SYMptom monitoring with Patient-Reported Outcomes using a web application among patients with Lung cancer in the Netherlands (SYMPRO-Lung): study protocol for a stepped-wedge randomised controlled trial

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ABSTRACT

Introduction Lung cancer and its treatment cause a wide range of symptoms impacting the patients’ health-related quality of life (HRQoL). The use of patient-reported outcomes (PRO) to monitor symptoms during and after cancer treatment has been shown not only to improve symptom management but also to improve HRQoL and overall survival (OS). Collectively, these results favour implementation of PRO-symptom monitoring in daily clinical care. However, these promising outcomes have been obtained under trial conditions in which patients were selected based on stringent inclusion criteria, and in countries with a dissimilar healthcare system than in the Netherlands. The primary aim of the SYMptom monitoring with Patient-Reported Outcomes using a web application among patients with Lung cancer in the Netherlands (SYMPRO-Lung) study is to evaluate the effect of PRO-symptom monitoring during and after lung cancer treatment on HRQoL in daily clinical practice. Secondary objectives include assessing the effect of PRO-symptom monitoring on progression-free survival, OS, the incidence and grade of PRO symptoms, medication adherence, implementation fidelity and cost-effectiveness.

Methods and analysis The SYMPRO-Lung study is a prospective, multicentre trial with a stepped wedge cluster randomised design. Study participants (n=292 intervention, n=292 controls) include patients with lung cancer (stages I–IV) starting treatment with surgery, systemic treatment, targeted treatment and/or radiotherapy. Every participating centre will consecutively switch from the control period to the intervention period, in which patients report their symptoms weekly via an online tool. In the intervention group, we evaluate two alert approaches: the active and reactive approach. If the symptoms exceed a predefined threshold, an alert is sent to the healthcare provider (active approach) or to the patient (reactive approach). Both the control and intervention group complete HRQoL questionnaires at 4 time points: at baseline, 15 weeks, 6 months and 1-year post treatment). Differences in HRQoL between the groups will be compared using linear mixed modelling analyses, accounting for within-centre clustering, potential time effects and confounding.

Ethics and dissemination The study protocol was approved by the Institutional Review Board and the Medical Ethics Committee of the Amsterdam UMC (under number NL 68440.029.18) and the institutional review boards of the participating study sites. The dissemination of the results will be conducted through publication in peer-reviewed journals and through scientific conferences.

Trial registration number Trial register identifier: Netherlands Trial register Trial NL7897. Date of registration: 24 July 2019. https://www.trialregister.nl/trial/7897.

Strengths and limitations of this study

► A pragmatic stepped-wedge design is used allowing revelation of the effect in the real world.
► This multicentre study compares the effect of an active approach with a reactive approach.
► We include a heterogeneous lung cancer group comparable to real-world clinical practice.
► The use of items from the Food and Drug Administration (FDA)-approved Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (CTCAE) is a perfect fit to the commonly used CTCAE.
► Most participating centres do not allow to fully integrate the web application within the electronic health record.

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INTRODUCTION
In the Netherlands, approximately 13 000 people are diagnosed with lung cancer each year.1 Treatment options include surgery, systemic treatment, targeted treatment, radiotherapy or a combination of these treatments. Lung cancer and its treatment can cause a wide range of symptoms including fatigue, dyspnoea, cough and pain both during the period of treatment and thereafter.2 These symptoms can have a significant impact on a patient’s health-related quality of life (HRQoL), and may negatively affect further treatment.3 In addition, these symptoms can also be a signal of cancer relapse.4

The current strategy for symptom monitoring is primarily based on the report and grading by healthcare providers (HCPs). Increasing evidence suggests that this leads to suboptimal symptom management,5–7 since HCPs miss a significant proportion of the symptoms experienced by patients due to underestimating and underreporting of the onset, frequency and severity of symptoms.6–9 Partially, this is due to the limited time typically available for a clinic visit. Furthermore, patients might be reluctant or tend to forget to contact the HCP in case of symptoms experienced when at home.6 7 9 Therefore, more efficient strategies for monitoring symptoms at home during and after treatment are warranted.

A potentially useful strategy is the use of an online patient-reported outcome (PRO) measure that monitors symptoms and activates an alert based on a predefined algorithm, which is subsequently send to the HCP. PRO-symptom monitoring provides improved accuracy in symptom assessment compared with HCP-reported outcomes.10 Recent randomised trials have demonstrated that PRO-symptom monitoring does not only improve symptom management, but also significantly improves HRQoL and overall survival (OS).11–13 Basch et al conducted a large trial (n=766) assessing the effect of PRO-symptom monitoring in patients treated with chemotherapy for advanced solid tumours on HRQoL and OS.11,14 The results showed that weekly PRO-symptom monitoring significantly improved HRQoL compared with usual care. When comparing HRQoL at 6 months, patients in the PRO-symptom monitoring group had a 16% improved HRQoL score from baseline compared with those in the standard care group. Denis et al also reported a positive effect of PRO symptom monitoring on HRQoL in a randomised study of 121 patients with lung cancer treated with systemic therapy. Six months post baseline, 81% of the patients in the PRO-symptom monitoring group had a significantly improved or stable HRQoL score versus 59% of patients in the control group. Furthermore, disease recurrence was detected earlier, and patients in the PRO-symptom monitoring group had a better performance status compared with patients receiving usual care.15 Both of these trials found a significantly improved OS in the PRO-symptom monitoring group, with a survival benefit ranging from 5 to 7 months.14 PRO-symptom monitoring as well demonstrated positive results in other fields of oncology and outside the field of oncology.16–18 The potential underlying mechanisms for these positive results include earlier and therefore more effective response to emerging symptoms by starting supportive treatment with comedication, more timely dose modifications, improved detection of cancer recurrence and early referrals.19 20

However, these studies also have some limitations. The promising effects of PRO-symptom monitoring on HRQoL and OS have been obtained under clinical trial conditions with 24/7 availability of a clinical trial nurse. Also, these trials used an active approach in which generated alerts required direct action taken by specialised and trained personnel.15 14 Although this approach has the advantage of timely communication and subsequent intervention, its implementation in daily clinical practice may be hampered by high costs and a heavy logistical burden. A more reactive approach, in which patients are instructed to act themselves instead of HCPs, may be easier to implement in routine/daily clinical practice.

To date, few studies have assessed whether PRO-symptom monitoring can be successfully implemented within daily clinical care, and whether a more reactive, patient-based approach would achieve similar results compared with an active approach for all patients with lung cancer.

The SYMptom monitoring with Patient-Reported Outcomes using a web application among patients with Lung cancer in the Netherlands (SYMPRO-Lung) study aims to test the effectiveness of PRO-symptom monitoring within daily clinical practice on HRQoL, by making use of a pragmatic stepped-wedge design. Additionally, we aim to compare the differential effect of an active follow-up approach with a reactive follow-up approach.

METHODS AND ANALYSIS
Study design
The SYMPRO-Lung study protocol is reported following the Standard Protocol Items: recommendations for Interventional Trials (SPIRIT) 2013. The SPIRIT checklist can be found as online supplemental appendix 1.21 22

The SYMPRO study uses a stepped wedge cluster design. This is a pragmatic design enabling insights in both the effect of the intervention, the implementation fidelity and the barriers and facilitators for implementation within daily clinical care. This design is characterised by the fact that all participating centres are randomised to one of several different sequences which dictate the time at which the centre will switch from the control period to the intervention period. The main advantage of this study design is the fact that all centres ultimately receive the intervention condition. This guarantee of receiving the intervention allows for an evaluation within the context of a real-world setting in all participating sites. The design is typically used to evaluate how interventions work in real-world settings.23

To accurately reflect the general lung cancer population, two academic and 11 non-academic centres in the Netherlands are participating in this multicentre study. The centres are clustered as academic/non-academic, and referring
hospitals are clustered as well. Thereafter, the clusters are randomised for an active or reactive intervention approach. Each participating centre starts with including patients in the usual care control condition. During a total inclusion period of 16 months, the centres will randomly switch from the control to intervention condition (figures 1 and 2). Patient recruitment and data collection started in October 2019 and will end in September 2022.

**Eligibility criteria**

Patients are eligible to participate in the study when the following criteria are met:

- Cytologically/histologically proven or radiological suspect small or patients non-small cell with lung cancer;
- Starting treatment (combination) with radiotherapy, surgery, chemotherapy, immunotherapy, targeted therapy;
- 18 years and older;
- Eastern Cooperative Oncology Group (ECOG) Performance Status classification of 0, 1 or 2;
- Internet access.

Patients are ineligible if they meet any of the following criteria:

- Already participating in a treatment study that includes structured symptom reporting;
- A life expectancy of less than 15 weeks at time of inclusion in the study;
- Either treatment or follow-up of a patient takes place in a centre that does not participate in the study.

**Recruitment**

Potentially eligible patients are identified by the HCP involved at the start of treatment. The HCP informs the patient about the study before starting treatment.
and provides written patient information including an informed consent form and a prestamped return envelope. By request, a patient can be contacted by one of the researchers to address additional questions. In this case, the patient signs a separate form and is contacted by telephone. On return of the informed consent, the patient receives an email with log-in information on using the web application. To provide guidance in starting with the study, every patient is contacted by the research team after returning the informed consent form, including patients in the control group.

**Control group**

Patients in the control group receive care as usual. Additionally, they will electronically complete the standard study questionnaires on HRQOL, patient satisfaction and medication adherence (table 1).

**Intervention**

**Weekly PRO-symptom monitoring**

Patients in the intervention groups (both the active and reactive approach) are asked to weekly report their symptoms and, if applicable, their oral anticancer agents (OACAs) use via the web application. Patients have access to the web application for 1 year after inclusion in the study and can use it on either their smartphone, laptop, computer or tablet. Patients are encouraged to use the web application minimally once weekly and maximally once daily. Adherence is encouraged by reminders through a push notification or email. The web application is used in addition to the standard care provided by each participating centre. This study uses the web application developed within the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship Registry. The web application is classified as an open-source application, meaning that the code is available for modifications and improvements. It supports a user-friendly interface that can be accessed from any device with internet access. The system is compliant with current data protection regulations and optimised for users with disabilities.

**Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)**

The web application contains a subset of nine items of the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). The PRO-CTCAE was developed specifically for patient reporting of symptomatic side effects in oncology. The PRO-CTCAE was comprehensively evaluated in English-speaking patients and its translation into Dutch has recently been linguistically validated. The subset of the PRO-CTCAE items for patients with lung cancer used in this study was created by a mixed method study based on the European Organization for Research and Treatment of Cancer (EORTC) phase 1 procedure for designing questionnaires. This procedure includes a literature review, patient interviews (n=25) and interviews with HCPs (n=22). Based on these three sources a final round was organised in which experts selected the most relevant items for this patient population. It resulted in the following items: decreased appetite, nausea, constipation, dyspnoea, cough, general pain, fatigue and sad or unhappy feelings. Each item includes 1–3 questions with a five-item response scale assessing frequency, severity and/or interference of the symptom. In order to limit data collection for this study, the web application uses computerised adaptive testing; that is, in case the patient reports that (s)he has not experienced a given symptom, the follow-up questions are not posed. The five-item response scale of the PRO-CTCAE questions is converted to a 0–4 score. A scoring algorithm is used to assess the clinical toxicity grade (0–3) of the reported symptoms.

Other symptoms

In addition to the selected PRO-CTCAE subset, three clinically relevant items were added on recommendation of Dutch HCPs: weight (in kilograms), fever (body temperature above 38.5°C), diarrhoea and haemoptysis. The SYMPRO-Lung study uses formative evaluation as part of the implementation character of the study. This means that feedback to the study team is being used during the study to improve the implementation and the willingness for the users to adopt this new approach. The SYMPRO study team has decided to add the item ‘diarrhoea’ based on expert opinions during the startup phase of the study. During immunotherapy, diarrhoea is considered a required symptom that HCPs want to monitor. Therefore, it was decided to add this item to the core subset after 3 months following study initiation.

Additionally, open fields are available where patients can report the presence and severity of any other symptom in the same manner as the PRO-CTCAE items. Lastly, there is an open field where patients can add additional comments. For safety reasons, patients are instructed to call the hospital immediately in case of an emergency (the usual instructions) and also to contact the HCP when in doubt about any of their symptoms.

**Alerts and reports**

An alert indicating the need for intervention is triggered when the predefined conditions are met (table 2). The weekly PROs are visualised in a report including graphs of the course of symptoms over time. This report was developed with the input of web designers, and was pilot tested in both patients (n=6) and HCPs (n=4) using the think-aloud method. Both patients and HCPs can download the report. The HCP report consists of three consecutive tabs with successive degree of detail; (1) overview of the symptoms that triggered an alert, (2) the sum score of all queried symptoms over time and (3) the response to each symptom item over time. For the feasibility, a single question is activated above the reports of the HCP to indicate
| Variable | Measure | Details | Assessment |
|----------|---------|---------|------------|
| Sociodemographic data | Patient report | | T0 |
| Primary outcome | | | |
| Health-related quality of life | | | |
| Quality of life for patients with cancer | EORTC QLQ C30 | 30 items, 4 point scale | T0, T1, T2, T3 |
| | | Score range: 0–100 (sum score) | |
| | | Time frame: 1 week | |
| | | The summary score will be calculated as the mean of the combined 13 QLQ-C30 scale scores (excluding financial impact and a two-item global quality of life scale). | |
| | | All included scale scores will be reversed so that higher scores indicate improved outcomes | |
| Quality of life for lung cancer | EORTC QLQ LC-13 | 13 items, 4 point scale | T0, T1, T2, T3 |
| | | Score range: | |
| | | Time frame: 1 week | |
| Secondary outcomes | | | |
| Progression free survival and overall survival | | | |
| PFS and OS | Clinical data HCP/NKR | Stable disease, recurrence or death. | T1, T2, T3 |
| | | PFS and OS are defined from start of treatment until recurrence or date of death. | |
| Medication adherence (only measured in patients using OACAs) | | | |
| Frequency of non-adherent behaviour | MARS-5 | Medication Adherence Report Scale (MARS-5) | T1, T2 |
| | Frequency of non-adherent behaviour | 5 items, 5 point scale | |
| | | Score range: 5–25 | |
| | | A score of >25 points will be considered therapy adherent. | |
| | | Time frame: current behaviour | |
| Patients’ beliefs about OACA | BMQ-specific | Beliefs about Medicines Questionnaire specific | T2 |
| | | 10 items, 5 point scale | |
| | | Subscale: necessity and concern | |
| | | Score range per subscale: 5–25 | |
| | | Time frame: current | |
| HCPs perception about medication adherence and activities aimed at the improvement of medication adherence | HCP | Perceptions of adherence management questions | T0, T3 |
| | | 5 items, 5 point Likert-scale | |
| | | Score range: 0–5 | |
| | | Time frame: current | |
| | | The adapted, care usually provided in supporting adherence to treatment with OACA- list | |
| | | 18 items, 2 point scale | |
| | | Max score: 18 | |
| | | Time frame: past 6 months | |
| Cost-effectiveness | | | |
| Quality of life in general (description of one's health status) for the cost-effectiveness analysis | EQ-5D-5L | 5 items, 5 levels | T0, T1, T2, T3 |
| | Description of one's health status | Time frame: today | |
| | | For the cost-effectiveness analysis we will use the EQ-5D-5L to obtain utilities | |
| Implementation fidelity | | | |
| Evaluation of the app | PRO | | T1, T3 |
| | | 13 items | |
| | | Open and closed ended questions (eg, likert scales) to assess how the app is evaluated. | |
| | | Higher scores indicate better evaluation | |
| | | Time frame: current attitude | |
| | | Based on the MIDI[6] | |
| | HCP | | T1, T3 |
| | | 8 items | |
| | | Open and closed ended questions (eg, likert scales) to assess how the app is evaluated. | |
| | | Higher scores indicate better evaluation | |
| | | Time frame: current attitude | |

Continued
the type of action taken as a result of the alert (eg, no action needed, extra (phone) consult, referral to General Practitioner (GP), psychological help, emergency department or other action).

The active versus the reactive intervention approach

The active and reactive approach differs in the way the alerts are handled. In the active approach, the HCP receives an alert via a (secured) email and is instructed to contact the patient within 24 hours during office hours on weekdays, to perform triage, give tailored advice and to intervene when needed (eg, a visit to the hospital, comedication, etc). In the reactive approach, the patient receives an alert via a pop-up notification and an email with the advice to contact the hospital within 24 hours on weekdays.

If a patient does not complete the weekly symptom monitoring subset for four consecutive weeks, a researcher contacts the patient by email or telephone to check whether (s)he is experiencing any problems with using the web application.

Medication adherence

For patients treated with OACAs, the web application monitors medication adherence by asking whether the patient has taken his/her medication in the past week (yes/no). A ‘no’ is considered non-adherent and in that case, patients are asked to clarify the reason for

| Variable                      | Measure | Details                                                                 | Assessment |
|-------------------------------|---------|-------------------------------------------------------------------------|------------|
| Patient satisfaction with care | PRO     | ▶ 3 items, 5 point scale                                                | T1, T3     |
|                               |         | ▶ Score range: 3–15                                                     |            |
|                               |         | ▶ Higher scores indicate higher satisfaction                           |            |
|                               |         | ▶ Time frame: current attitude                                          |            |
| Treatment adjustments         | Clinical data | ▶ 3 questions if the treatment has been altered do to the reported symptoms | T1         |
|                               | HCP     | ▶ 3 questions if patients have chosen to not contact their HCP after an alert (only for the reactive group) |           |
| Implementation fidelity       | Semistructured interviews | ▶ Interviews with patients and HCPs to evaluate the implementation and use of the app, topic list based on the MIDI | T1, T3   |

BMQ, Beliefs about Medicine Questionnaire; EORTC QLQ C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30 items; EORTC QLQ LC-13, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 items; EQ-5D-5L, European Quality of Life Scale-5 Dimensions with 5 Levels; HCP, healthcare provider; MIDI, Measurement Instrument for Determinants of Innovations; NKR, Netherlands Cancer Registry; OACAs, oral anticancer agents; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome.

Table 2 Set of predefined rules to trigger an alert

| Symptom                  | Rules for alert                                                                 |
|--------------------------|---------------------------------------------------------------------------------|
| PRO-CTCAE symptoms       |                                                                                 |
| Decreased appetite       | 1. If the symptom reaches grade 3                                                |
|                          | a. The symptom has not reached a grade 3 in the last 2 weeks (<15 days)         |
|                          | b. If the symptom stays a stable grade 3 for 4 consecutive weeks, the fourth week will provide the next alert |
| Cough                    | 2. If the symptom worsens by ≥2 grades                                            |
| Shortness of breath      | a. in 2 weeks                                                                    |
| Fatigue                  | b. if the checklist has not been filled in for 4 consecutive weeks               |
| Constipation             |                                                                                 |
| Nausea                   |                                                                                 |
| Diarrhoea                |                                                                                 |
| Sad or unhappy feelings  |                                                                                 |
| General pain             |                                                                                 |
| Other symptoms           |                                                                                 |
| Fever                    | 3. If ‘yes’ is scored (independent of earlier reports about fever)               |
| Haemoptysis              | 4. If ‘a little’ or ‘a lot’ is scored (independent of earlier reports about haemoptysis) |
| Weight                   | 5. Loss of weight ≥3 kg in 1 or 2 weeks                                           |
|                          | a. If the questionnaire was not filled-in for 4 consecutive weeks a loss of weight of ≥3 kg since the last measurement will also summon an alert |
|                          | b. Patient has scored ‘I did not weight myself’ is seen as rule 5a               |

PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events.
non-adherence (forgotten, instructed by the doctor, decided not to take the medication or other). When a patient is non-adherent, the web application automatically advises the patient to discuss this during their next consultation with the HCP.

**Patient and public involvement**

Patients were involved in the design of the web application. Study participants receive emails every 3 months to update them about the progress of the project.

**Outcomes**

**Primary outcome measure**

The primary outcome is the mean difference between HRQoL at baseline (T0) and 15 weeks (T1), 6 months (T2) and 12 months (T3) post baseline between the intervention and control groups. HRQoL is measured by the EORTC QLQ-C30.31 The Quality of Life Questionnaire Cancer 30 items (QLQ-C30) summary score is calculated as the mean of the combined 13 QLQ-C30 scale scores (excluding financial impact and a two-item global quality of life scale).32 Our main HRQoL endpoints are physical functioning and the QLQ-C30 summary score. We chose the QoL summary score and physical functioning domain because they recently showed to be a more robust measure of HRQoL over the global QOL domain.33 Furthermore, a recent study of Husson et al also showed that both the summary score as well as physical functioning had more prognostic value than the global QoL domain.33

**Secondary outcome measures**

See table 1 for an overview of all outcome measurements and timing secondary outcome measures include:

- 1-year progression-free survival (PFS);
- 1-year OS;
- 1-year recurrence rate;
- Symptom incidence and severity over time (PROCTCAE for the intervention group only and EORTC QLQ lung module-13 for both groups);
- Medication adherence (OACA) (Medication Adherence Report Scale-5) and Believes about Medicine Questionnaire;
- Cost-effectiveness (Euroqol-5 Dimensions with 5 levels (EQ-5D-5L)36 and clinical healthcare costs data);
- Implementation fidelity (intervention group only; quantitative and qualitative patient and HCP reported).

**Timing of measurements**

The standard study questionnaires on HRQoL, medication adherence (if applicable) and patient satisfaction with care are collected in all groups at baseline, 15 weeks, 6 months and 12 months after the start of the treatment via the web application (table 1).

**Sociodemographic and clinical data**

All data were recorded electronically. At baseline, patients are asked to report their demographic characteristics (education, employment status, marital status) and comorbidity. HCPs report treatment characteristics (ECOG Performance Status, histological tumour type, cancer stage according to the Tumour, Nodes, Metastases (TNM) eighth edition and (previous) treatment) at baseline. During the follow-up assessments at 15 weeks, 6 and 12 months, the HCPs are asked to report ECOG Performance Status, current treatment and treatment response (ie, cured, complete or partial response, stable disease, progression, relapse, death and or other).

Other observational data (OS, direct medical costs including, CT scans, hospital admissions and emergency room visits) will be retrieved from the Netherlands Cancer Registry and Dutch Hospital Data.

**Statistical considerations**

**Randomisation**

Randomisation between the active and reactive group is performed upfront using the independent randomisation tool provided by CASTOR Electronic Data Capture (EDC).37 The randomisation follows a stratified randomisation procedure, accounting for (1) an even distribution of the type of centre (academic/non-academic centre) and (2) a similar intervention approach in centres that collaborate when referring patients.

**Sample size calculation**

We based our power calculation on two main assumptions;

1. We want to demonstrate superiority in patient-reported symptom monitoring compared with care as usual with a minimum HRQoL benefit of 0.4 (effect size (ES)).
2. We want to demonstrate non-inferiority between the active and reactive intervention approach, with a maximum HRQoL difference of 0.2 ES between the active and the reactive approach.

Our trial is powered to demonstrate a clinically relevant ES of 0.4 between the intervention and control group (80% power (β), with a one-sided alpha (α) of 5%), compared with the trial of Basch et al.14 To detect an ES of 0.4 (β 0.80, α 0.05) in HRQoL, inclusion of at least 148 control and 148 intervention patients (74 patients in the active and 74 patients in the reactive approach) is required. Since our study entails a stepped wedge cluster design, we need to account for within-centre clustering. Assuming an intra-class correlation coefficient (ICC) of 0.25, the design effect ((1+(6−1)*ICC)) is 1.125 and the necessary sample size for the clustered study is therefore inflated to respectively 167 and 168 patients (84 per study arm).

To demonstrate non-inferiority between the active and reactive approach, we require an ES of less than 0.2 between the two approaches. This necessitates at least 146 patients per intervention arm. This means that a total of 292 patients in the control group and 146 patients per intervention group are needed to be included in the trial.

The stepped wedge design is used to implement the intervention in 13 centres (clusters). Based on the average number of newly diagnosed patients plus the additional number of prevalent patients starting a new
therapy in the participating centres, we expect to enrol an average of 5 patients per centre per 5 weeks (1 patient per week). Therefore, the average length of the steps is 5 weeks. Given this expected step length and the number of participating clusters, the follow-up period is 16.1 months (70 weeks) with 55 control clusters, 28 active intervention clusters and 27 reactive intervention clusters.

For the primary endpoint, the analyses will be stratified for the active and reactive approach. Therefore, the study consists of three groups: control, active approach and reactive approach. If one of the intervention approaches is significantly associated with an improved HRQoL compared with the control group, this intervention will be favoured for broader implementation. When both interventions are significantly better compared with the control group, the decision to favour a certain approach will be based on the estimated difference in HRQoL between both approaches, the costs and practical considerations.

**Analyses**

**Quantitative data**

Baseline characteristics of the patients in the control and intervention groups will be compared using a χ² test for categorical data and an independent samples Student’s t-test for normally distributed variables or a non-parametric Wilcoxon signed-rank test for continuous variables with a skewed distribution (two sides, \( p<0.05 \).

Primary analyses will be performed on an intention-to-treat basis. Mean differences in HRQoL between baseline and post-treatment measurements will be compared using independent samples t-tests (in case of a normal distribution) or a Wilcoxon signed rank-test (in case of a skewed distribution). Missing data on HRQoL will be imputed using multiple imputation. Differences in HRQoL over time between the groups will be compared using linear mixed modelling analyses, accounting for within-centre clustering and potential time effects. The final model will be adjusted for potential confounders known from scientific literature, such as age, sex, educational level, comorbidities and disease characteristics. Statistical significance level is defined as \( p<0.05 \).

Kaplan-Meier curves with log-rank two-sided tests will be used to compare OS and PFS of the intervention versus control group, also stratifying for the active versus reactive intervention group. Cox proportional hazard analyses will be performed to estimate the effect of PRO-symptom monitoring on OS and PFS, adjusting for potential confounding.

The association between baseline characteristics and medication adherence over time will be analysed using generalised estimating equations. An incremental cost-utility ratio (ICUR) will be calculated to measure the cost per gained quality-adjusted life year (QALY). The ICUR will be calculated by dividing the incremental costs by the incremental QALYs using the formula: ICUR = (Costs_intervention – Costs_control)/(QALY_intervention – QALY_control). Total costs will be calculated using a healthcare perspective, including intervention costs and direct medical costs. If available, direct medical costs will be calculated by multiplying resource use by integral cost prices as presented in the Dutch Health Care Insurance Board guidelines on cost studies. The utility scores linked to the various health states of the EQ-5D will be used to calculate QALYs by weighing the length of time spent in a particular health condition by the utility. Missing data on direct medical costs and utilities measured using the EQ-5D will be imputed using multiple imputation. Because follow-up of the study is approximately 1 year, neither costs nor effects will be discounted. The uncertainty surrounding the ICUR will be assessed using bootstrapping with 5000 replications and projected on a cost-utility plane. In addition, cost-utility acceptability curves will be presented and sensitivity analyses will be performed, focusing on uncertainty around the most important cost parameters.

**Qualitative data**

To evaluate the app and assess the implementation fidelity, interviews will be conducted with both patients and HCPs. Patients and HCPs, from each centre who agreed to be contacted for an interview will be approached after 15 weeks and 1 year until data saturation is reached. These interviews are guided by a topic list based on the framework for implementation fidelity and by the results of the evaluation of the web application questionnaire at 15 weeks. The interviews will be audiotaped and transcribed. The transcripts will be evaluated by use of the framework approach for (inductive) thematic analysis. Two independent researchers will openly code the data. In this analysis we will focus on the topics in our topic list. Differences are discussed until consensus is achieved. Qualitative data are analysed using Atlas.ti software V.7 (GmbH, Berlin).

Quotes from the qualitative interviews will be used to illustrate the quantitative data.

**ETHICS AND DISSEMINATION**

The study protocol (24 March 2021, V.10) has been approved by the Institutional Review Board and Medical Ethical Committee (METC) of the Amsterdam UMC, location VUmc (under number NL 68440.029.18), as well as by the review boards of all participating centres. Amendments are changes made to the research methods after approval by the accredited METC. All amendments are notified to the METC, principal investigators from each participating institution, and to the trial register (https://www.trialregister.nl/).

This study will be conducted according to the principles of Good Clinical Practice and General Data Protection Regulation.

A written informed consent is obtained from all participants on participation (see online supplemental appendix 2).
DISCUSSION

This study is hypothesised to demonstrate the beneficial effects of electronic PRO-symptom monitoring in daily clinical care on the HRQoL of patients with lung cancer. In addition, due to the pragmatic stepped wedge design and inclusion of a reactive approach, it gives more insights in the most feasible and effective approach for use of PRO-monitoring within daily clinical care. Moreover, barriers and facilitators of the implementation process are investigated.

The study has several core strengths. First, the use of a more pragmatic stepped wedge cluster design allows all participating centres to implement the intervention and the centres provide data in both the control and intervention period, and accordingly act as their own control.\(^4\) Second, the use of items from the Food and Drug Administration (FDA)-approved PRO-CTCAE is a perfect fit to the CTCAE, which is widely used in daily clinical oncology care to report symptomatic adverse events. Third, this multicentre study includes patients with lung cancer of all stages and treatment options from 13 centres, which provides a heterogeneous group comparable to real-world clinical practice. Last, the evaluation of the implementation fidelity of the active intervention and newly designed reactive intervention approach, and the cost-effectiveness evaluation, will create insight into the barriers and facilitators of efficient implementation of PRO-toxicity monitoring within daily clinical care. Therefore, this study will provide considerable knowledge on whether PRO-symptom monitoring is not only feasible, but also cost-effective in a real-world clinical setting. We expect to be able to inform future policy making about the most efficient ways to use PRO-symptom monitoring alongside clinical care in patients with (lung) cancer. Although developed for patients with lung cancer, this project will serve as a template for other diseases and situations.

There are several limitations of the study that need to be addressed. First, most participating centres do not allow to fully integrate the web application within the electronic health record, making it more difficult to use by HCPs during consultations. This might decrease the uptake of the intervention; however, this is a first step towards implementing PRO-symptom monitoring in standard lung cancer care in the Netherlands. Second, the web application is not a downloadable mobile application, potentially hindering user experience and ease of use. However, the web application is designed specifically for this target group and was tested by patients with lung cancer prior to the intervention. Therefore, we expect this to have a small effect on user experience and ease of use. Lastly, since direct feedback is a fundamental part of the intervention, paper surveys are not offered as an alternative. Therefore internet access can be a barrier for participation by patients of older age. We estimate this problem to be minimal since internet was present in 98% of the Dutch households in 2017.\(^4\) In 2016, 84% of the Dutch population aged 65–75 years, and 51% of age 75 years and older made use of internet.\(^4\)

In conclusion, the SYMPRO-trial aims to evaluate the effect of PRO-symptom monitoring during and after lung cancer treatment on HRQoL. It is anticipated that such an approach will have direct benefits on a patient’s HRQoL and potentially also on PFS and OS. If successful, this study may provide hands-on guidelines on how to efficiently implement PRO-symptom monitoring within daily clinical care, and thereby enhance clinical outcomes of patients with lung cancer by improved symptom management.

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