruitment and randomisation is shown in figure 1.

Study setting

Patients will be recruited from three oncologic sites in Italy: Fondazione IRCCS Policlinico San Matteo (Pavia), Fondazione IRCCS Istituto Nazionale dei Tumori (Milan), San Luigi Gonzaga Hospital (Orbassano). The LuCApp study is led and sponsored by Bocconi University (Milan, Italy) and is registered on ClinicalTrials.gov (NCT03512015). A data management committee was not needed as the trial was deemed of minimal risk.[20]

Participants screening and recruitment

Eligible patients will be identified according to the inclusion and exclusion criteria described in table 1 from outpatient and/or inpatient oncology settings at each site. Once eligibility has been established, patients will be invited to join the study by the local clinical team. During the pre-enrolment phase, patients will receive an invitation letter, the study leaflet and the informed consent form. Patients will be given a sufficient period of time to consider participation and they will be advised that they can discuss the study with any significant others prior to making a final decision. If patients agree to participate, written informed consent will be obtained during the enrolment visit. At this stage, patients will receive adequate training and detailed information about the app usage by the research staff, including research nurses, data managers and oncologists, who will also help patients download the application on their own device. Before the arranged appointment for the beginning of the therapy, all patients will be asked to fill-in the baseline questionnaires on paper.

This is not a purely web-based trial, since face-to-face encounters will still be present: patients included in the intervention arm will complete follow-up questionnaires via the app, while patients in the comparator arm (SoC) will complete follow-up paper questionnaires during

clinic visits or via telephone interviews with the research team.

Randomisation

Once informed consent has been received and baseline PROMs collected, the research staff dedicated to the recruitment will obtain a randomisation code, from randomly permutated blocks stratified by site and therapy (ie, chemotherapy, immunotherapy and targeted therapy), generated electronically and assigned to the patient via a secure web-based electronic case report form. The electronic data capture system used for the study is validated, secure and redundant and complies with standard Food and Drug Administration requirements. Standard operating procedures are in place for data management process.

The study is non-blinded, as it is not possible to blind participants and personnel when this type of intervention and PROMs are under investigation. However, the clinician version of LuCApp does not allow the doctors to monitor HRQoL questionnaires completed by the patients and patients will receive information about genuine lack of evidence in relation to the effectiveness of the app and will be blinded to study hypotheses. Participants will remain into the study until the end of the 24-week intervention period unless early discontinuation occurs due to cessation of cancer treatment, voluntary withdrawal or death.

Intervention

Patients assigned to the intervention arm, with the help of the local team, will download the app on their mobiles and log in by inserting a newly generated custom e-mail address and a self-chosen password. Patients assigned to this arm will be trained to use LuCApp as a tool for self-reporting of lung cancer symptoms and therapies' side effects and PROMs during the enrolment visit. They will be assisted during the whole study period by a technical 'helpdesk'. Furthermore, the Data Manager will regularly check upload of data from the intervention group and, for the purpose of this research only, the research team will be in contact approximately biweekly by email or phone to verify if there are technical problems and to encourage app use. LuCApp is currently at its fifth version and we do not anticipate any updating during the study period (figures 2–3).

During the study, the use of the app will 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 collected and that only patients can access to sensitive data. The Android and iOS versions of the app (patient version) serve as a data capture interface that collects and transfers data, under https security protocol, to the database behind the electronic data capture platform. Patients will not be compensated (by cash or in-kind) for their participation in the trial, nor will they be asked to pay for the app, which will be freely available for download.

The intervention presents several different and unique functionalities and components that were designed to aid symptom self-reporting and management:
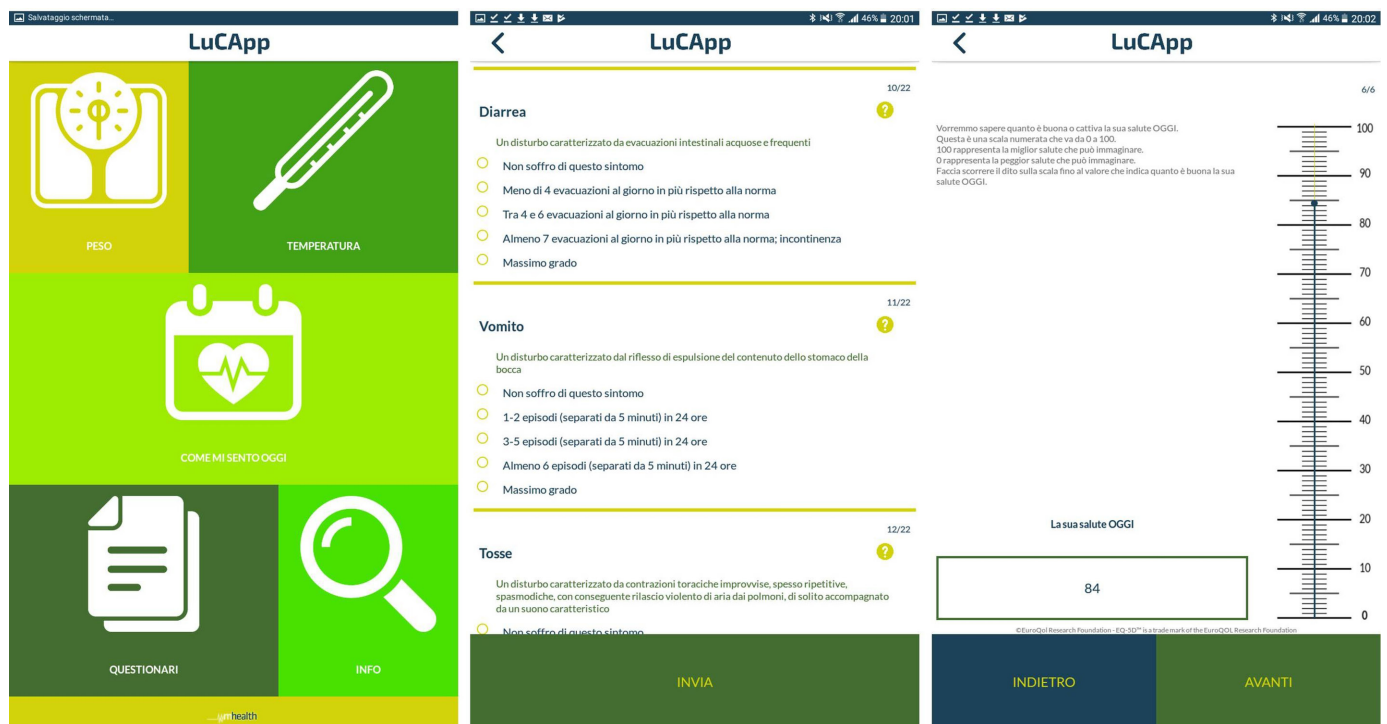

Figure 2 Lung Cancer App (LuCApp) patient version. Home screen where the patient can access self-monitoring, info and questionnaires; example of daily symptom questionnaire and health-related quality of life visual analogue scale.
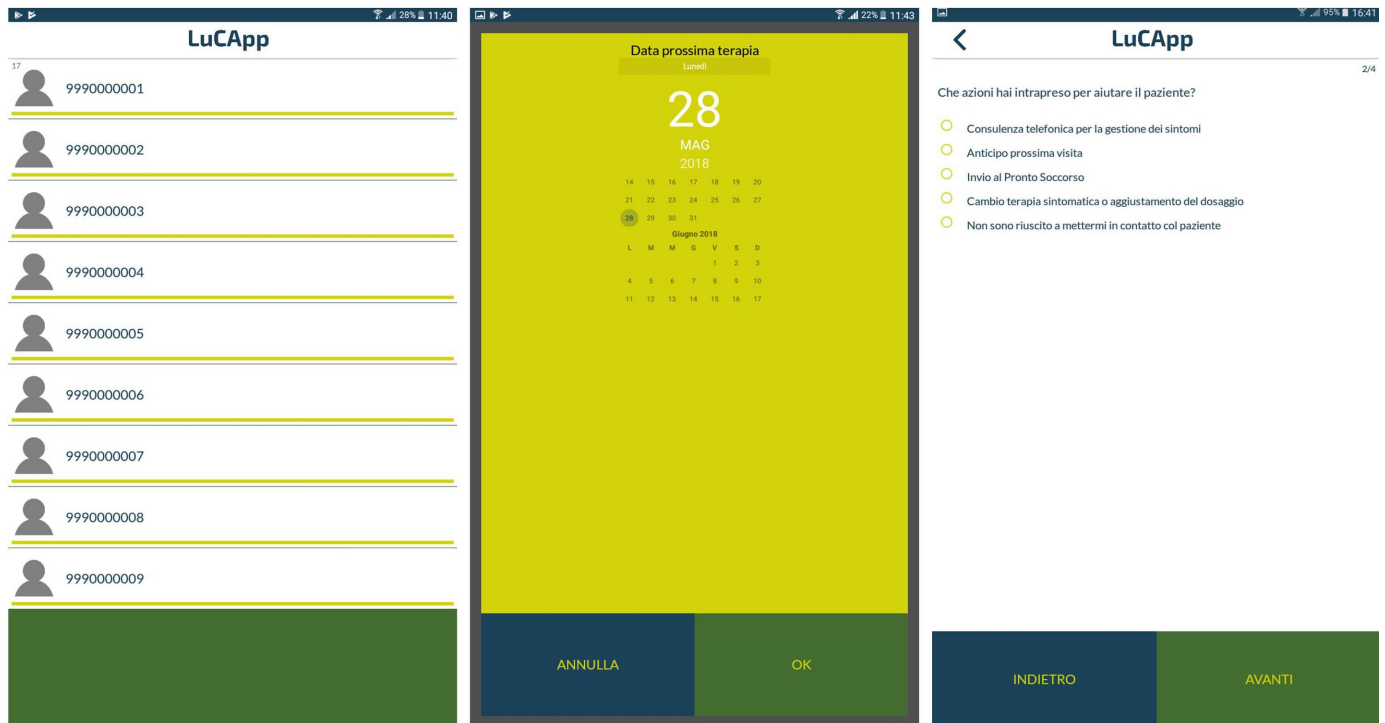
Figure 3 Lung Cancer App (LuCApp) clinician version. Home screen and examples of actions taken in response to alerts.

"How do I feel today?" This component of the app allows participants to fill in a questionnaire to report their daily situation with respect to side effects commonly experienced during therapies for lung cancer and identified from the literature.[21–24] From an initial list of 68 symptoms, 2 teams of lung cancer specialists checked those symptoms that they consider relevant for the patient population under investigation and cross-validated the respective selection to arrive to a final list of 22 items. 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).[25] LuCApp will trigger alerts to healthcare professionals whenever a symptom of level ≥3 is inserted. Patients will be aware that reporting symptoms above that threshold will produce an alert to the clinicians: in order to elicit truthful answers, for each symptom we included a detailed description and a set of options with specific criteria referred to the exact grade listed in the CTCAE.

Although compilation is possible several times per day, patients will receive a reminder (as a mobile banner or email) to fill in this questionnaire every 3 days. Up to three different reminders will be sent at 12:00, 18:00 and 21:00 hours to encourage patients to self-report their symptoms using a recall period of the past 24 hours. Symptom reports will be available to clinicians only.

► 'Temperature' and 'weight'—patients in the LuCApp arm will be asked to enter their body temperature daily and their weight once per week again via mobile banners or emails. 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. Whenever body temperature exceeds the 38°C or a 5% reduction in body weight over two consecutive weeks is observed, specific alerts will be generated to inform the clinical team.

► 'Tip of the day'—whenever a patient logs into the app, a daily tip, a short suggestion to better manage the side effects of the therapies, is shown. 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.[26 27]

► 'Questionnaires'—this section allows patients to fill-in several PROMs about their HRQoL and experience with supportive care needs and LuCApp: EQ-5D-5L, FACT-L, HADS, SCNS-SF34, usability and satisfaction questionnaire.

► 'Info'—in order to increase the overall patient's awareness about his/her condition and management options, this section collates relevant educational material such as general information on lung cancer, therapies, patients' rights, useful institutional links.

As a direct consequence, although the inclusion of targeted therapies as well as chemotherapies may imply that some patients will be undergoing oral treatments at home and not in hospitals or clinics, the app does not aim at managing, at least not directly, medication adherence.

Continuity in the utilisation of the app will be strongly recommended and encouraged by automated reminders when the data input is scheduled.

Through LuCApp, clinicians will receive alerts on their dedicated LuCApp device (ie, smartphone, laptop) and will be required to respond within 24 hours and document the type of intervention performed (eg, referral to the emergency room/hospital, telephone counselling about symptom management, dose modification, supportive medication initiation/change, visit anticipation).[8] In the healthcare professional app only, clinicians can view the longitudinal trend of their patients' clinical parameters. Side effects, temperature and weight are displayed in charts over a timeframe of choice.

Healthcare professionals will be trained through dedicated sessions prior to the launch of the study. 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 or national holidays, 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 (eg, out-of-hours service doctor, emergency department).

Standard of care

Standard of care in this setting consists of procedures currently available at participating centres for monitoring and documenting treatment-related symptoms in patients with lung cancer and aligned with the guidelines developed by the Italian Association of Medical Oncology.[28] Participating centres are either research dedicated hospitals (San Matteo Hospital, Istituto Nazionale Tumori) or teaching hospital (San Luigi Gonzaga Hospital). Symptoms for control arm patients will be discussed and registered during scheduled clinical visits with the oncologists. Patients are usually allowed to contact their sites for concerning symptoms that occur between scheduled visits or advised to see the out-of-hour doctor. An emergency department is available at San Matteo Hospital and San Luigi Gonzaga Hospital, but not at Istituto Nazionale Tumori. PROMs will be filled in following the same schedule identified for LuCApp patients with paper questionnaires during clinic visits or via telephone interviews with the research team.

Outcomes

As part of this RCT, LuCApp will be evaluated in terms of impact on: (1) HRQoL, (2) cancer supportive care needs, (3) burden for caregivers, (4) resource use, (5) usability and patients' satisfaction. The rationale for selecting these measures and their characteristics are detailed below.

Health-related quality of life

The selection of HRQoL measures was based on the availability of a validated Italian version of the tool, for self-report use, that can be administered both on paper and via smartphones, and commonly used in patients with lung cancer.

Symptoms are subjective experiences self-reported by the patient, and are a subset of patient perceptions of health status and HRQoL.[29] HRQoL is a multidimensional construct of diverse functional scales (eg, physical function, psychological function, social role function) and symptom scales (eg, disease-related or treatment-related symptoms). Three questionnaires were selected.

a. FACT-L questionnaire is a disease-specific measure capturing multidimensional aspects of quality of lives of patients with lung cancer.[13] 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 (LCS). Evidence suggests that while there are small differences in the way people respond based on mode of administration (ie, in-person or telephone/in the clinic or by mail/computer administered), these alternate formats are essentially equivalent, particularly when reporting data at the group level.[30] The questionnaire will be administered at baseline, at 12 weeks and at the end of the study period.

b. 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 used within an economic evaluation model.[14] This tool is also commonly used in lung cancer trials.[31] It includes 5-level questions covering five domains: mobility, self-care, usual activities, pain and discomfort and anxiety and depression. Additionally, patients are asked to fill in how they feel today on a vertical visual analogue scale. 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, and at the end of the study period.

c. HADS is a self-assessment scale developed to detect states of depression, anxiety and emotional distress among patients treated for a variety of problems in the setting of outpatient clinics.[15] It is composed of two 7-item scales for depression and anxiety, respectively. HADS was identified as one of the most commonly used PROMs in advanced-staged lung cancer clinical trials of pharmaceutical agents,[32] and has been used to measure HRQoL in patients with non-small cell lung cancer.[33] Literature shows HADS is a reliable and valid tool to identify patient with emotional disorders.[34] The questionnaire will be administered at baseline, at 12 weeks and at the end of the study period.

Cancer supportive care needs

Patients with lung cancer have greater unmet supportive care needs than patients with other cancer.[35] 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.[36 37] It consists of 31 items covering 4

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.[37] 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.[37] The SCNS-SF34 is available on LuCApp for the intervention group and will be administered at the end of study to assess whether supportive care needs were fulfilled in the different study arms.

Burden on caregivers

The 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. The total burden is obtained by adding the scores across all 22 items: the higher the score, the higher the burden. The ZBI has been widely referenced in studies measuring caregiver burden of patients with cancer.[38 39]

Assessment timing of the ZBI will be at the end of the study, and will be administered in paper format or via phone.

Usability and satisfaction of LuCApp

Patients in the intervention arm will have an opportunity to provide feedback on strengths and shortcomings of the application, including unintended/unexpected effects. 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 CSUQ 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 90s.[40] The CSUQ was later adapted for mobile apps usability testing to elicit participant satisfaction with the PAediatric Risk Assessment app, a mHealth tool developed to help healthcare professionals in resource-limited settings detect patients at high risk of both in-hospital and postdischarge mortality.[41] The final version consists of 12 items evaluated on a Likert scale. In addition, three qualitative questions were added to draw further information on the application and on the generalisability 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?". The questionnaire will be administered at the end of the study.

Resource use

Resource use will be captured through patients' reports of symptoms and clinicians' actions in response to those symptoms (eg, prescriptions, hospitalisations including emergency access, change in therapy). Moreover, additional information will be obtained for both control and treatment group patients via a form administered during the clinics on instrumental and diagnostics tests performed, general practitioner or specialist visits, additional medicines or dietary supplements taken, hospitalisation or emergency access occurred between visits. Average per-patient clinician time spent for LuCApp management, including troubleshooting or reminder contacts established with the patients, or standard care management of lung cancer therapies' symptoms will be elicited with questionnaires administered to the clinicians at different time points during the study.

Study close-out

At study close-out at week 24, patients in the intervention arm will not continue to use the app and will be lead back to standard of care. They will fill all PROMs in through the app, while for standard of care patients PROMs will be collected in the hospital during an ad hoc closing visit. As for the ZBI, which will be administered to the main caregiver at the end of the study, it will be completed either in person or via phone.

Sample size calculation

The change in the Trial Outcome Index (TOI) of the FACT-L questionnaire from baseline to 12 weeks was used as primary end point for this study. FACT-L questionnaire contains four general and one lung cancer symptom-specific subscales. General subscales include: Physical Well-Being (PWB), Social/family Well-Being, Emotional Well-Being and Functional Well-Being (FWB).[42] The LCS assesses symptoms commonly reported by patients with lung cancer (eg, shortness of breath; loss of weight; tightness in chest). The 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 5-point Likert-type scales ranging from 0 ('not at all') to 4 ('very much'). TOI scores range from 0 to 84 where higher scores represent better HRQoL or fewer symptoms. After accounting for about 20% attrition rate, we estimated that with 120 patients allocated 1:1 between LuCApp and usual care groups, the study would have 90% power with a two-sided α of 0.05 to detect a significant between-group difference of 5 points[43] in the change in the TOI score from baseline to 12 weeks, given a pooled SD of 15.[44]

Data analysis plan

Baseline demographic and clinical characteristics will be tabulated by treatment groups and descriptive statistics will be provided. For the primary HRQoL end point of changes from baseline in FACT-L TOI 12 weeks after randomisation, a repeated-measures analysis using mixed models to test the difference between LuCApp and standard care groups will be performed, adjusting for baseline values and characteristics, pharmacological treatment,

site and length of treatment. 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.[43] For all other questionnaires, changes from baseline, or follow-up values only, in the LuCApp group and in the control group at 12 and 24 weeks after randomisation will be computed and compared. Repeated measures of the outcomes will be analysed again with mixed models adjusted for relevant covariates, as with the primary end point, up to 24 weeks.

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 enrolment 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. Primary analyses will be based on the intention-to-treat principle. Secondary per-protocol analyses will be performed taking into account use and adoption metrics available through the app embedded tracking system.

By combining EQ-5D-derived utilities and survival, 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.[45] The perspective taken for the evaluation of resource consumption will be that of the National Healthcare System. Unitary costs will be expressed as EUR 2018. Drug unitary costs will be derived from national price listings, visits, laboratory and instrumental tests, will be valued according to the outpatient procedures formulary, while hospitalisations and emergency access will be valued according to tariffs and special funding mechanisms in place in Lombardy Region.

Two-sided p values of <0.05 will be considered to indicate statistical significance. All statistical analyses will be performed using STATA V.14.2 (StataCorp, Texas, USA).

Patient and public involvement

A panel of patients with cancer was involved via focus group in the development of LuCApp. A lay summary of study results will be prepared and made available online and at the three oncology sites. A battery of patient-reported outcomes will be collected to assess the burden of the intervention.

Ethics and dissemination

Any major study protocol amendments will be submitted to the following three clinical sites: Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Fondazione IRCCS Istituto Nazionale dei Tumori and Azienda Ospedaliero-Universitaria San Luigi Gonzaga. Study-related adverse events will be reported to the Italian competent authority and to the local ethics committees. Trial results will be disseminated through publications in scientific journals and presentations at national and international conferences.

CONCLUSIONS

The electronic health and mhealth revolution holds great potential for improving symptom management strategies in chronic conditions. With spending review reforms under way, using web-based and mobile-based technology to develop low cost and pragmatic patient-centred intervention is key to lessening the healthcare costs and advancing the science of symptom management. In parallel with the development of new strategies and products, the evaluation of such interventions becomes critical in order to bring to patients and to healthcare systems effective and cost-effective solutions. LuCApp trial is now open and recruiting to test the usability, effectiveness and cost-effectiveness of a new mobile technology to improve the management of symptoms and side effects in patients undergoing pharmaceutical treatments for lung cancer. Compared with previous trials, LuCApp has a focus on this specific solid tumour while allowing for monitoring of patients treated with different pharmaceutical therapies, including newly approved immunotherapy agents whose safety and effectiveness evidence is progressively increasing.[46] Inclusion of patients confident with the use of mobile technologies as well as impossibility of blinding participants may represent potential sources of bias in this study. While this might influence recruitment speed and generalisability of results to mobile device non-users, a greater likelihood that patients will use the device more frequently is guaranteed.[47] Moreover, different modes of questionnaires administration (app-based vs paper/phone-based) may result in different response rates and missing data across the two arms, although monitoring of outcomes collection at prespecified time points will occur for both intervention and control groups.

Although conducting mHealth research with mobile phones is complex, this is a promising field to create tools that can have meaningful impact on the lives of people and delivery of care. This trial will be a timely opportunity to test and address the challenges unique to a mobile-based application to improve the HRQoL of patients with a lung cancer condition.

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