Patient Reported Outcomes used for Weekly Internet-based DEtection of progressive disease in lung cancer;

a randomized controlled trial

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Study title	**ProWide** Patient Reported Outcomes used for Weekly Internet-based DEtection of progressive disease in lung cancer; a randomized controlled trial
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Institutions	Oncology departments in Denmark
Population	Lung cancer patients who have finished induction treatment for lung cancer. Eligible are patients with stage III disease treated with palliative intent, and stage IV lung cancer, regardless of treatment intent. Maintenance treatment is allowed.
Background	According to the national Danish follow-up program for lung cancer, patients are followed with clinical controls and a contrast enhanced CT-scan of the thorax and upper abdomen, every 3 months the first 2-3 years, then every 6 months until 5 years[1]. In a palliative follow-up, CT scans are performed every 3 months after ended induction treatment. In case of continuous maintenance treatment, CT scans

	are performed at prespecified intervals, usually every 8th, 9th or 12th week depending on treatment type. Recently, a study by Denis et al.[2] suggested, that weekly patient-reported (PRO) symptoms monitoring during maintenance therapy or follow-up of lung cancer patients, could help to early identify patients with relapse or progression of disease. In their randomized phase III trial, conducted in France, they found a median survival of 19.0 months (12.5- non-calculable) for the PRO intervention group vs 12.0 months (8.6-16.4) in the control arm (p=.001). HR=0.325(0.157-0.673). One-year survival was 74.9% (56.6-86.4) vs 48.5% (31.9-63.2) (p=.05) with a benefit of 26 %. A significant benefit in both quality of life and survival has also been shown in another phase III study by Basch et al that tested weekly PRO monitoring of patients undergoing treatment for metastatic cancer, of whom approximately 25% had lung cancer[3,4]. The median overall survival was 31.2 months (24.5-39.6) in the PRO group and 26.0 months (22.0-30.9) in the standard of care group, HR=0.83 (0.70-0.99). One-year survival was 75.1% (70.7-79.0) vs 68.6% (63.2-73.6) (p=.05), showing a survival benefit of 6.5 %. Inspired by these encouraging results, we propose to test, in a Danish setting, whether adding weekly monitoring of patient-reported symptoms, can improve survival by early detection of progressive disease in lung cancer patients. The weekly monitoring will be added to the standard CT evaluation scans with clinical control and contrast-enhanced CT of thorax and abdomen.
Endpoints	<u>Primary endpoint</u>: • Overall Survival <u>Secondary endpoints</u>: • Performance status at the time of progressive disease • Progression-free survival • Quality of life • Cost-effectiveness and hospital resource use and costs • Type of treatment at the time of progressive disease

Evaluation criteria	All patients will have a baseline CT-scan of the thorax and upper abdomen performed prior to treatment and an evaluation CT scan at the time of enrolment. CT scan will be repeated for assessing signs of relapse or progression due to standard follow-up/response evaluation procedures. Health-Related Quality of life (HRQoL) will be measured using EORTC QOL-C30[5]/ LC13[6], EQ-5D-5L[7] and HADS[8] every 2 months during the study period.
Methodology	Multicentre phase III trial
Sample size	A total of 492 patients will be included in the study with 246 patients in each group. The power calculation is based on a presumed improvement in 1-year survival on 13.2 % corresponding to half of the effect in the study by Denis et al. and a compliance rate at 90%.
Intervention	*In the experimental arm*, patients will fill in a web-based PRO questionnaire every week. If their weekly reported symptoms exceed a predefined threshold of severity, this results in a notification sent to the hospital and a nurse will contact the patient for verification of symptoms. If progression of disease is suspected, a CT scan will be made. Otherwise, the nurse will schedule a visit at the clinic for physical examination and evaluation by a clinician. If progressive disease is not suspected, supportive care will be adjusted, and the patient will continue follow up/CT evaluations according to the usual schedule.
Inclusion criteria	1. Patients with lung cancer (NSCLC or SCLC) with stage III treated with palliative intention, or stage IV, regardless of treatment intention. 2. 1st line induction treatment* started/completed prior to the current evaluating scan 3. Non-progressive** disease at first CT scan evaluating 1st line induction treatment 4. Diagnosis proved by cytology or histology 5. Age ≥ 18 years 6. Performance status (PS) ≤ 2 7. First evaluation CT scan performed within four weeks from enrolment 8. The patient has given his/her written informed consent before any specific procedure from protocol * *Induction treatment includes:* • *Standard doublet chemotherapy*

	• *Immunotherapy* • *Targeted therapy* • *Palliative radiotherapy* • *Local treatment of oligometastatic disease, including surgery and stereotactic radiotherapy* • *Any combination of the above-mentioned treatment modalities. Patients are eligible regardless of whether they at the time of inclusion continue maintenance treatment or not* ** *Patients with stable disease or better response, defined by the treating clinician, are eligible. Patients receiving immunotherapy are eligible if pseudoprogression is suspected based on clinical response and treatment is continued. Patients receiving 1^{t} line "treatment beyond progression" are eligible*
Exclusion criteria	1. No internet access 2. No E-boks access 3. No mobile phone 4. Persons deprived of liberty or under guardianship or curators 5. Dementia, mental alteration or psychiatric disease that can compromise informed consent from the patient and / or adherence to the protocol and the monitoring of the trial 6. Pregnant or breastfeeding women 7. Patient participating in another interventional study during the surveillance period. This is only relevant for studies that might interfere with the intervention. Participation in protocols related only to treatment will not preclude participation in the present study. Cases of doubt will be settled by the protocol committee.
Time of Enrolment	Patient enrolment is always at the time when the patients are informed of the results of their first evaluation scan after treatment induction.
Statistical analysis	The study will be conducted as a randomized phase III study. First analyses will be conducted after 2 years of inclusion. No predefined criteria for termination of the trial has been determined.

Introduction

Lung cancer is a serious disease with a dismal prognosis. The 5-year survival rate of Danish lung cancer patients diagnosed with loco-regional disease ranges from 43% for patients with stage I lung cancer, through 27% for stage II to 21% for patients with stage III disease. Patients with stage IIIb-IV receiving palliative treatment have an even worse outcome, with a 5-year survival of only 4 and 2% estimated in 2015. Of the more than 4500 patients who were diagnosed with lung cancer in Denmark in 2015, 55.6% were in stage IIIb-IV[9].

According to the national Danish follow-up program for lung cancer, patients are followed with clinical controls and a contrast enhanced CT-scan of the thorax and upper abdomen, every 3 months the first 2-3 years, then every 6 months until 5 years. The purpose of follow-up is to find relapse as soon as possible to increase the probability of curative treatment of the relapse, or if curative treatment is not possible, optimal palliative treatment[1]. In case of treatment with palliative intent, patients are usually scanned every 3 months after they have finished treatment to determine the present status of the disease. However, during palliative treatment, patients are often scanned more frequently to evaluate the effect of the ongoing treatment.

There have been conducted numerous studies of symptom monitoring by patient-reported outcomes (PRO), reviewed recently[10]. PRO's are any measurements provided directly from the patients, which give information on aspects of their health status, often relevant to their quality of life. These studies of PRO use for symptom monitoring, have shown improvement in patient-caregiver communication, but have not been able to show improvement in clinical outcome[10]. Now, evidence is emerging, showing that a proactive approach of symptom monitoring by use of PRO data, might lead to a better quality of life and improved survival among patients with lung cancer[2–4].

Recently, a study by Denis et al.[2] suggested, that including weekly patient-reported (PRO) symptom monitoring in the follow-up of lung cancer patients in all stages, could help identify earlier patients with progression or relapse of disease. In their randomized phase III trial, conducted in France, they found a survival benefit of 26% for the PRO intervention group, with a hazard ratio of 0,325 (0,157-0,673). In the study, clinicians were alerted when patients had reported detrimental changes in PRO symptoms, leading to earlier clinical evaluation and CT-scan, if indicated. Earlier detection of progression or relapse allowed for an earlier start of secondary treatment and patients were found in better performance status, leading to improved overall survival.

A significant benefit in quality of life and a survival benefit has also been shown in a study of patients undergoing treatment for cancer, including lung cancer[3,4]. The patients were randomized between the standard of care vs. regular PRO symptom reporting. When detrimental changes were reported by the patients, they were contacted by the healthcare team for symptom management. The median overall survival was 31,2 months (24,5-39,6) in the PRO group and 26,0 months (22,0-30,9) in the standard of care group, HR=0,83 (0,70-0,99).

Aim

Inspired by the impressing survival benefit found by Denis et. al.[2], we propose to test, in a Danish setting, whether adding weekly monitoring of patient-reported symptoms, can improve early detection of progressive disease and improve survival for lung cancer patients. The weekly monitoring will be added to the standard evaluation program with clinical control and contrast-enhanced CT of the thorax and upper abdomen.

We will conduct a randomized controlled trial (RCT), comparing the two arms with respect to overall survival, progression-free survival, performance status at relapse, quality of life during follow-up/ and type of treatment initiated at the time of progressive disease. Finally, the use of healthcare resources will be calculated and compared at the end of the study.

Methods

The study is divided into two consecutive phases.

1. **Defining the PRO application** for symptom monitoring is inspired by a literature review, the Danish national lung cancer clinical guidelines[11], analysis of historical PRO data and study group consensus. The questions have been adapted to a Danish setting with feasibility testing prior to trial initiation. The process includes the construction of an application for mobile phones, tablets and laptops with an algorithm for sending notifications to clinicians.
2. Testing the PRO-tool in a **randomized multicentre trial**. See below for details.

Defining the PRO application

Denis et al have validated and published a list of 12 core symptoms in lung cancer and developed an algorithm for a web application. Certain combinations of symptoms and symptom-scores will send a notification to the hospital. Denis et al. found that the combinations and severity of the above symptoms had a high sensitivity and specificity for detecting relapse[12–14].
The details of the algorithm have however not been fully published, which is why the model could not be fully adapted to this study.

We did a critical review of the symptoms published by Denis et al[2] and compared them to the symptoms described in the official recommendations of the Danish national lung cancer clinical guidelines[11]. Based on consensus in the study group we decided to exclude depression, as otherwise proposed by Denis et al[2], from the list of relevant symptoms. Already validated single items from both cancer and lung cancer-specific EORTC QLQ-C30/LC13 questionnaires were used to describe the relevant symptoms for the final questionnaire. The EORTC Global Quality of Life score has in several studies[15–18] proven to be an important prognostic factor in lung cancer. By another consensus decision in the study group based on the use of patient-reported outcomes in the clinic, we chose to incorporate self-rated overall health as a single item in the questionnaire. Supplementary symptoms that were not described in the EORTC questionnaires were formulated as questions by members of the study group

and added to the questionnaire. We then ended up with 12 core symptoms and a comment field for the following feasibility study.

Individual severity thresholds for each symptom were defined for the algorithm that triggers the notifications to the department.

A feasibility study was then conducted at the department of oncology in Herning (details to be published). Initial interviews that were conducted with 7 patients for face validity and usability revealed issues with the understanding of the supplementary questions, the weekly timeframe and the login procedure. The questions were then adjusted prior to the feasibility study where 20 patients with stage IV lung cancer tested the system with weekly questionnaires for 3 weeks. At the end of the study, patients gave a written evaluation and interviews with two nurses involved in the system-process were made. Additional changes based on the results were then made to the questionnaire and the threshold mechanism.

We did, however, choose to include both items from the EORTC Global Quality of Life score (self-rated overall health and quality of life) in the final questionnaire. Though only self-rated overall health was chosen to send notifications in case of worsening.

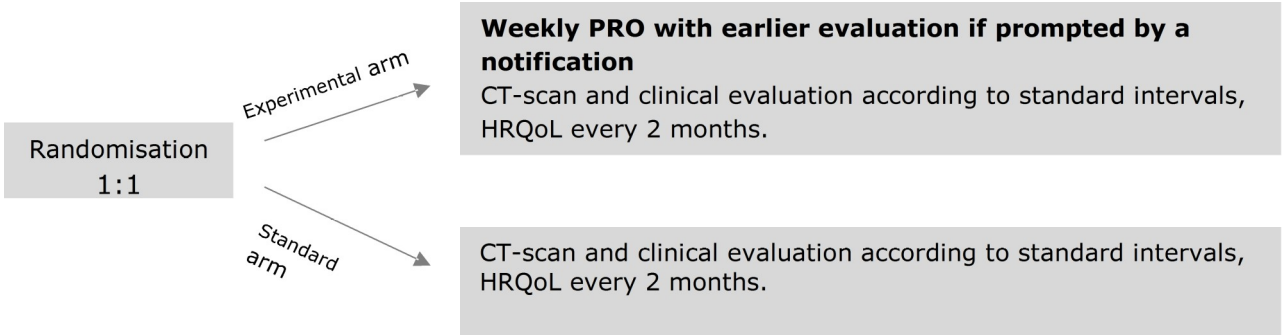
The definitive version of the questionnaire in Danish and the threshold algorithm for the RCT study can be found in the Appendix.

The protocol committee holds the right to adjust the threshold algorithm during the study period if deemed necessary.

The randomized clinical trial of adding weekly PRO

Design and setting

The main part of the study consists of a multicenter randomized trial in order to assess the effects of the weekly PRO intervention. The design follows the overall setup presented in the publication by Denis et al, however, adapted to a Danish setting, as described above, including the Danish guidelines for evaluating CT scan in both arms[2]. The randomization and baseline data collection will be made in the IT system (AmbuFlex) by the oncologist at the time of enrollment.



Implementation of the intervention
The intervention is illustrated in Figure 1. *In the experimental arm*, patients will be asked to fill in the PRO questionnaire every week via an internet connection, and they will also be asked to fill in HRQoL questionnaires at any outpatient attendance. However, if their weekly reported symptoms result in a notification, the clinician will contact the patient, and after verification of symptoms, schedule a visit at the clinic for physical examination and evaluation. If relapse or progression of disease is suspected an extra CT scan will be made, otherwise the patient will continue response evaluation/follow-up according to the usual schedule. The clinicians are allowed to reschedule the CT scan based on the phone call alone.

Both the HRQoL measurements and the web application will be administered through a web page that is designed for use on mobile phones, tablets and laptops(AmbuFlex[19]). The data will automatically be transferred in real time to a computer server, where notifications are generated and sent to clinicians if the prespecified symptom thresholds are exceeded. Data is automatically scored and will be available in easily interpretable visual reports in the AmbuFlex system.

If participants do not fill in the web-based questionnaire at pre-specified times, a reminder will be sent using a text message to their mobile phone and a message will appear for the clinical staff at the daily notification list.

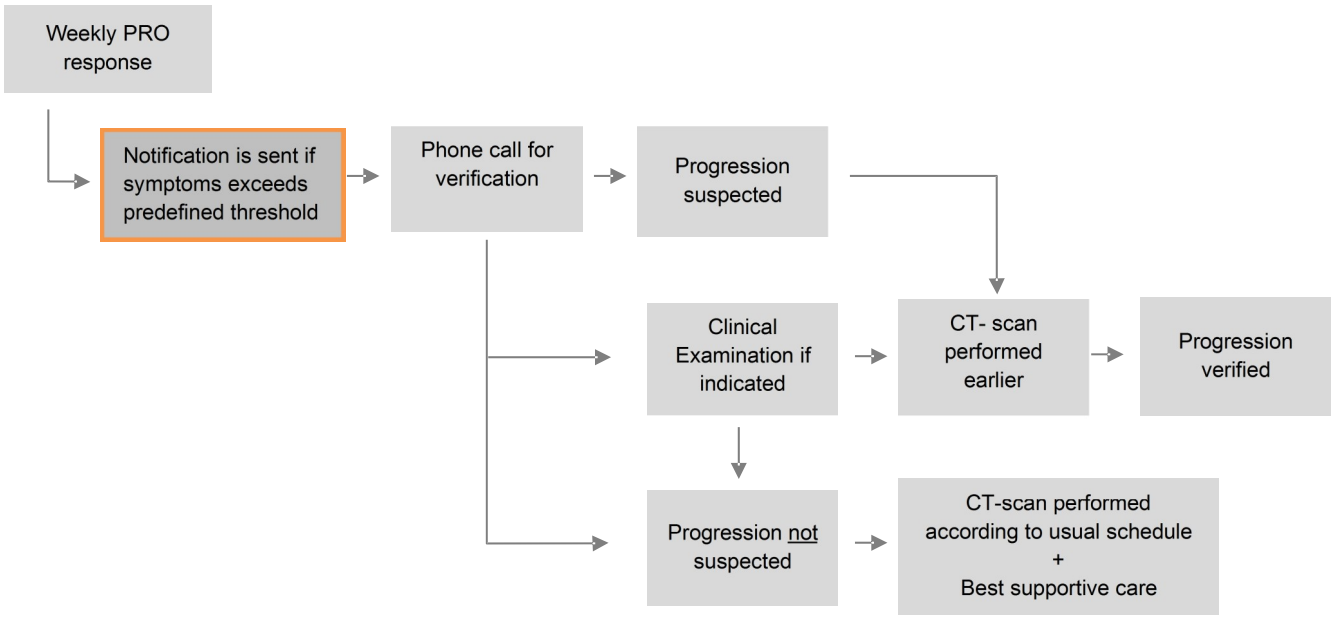


Figure 1. Flow-chart showing the PRO-intervention in the randomized clinical trial.

To examine the participants quality of life during the study period and at the time of relapse/progressive disease, patients in both arms will be asked to fill in the health-related quality of life (HRQoL) questionnaire every 2 months. The HRQoL questionnaires used are the EORTC QoL-30/LC13 and HADS questionnaire. EORTC-QoL-30 is a questionnaire containing 30 questions with five functional scales (physical function, role function, cognitive function, emotional function and social

function), three symptom scales (tiredness, nausea/vomiting, pain), a global health question and questions regarding frequent symptoms among cancer patients, such as dyspnea, sleep disturbances, loss of appetite, obstipation and diarrhea. The EORTC-QoL-30 also contains a question about financial difficulties. All scales will be linearly transferred to a score between 0-100. For functional scales and global health question, a score of 100 represents the best possible function, while a score of 100 on a symptom scale represents the worst possible symptom. A change in the score by 10 or more is considered a clinically significant change[20]. LC13 is a supplementary questionnaire to the QLQ-C30 and includes 13 lung cancer-specific questions.

The HADS (The hospital anxiety and depression scale) is a fourteen-item scale. Seven items relate to depression and seven to anxiety. The tool has been developed for detection of anxiety and depression in patients with physical health problems. All items are scored from 0-3 with a possible total score between 0 and 21 for anxiety and depression respectably[8].
Bjelland et al[21] identified, in a systematic review, a cut-off point of 8/21 for anxiety or depression. For anxiety, the specificity was 0.78 and the sensitivity 0.9. For depression a specificity of 0.79 and a sensitivity of 0.83 was determined.

The generic EQ-5D-5L[7] questionnaire will be used to asses quality-adjusted life years (QALY) for a health economic evaluation (*see statistics for details*).

Study design
The study is a multicenter randomised phase III study. After signing informed consent, the patient will be randomized in 1:1 fashion, to the *standard of care arm*, with planned CT-scans according to a standard schedule and measurement of quality of life every 2 months, or to the *experimental arm*, adding weekly PRO monitoring and quality of life measurements to standard of care.

Study population
Eligible are patients with stage III lung cancer where the treatment intention is palliative and stage IV lung cancer regardless of treatment intent, who have received first-line induction treatment and have stable disease or better response after induction therapy. Maintenance treatment of any kind is allowed during the study period. Patients will be stratified by centre, stage and by main histology; small-cell lung cancer vs. non-small cell lung cancer.

Inclusion Criteria

1. Patients with lung cancer (NSCLC or SCLC) with stage III treated with palliative intention, or stage IV, regardless of treatment intention.
2. 1st line induction treatment* started/completed prior to the current evaluating scan
3. Non-progressive** disease at first CT scan evaluating 1st line induction treatment

4. Diagnosis proved by cytology or histology
5. Age ≥ 18 years
6. Performance status (PS) ≤ 2
7. First evaluation CT scan performed within four weeks from enrolment
8. The patient has given his/her written informed consent before any specific procedure from protocol

** Induction treatment includes:*

- *Standard doublet chemotherapy*
- *Immunotherapy*
- *Targeted therapy*
- *Palliative radiotherapy*
- *Local treatment of oligometastatic disease, including surgery and stereotactic radiotherapy*
- *Any combination of the above-mentioned treatment modalities. Patients are eligible regardless of whether they at the time of inclusion continue maintenance treatment or not*

*** Patients with stable disease or better response, defined by the treating clinician, are eligible. Patients receiving immunotherapy are eligible if pseudoprogression is suspected based on clinical response and treatment is continued. Patients receiving 1st line "treatment beyond progression" are eligible*

Exclusion Criteria

1. No internet access
2. No E-boks access
3. No mobile phone
4. Persons deprived of liberty or under guardianship or curators
5. Dementia, mental alteration or psychiatric disease that can compromise informed consent from the patient and/or adherence to the protocol and the monitoring of the trial
6. Pregnant or breastfeeding women
7. Patient participating in another interventional study during the surveillance period. This is only relevant for studies that might interfere with the intervention. Participation in protocols related only to treatment will not preclude participation in the present study. Cases of doubt will be settled by the protocol committee.

Time of enrolment

Patient enrolment is always when the patients are informed of the results of their first evaluation scan after treatment induction. Patients with stable disease or better response, as described, are eligible.

- In case of treatment end (planned or discontinued) at the time of enrolment, the patient will be included prior to standard follow-up

- In case of ongoing treatment, the patient will be included and continue treatment as scheduled with standard CT based response evaluations
- In the case of local treatment of oligometastatic disease or palliative radiotherapy, the patient will be included if there is no sign of relapse/progression at first evaluation CT scan after treatment and continue follow-up

Inclusion procedure

The patient will have to sign an informed consent at enrolment. The National Committee on Health Research Ethics has been requested and the study does not require approval. Time for consideration before the submission of informed consent is therefore not required and the patient can be enrolled immediately at attendance. Information regarding the study and login procedures for the weekly PRO questionnaire will be provided.

Evaluation criteria

All baseline CT-scans will be evaluated at each site by usual practice. Health-related quality of life (HRQoL) during the observation period will be measured using EORTC QOL-C30/LC13 and HADS. The HRQoL questionnaires including the EQ-5D-5L will be filled in at baseline at randomisation and at every 2 months. The questionnaires will be electronically answered via the AmbuFlex system.

Study plan

The study plan for the randomized clinical trial is outlined in Table I. In the standard arm, all patients will be followed with CT-scan with the standard of care intervals and asked to fill in the web-based HRQoL questionnaires every 2 months. In the experimental arm, patients will additionally be asked to fill in the web-based PRO questionnaire on a weekly basis. If a detrimental change (See appendix) is noted in the patient's weekly responses to the PRO questionnaire, the patient will be contacted by a study nurse for verification of symptoms. If the symptoms are verified, the patient will be treated by the clinical staff according to standard procedures. If progressive disease is suspected, the patient will have the CT scan rescheduled to as soon as possible. All CT-scans will be described and evaluated by standard practice. It will entirely be up to the treating physician to interpret the results of the CT scans and to define the time of progression as well as the following treatment.

Evaluation at screening, prior to inclusion

The objective of these evaluations is to identify patients, who meet the specified Inclusion- and exclusion criteria. The patient will be informed verbally and in writing. Only patients who have signed informed consent will be included. Following examination and data will be collected prior to inclusion:

- Histological or cytological verification of lung cancer
- Disease stage at treatment start
- Prior treatment and/or maintenance treatment

- Baseline CT scan of the thorax and upper abdomen, showing no signs of progression, after completion of the first treatment for lung cancer, performed within 28 days of randomization.
- Baseline performance status (according to the ECOG's scale[13]), estimated within 14 days of randomization

The patient will be asked to fill in baseline health-related quality of life (EORTC QoL-30/LC13, HADS, EQ-5D-5L) questionnaires via E-Boks immediately after inclusion and then every 2 months.

Additional evaluation for the intervention arm, after inclusion

- Weekly response to the PRO application
- If detrimental changes in PRO responses, earlier evaluation, described above

CT *evaluation according to standard follow-up/response evaluation, all participants*

- CT-scan of the thorax and upper abdomen, to evaluate the time of progression (or relapse)

Evaluation at relapse or progression

- CT-scan of the thorax and upper abdomen
- Performance status
- Planned 2nd line treatment
- Categorization of the performed CT scan as prescheduled as a result of a PRO notification

Study period:
Patients will be followed for two years after inclusion in case of non-progressive disease. In case of progressive disease or relapse, the patient will exit the study. For survival analysis and further evaluation, patients will be followed until death or up to 5 years from inclusion.

Endpoints:
The primary outcome measures that will be compared between the experimental and control arm is overall survival with an observation time of 24 months.

The secondary outcome measures are

- Performance status at the time of progressive disease
- Progression-free survival
- Health-related quality of life
- Cost-effectiveness and hospital resource use and costs
- Type of treatment at the time of progressive disease

Time to progression as well as performance status at progression compared to performance status at enrolment into the study may be used to investigate, whether the intervention leads to earlier detection of and better performance status at the time of progression. Quality of life differences may provide insights on possible other patient perceived benefits to the web-mediated follow-up.

Sub-studies
A parallel research project has been financed and will focus on benefit in terms of quality of life and better patient involvement through qualitative interviews with patients included in the study. With qualitative interviews, we aim to describe how participants experience the web-based PRO application and to explore the mechanisms of action related to PROs as a mean of patient involvement. Moreover, we aim at exploring how the intervention influences patients' fear of cancer recurrence and their psychosocial well-being. We will apply the method of an interpretive description as an inductive, flexible research strategy to generate knowledge relevant within a clinical context[22]. Individual semi-structured interviews will be conducted with 8-10 patients from each arm. After one year, follow-up interviews will be conducted with the same participants in order to explore transformations in the patients' experiences and give new insights in barriers and opportunities for patient involvement in follow up of lung cancer (For details, see appendix, sub-study 1).

Generalizability of any study finding is important when considering future implementation processes. Previous trials of behavioural interventions among cancer patients have found that patients who choose not to participate have lower education and income, are more often single and have lower survival compared to participants[23–25]. In another parallel study, we will use registry data and baseline health-related quality of life to compare differences between participants versus non-participant. The aim is to assess differences in their lung cancer disease, symptom- and comorbidity burden, and socioeconomic characteristic. By understanding these differences, we hope to be able to improve future planning of PRO use in lung cancer follow-up for all patients (See appendix for details, sub-study 2).

Intervention costs, and the derived hospital resource use and costs (number of contacts, visits, scans etc.) can be used to estimate the difference in costs in the two arms. Data will be collected retrospectively upon completion of the trial (see Appendix, sub-study 3). Together with information on effects regarding the other endpoints (including health-related quality of life), this can provide a basis for a health economic evaluation of the intervention.

Data collection and analysis

Baseline information on age, gender, Charlson's comorbidity index (extracted from central registry), histology (extracted from the pathology database), TNM stage and treatment type will be noted. During the study period, the number of CT scans will be recorded, as well as disease status and deaths including the cause of death. After verification of progressive disease, the following cancer treatment modalities will be registered. Data will be filed in and stored electronically using the AmbuFlex system and transferred to REDCap (Research Electronic Data Capture) for further data management.

Data on resource use and costs for the health economic evaluation will be collected as a retrospective study upon completion of the trial, using 1) expert assessment for time and material spent on the intervention and 2) individual patient cost data

extracted from the National Patient Registry linked to the National Cost Database (See appendix).

Power calculation

In the randomised study by Denis et al.[2] the difference in 1-year survival in control vs. PRO arm was 49% vs. 75% with the significant hazard ratio of 0.33 in their sample of 60 vs. 61 individuals in the two study arms. A power calculation based on a log-rank test for difference in survival with these anticipated survival rates and a follow-up time of 1-year results in for 53 patients in each arm. Given the remarkable difference between the two arms, a more conservative estimate has been calculated for a relative improvement of approximately half this size.

The crude overall 1-year survival in Denmark of 46.2%[9], but given that patients included in the study are responders of initiated treatment and presumably have better survival, 50 % 1-year overall survival is assumed to be the survival rate in the control arm. A relative improvement of approximately half the size found by Denis et al[2] would result in an anticipated survival rate of 63.2%. A difference of this size would require 221 individuals in each group (Alpha 5%, Beta-1 80%).

However, the feasibility study revealed a compliance ratio of 90%, which then requires a total number of 492 patients.

Power calculations were performed in STATA 14.2 using the procedure for two sample survival comparison with the log-rank test.

We aim to collaborate across hospitals to get as many participants as quickly as possible.

Statistics

The study will be conducted as a randomized phase III study. A temporary analysis will be made after 2 years of inclusion and determine whether the study holds enough promise to justify the continuation of patient enrollment. No predefined criteria for termination of the trial have been determined.

Cox proportional hazards regression will be used to estimate the hazard ratios for time to clinical deterioration, time or relapse, and the median time to deterioration.

OS will be compared between the control arms among all randomized subjects using a two-sided, log-rank test. Median OS will be estimated via the Kaplan-Meier method.

Health resources utilized are described in both arms. All hospital costs from the point in time from randomization to 1-year follow up are measured by DRGs (Diagnosis-related groups) and inflated to the price year 2018 using the Danish Hospital PL

(Price and Wage) index. CIs are estimated with bias-corrected non-parametric bootstrapping.

Cost-effectiveness of the PRO application versus standard monitoring is assessed with the incremental cost-effectiveness ratio (ICER), i.e. the ratio of net health care costs to net QALYs (Quality Adjusted Life Years). For a description of the data collection and the analysis, see appendix.

Statistical analysis plan of the Health-Related Quality of Life data

Health-related quality of life (HRQoL) measures are secondary endpoints in the ProWide trial and will be reported in a scientific paper published separately from the main paper. The primary endpoints of the HRQoL paper are Physical function (QLQ-C30), Pain (QLQ C-30), HADS-anxiety and overall EQ-5D-5L index score.

The statistical analyses were planned before any evaluation of the data collected in the trial was made.

Data collection

The HRQoL questionnaires are sent to the patients via the Danish public mail system (eBoks) every second months. All patients in the trial have access to the system. Non-respondents receive a reminder after one week. Responses delivered > 3o days after the invitation is sent is categorized as “missing”.

Specific endpoints of interest in the HRQoL analysis

The specific HRQoL scales that will be analyzed in the ProWide study are:

1. Physical function (QLQ-C30)
Rationale: Physical function is considered a PRO surrogate marker for performance status which is an important prerequisite for both toleration effect of medical antineoplastic treatment.

2. Pain (QLQ C-30)
Rationale: Pain is sensitive to change toward progression in cancer and a symptom that can be managed with analgesics. The symptom could then be improved through actions that are a result of the intervention.

3. HADS-anxiety
Rationale: The intervention could improve the sense of security in the patients and potentially reduce anxiety.

4. EQ-5D-5L index score
Rationale: The generic score represents an overall self-assessed health status and will be used report the effect of the intervention on the overall health.
The EQ-5D-5L score will be reported both in the main paper as a mean-score comparison between the two groups at six months and also analyzed in the HRQoL paper as described below.

HRQoL hypothesis

The HRQoL hypothesis is that the natural course of cancer-related symptom deteriorations can be overall reduced through actions taken on the basis continuous symptom monitoring throughout the study period. It is expected that the overall effect is larger than the effect on time to deterioration. This expectation applies to all the HRQoL endpoint.

Statistical analyses

The HRQoL data will be analyzed using a linear mixed model approach as the primary analysis to compare longitudinal data between study arms. Area Under the Curve (AUC) will be used as a confirmatory analysis. These analyses are based on the assumption that the scores can be considered as continuous variables[26].

Statistical significance

The mean EQ-5D-5L score will be reported for both study groups at six months in the main paper as the primary HRQoL endpoint.

The four HRQoL endpoints of primary interest will be analyzed and reported in the HRQoL paper.

A p-value of <.05 will be considered statistically significant.

Minimal Important Differences (MID)

MID will be used to report the proportion of patients with improvement, stable or deteriorating symptoms compared to baseline

Physical function (QLQ-C30) and Pain (QLQ C-30): a 50 % reduction of the expected mean deterioration without the intervention from baseline to time of progression is considered the MID. Based on clinical data from lung cancer patient treated in the department of oncology, Regional Hospital West Jutland, Denmark (to be published) the expected mean deterioration from baseline to progression is 10 points. A 50 percent reduction then corresponds to an MID of five point for this study.

HADS-anxiety: A 1.5-point change in the HADS anxiety score is considered an MID[27].

EQ-5D-5L index score: A change of 6 points is considered an MID[28].

Compliance and missing data

Reasons for missing data will be categorized as; administrative censoring (patients who have not reached the relevant time point at the time of the analysis), withdrawal and missing for participants still in the study. If the reason for non-compliance is death the data will not be categorized as missing.

Compliance is defined as the ratio between the number of responses and expected responses (death and administrative censoring as the reason for non-compliance are excluded at the specific time points).

A first look on the data before doing the HRQoL analysis will define the cut of point of the analysis according to the following rule. Data obtained from baseline up to 12 months will be analyzed as long as the compliance is at least 50 % in both study arms.

A supplementary analysis will explore potential differences in the HRQoL endpoint between patient with high or low compliance and the dropout rates will be compared between study arms.

Imputation

EORTC QLQ C30/L13

If at least half the items used in a scale are available, the mean scores of these items are imputed to the remaining missing items to calculate the specific scale. If more than half of the items in a scale are missing, this whole scale will be considered missing for the individual patient. This approach (the half rule) is recommended in the EORTC QLQ scoring manual[5,6].

Multiple imputation will not be used to adjust for missing data.

Ethics

All patients must give their written consent prior to the study according to local ethical standards and all data will be treated with confidentiality. The study has been approved by the Danish Data Protection Agency. Permissions to withdraw data from DLCR will be obtained.

Both study arms will be offered the CT-scans and clinical evaluations according to standard procedures. In the study presented by Denis et al.[2], patients in the experimental arm were offered less regular prescheduled CT-scans than control arm, which is not the case in the present study.

Perspectives

The French randomized trial of incorporating PRO data in the follow up of lung cancer patients has shown compelling evidence of a substantial improvement in median and overall survival by using a web-application mediated follow-up[5]. If this Danish adaption of the study shows similar positive results it holds great promise for the future strategy for lung cancer follow-up/response evaluation – and possibly also perspectives for improving follow-up for other cancer patients.

In Denmark there is a unique chance to conduct clinical trials of follow up due to the free and equal access to health care, and the possibility of complete follow up by use of the civil registration number, allowing for linkage between registries, a very low rate of patients lost to follow up and often high completeness of data, leading to good data quality.

The previous Danish findings of the collection of PRO from lung cancer patients across several regions in Denmark[29] indicated that lung cancer patients generally had positive feedback about their participation in the project. They felt they made a contribution to their own treatment and follow up, and that the PRO data facilitated their communication with their clinician. The patient felt better prepared for the consultation and that the clinician also had a better idea about their complaints and symptoms. Supported by these data, application of systematically collected PRO data in clinical practice might contribute to better clinical care of Danish patients. If we find similar results as our French colleagues, we might even find a survival benefit. Thus, our hope is to both improve clinical care and survival with the use of PRO data.

The planning of this study is coordinated with the group behind the SUPE-R trial, assessing the benefit of adding PET/CT scans and liquid biopsies in the follow up of patients with stage I-III lung cancer, enabling a comprehensive assessment, standardization and improvement of surveillance of all patients treated for lung cancer in Denmark.

Timetable

The study is expected to begin in January 2018 and end in December 2021. Below is the detailed description of each phase is presented.

January-May 2018	Construction of application
May-July 2018	Feasibility testing
May-July 2018	Data collection plan, including the establishment of a database for data from the study
September 2018	Recruitment of patients begins in Herning
November-December 2018	Recruitment of patients begins in Aarhus and Hillerød
January 2019	Recruitment of patients begins in Aalborg
February-April 2019	Recruitment of patients begins in Herlev and Copenhagen (Rigshospitalet)
Summer/Autumn 2019	Recruitment of patients begins in Sønderborg and Odense
Autumn 2019	Enrollment is competitive and continues until all patients are included.
July-December 2020	Follow up and publication of PhD dissertation and analyses of preliminary findings
December-July 2021	End of study, analyses and publications
2022	Health economic evaluation of the intervention

The final publication with full 24 months follow-up will be expected in the final half of the year 2022.

Feasibility of the project

The project is based in the Regional Hospital in Herning, but the intention is a wide collaboration across hospitals to recruit as many participants as quickly as possible which is also reflected in the broad collaboration of the project group (see organization below).

Implementation of PRO data for clinical practice is complex, both in terms of organization and technology. PRO data system AmbuFlex has already been incorporated in every day clinical practice in the oncology department in Herning, based in the Central Region of Denmark, and is already available in many oncology departments in Denmark, facilitating rapid recruitment and increasing the possibility of successful completion of the project[19].

PRO data collection in oncology departments, where PRO data is not incorporated in everyday practice, will be implemented by using the experience gathered by the collaboration between WestChronic /AmbuFlex and the Danish Cancer Society, where PRO data were collected from lung cancer patients from seven hospitals from different regions in Denmark in 2013-2015[29]. This project also demonstrated large differences between hospitals, which could be due to differences in regional health-it resources. To ensure fast and reliable implementation, the project will be started stepwise in phases in regions with actual access to AmbuFlex. The pilot phase will be conducted in the oncology department of the Regional Hospital in Herning. The first phase will be started in oncology departments of Central Denmark Region (in Herning and Aarhus), the second phase includes the North Denmark Region (in Aalborg). The third phase will include Region Zealand, and if technically possible, other regions.

Publications

The study will be published after completion, when the final analyses have been performed, in international peer-reviewed journals. The protocol committee writes the first draft and the Vancouver declaration will be followed in all publications based on this study. The names on the author list will be given according to the active participation in the design of the protocol, in the recruitment of patients.

Project organization

The project is intended for a PhD thesis.

Following are members of the protocol committee:

Rasmus Blechingberg Friis, MD, PhD student, West Jutland Hospital, Herning

Halla Skuladottir, MD, DMsc., Senior Consultant, West Jutland Hospital, Herning

Niels Henrik Hjøllund, MD, PhD, Senior Consultant, Professor, University Hospital Aarhus and West Jutland Hospital, Herning

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Marianne Ingerslev Holt, MD, Department of Oncology, Aarhus University Hospital

Torben Riis Rasmussen, MD, PhD, Senior Consultant, Associate professor, University Hospital Aarhus

Lone Bilde, health economist, Senior Project Manager, Danish Cancer Society

Budget

The project is intended as a 3-year Ph.D. study. Additional expenses include expenses for developing the web application, fees for using the web application system (including technical support) and storing the PRO data. Further, a biostatistician will be required to aid in the data analyses following the data collection and study nurses to aid the data collection coordination in the multiple sites. A health economic evaluation will also be conducted at the end of the study period.

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APPENDIX

Table 1. Study plan for the randomized clinical trial testing weekly PRO responses

	At baseline	At every CT eval.	At progression*
Histology	(x)		
Disease stage	x		
Charlson's comorbidity index	(x)		
Prior treatment	x		
Maintenance treatment	x		
Clinical examination	x	x	x
Performance status	x		x
Quality of life (every 2 months)	x		
CT-scan	x	-	-
Treatment type after progression			x
Weekly PRO (only the intervention group)	x	-	-

** Patients exit the study when progressive disease has been determined*
(x) data is extracted from central registry

EORTC QLQ-C30 (version 3.0)

Vi er interesserede i at vide noget om Dem og Deres helbred. Vær venlig at besvare alle spørgsmålene selv ved at sætte en ring omkring det svar (tal), som passer bedst på Dem. Der er ingen "rigtige" eller "forkerte" svar. De oplysninger, som De giver os, vil forblive strengt fortrolige.

	Slet ikke	Lidt	En del	Meget
1. Har De nogen vanskeligheder ved at udføre anstrengende aktiviteter, som f.eks. at bære en tung indkøbstaske eller en kuffert?	1	2	3	4
2. Har De nogen vanskeligheder ved at gå en lang tur?	1	2	3	4
3. Har De nogen vanskeligheder ved at gå en kort tur udendørs?	1	2	3	4
4. Er De nødt til at ligge i sengen eller at sidde i en stol om dagen?	1	2	3	4
5. Har De brug for hjælp til at spise, tage tøj på, vaske Dem eller gå på toilettet?	1	2	3	4

I den forløbne uge:

	Slet ikke	Lidt	En del	Meget
6. Var De begrænset i udførelsen af enten Deres arbejde eller andre daglige aktiviteter?	1	2	3	4
7. Var De begrænset i at dyrke Deres hobbyer eller andre fritidsaktiviteter?	1	2	3	4
8. Havde De åndenød?	1	2	3	4
9. Har De haft smerter?	1	2	3	4
10. Havde De brug for at hvile Dem?	1	2	3	4
11. Har De haft besvær med at sove?	1	2	3	4
12. Har De følt Dem svag?	1	2	3	4
13. Har De savnet appetit?	1	2	3	4
14. Har De haft kvalme?	1	2	3	4
15. Har De kastet op?	1	2	3	4

I den forløbne uge:	**Slet ikke**	**Lidt**	**En del**	**Meget**
16. Har De haft forstoppelse?	1	2	3	4
17. Har De haft diarré (tynd mave)?	1	2	3	4
18. Var De træt?	1	2	3	4
19. Vanskeliggjorde smerter Deres daglige gøremål?	1	2	3	4
20. Har De haft svært ved at koncentrere Dem om ting som f.eks. at læse avis eller se fjernsyn?	1	2	3	4
21. Følte De Dem anspændt?	1	2	3	4
22. Var De bekymret?	1	2	3	4
23. Følte De Dem irritabel?	1	2	3	4
24. Følte De Dem deprimeret?	1	2	3	4
25. Har De haft svært ved at huske?	1	2	3	4
26. Har Deres fysiske tilstand eller medicinske behandling vanskeliggjort Deres familieliv?	1	2	3	4
27. Har Deres fysiske tilstand eller medicinske behandling vanskeliggjort Deres omgang med andre mennesker?	1	2	3	4
28. Har Deres fysiske tilstand eller medicinske behandling medført økonomiske vanskeligheder for Dem?	1	2	3	4

Ved de næste 2 spørgsmål bedes De sætte en ring omkring det tal mellem 1 og 7, som passer bedst på Dem

29. Hvordan vil De vurdere Deres samlede helbred i den forløbne uge?

1	2	3	4	5	6	7
Meget dårligt						Særdeles godt

30. Hvordan vil De vurdere Deres samlede livskvalitet i den forløbne uge?

1	2	3	4	5	6	7
Meget dårlig						Særdeles god

EORTC QLQ – LC13

Patienter fortæller undertiden, at de har følgende symptomer eller problemer. Anfør venligst, i hvilket omfang du har haft disse symptomer eller problemer inden for den forløbne uge. Besvar spørgsmålene ved at sætte en ring omkring det tal, som passer bedst til dig.

I den forløbne uge:	Slet ikke	Lidt	En del	Meget
31. Hvor meget har du hostet?	1	2	3	4
32. Har du hostet blod op?	1	2	3	4
33. Har du haft åndenød i hvile?	1	2	3	4
34. Har du haft åndenød, når du gik?	1	2	3	4
35. Har du haft åndenød, når du gik op af trapper?	1	2	3	4
36. Har du haft ømhed i munden eller på tungen?	1	2	3	4
37. Har du haft svært ved at synke?	1	2	3	4
38. Har du haft stikken og prikken i hænder eller fødder?	1	2	3	4
39. Har du haft hårtab?	1	2	3	4
40. Har du haft smerter i brystkassen?	1	2	3	4
41. Har du haft smerter i din arm eller skulder?	1	2	3	4
42. Har du haft smerter i andre dele af kroppen?	1	2	3	4

Hvis ja, hvor? _____

43. Har du taget noget medicin for smerter?

1. Nej 2. Ja

Hvis ja, hvor meget hjalp det?	1	2	3	4

HADS – The Hospital Anxiety and Depression Scale (Danish version)

SIDE

Dette spørgeskema er udformet med henblik på at hjælpe læger med at finde ud af, hvordan du har det.
Læs hvert spørgsmål og sæt kryds ved det svar, som bedst beskriver, hvordan du har haft det følelsesmæssigt inden for den sidste uge

Jeg er anspændt eller opkørt	☐ Det meste af tiden	☐ Meget af tiden	☐ Engang imellem	☐ Overhovedet ikke
Jeg glæder mig stadig over de ting, jeg plejede at glæde mig over	☐ Helt bestemt	☐ Ikke helt så meget	☐ Kun lidt	☐ Næsten ikke
Jeg får en slags skræmmende fornemmelse, som om noget forfærdeligt skal til at ske	☐ Helt bestemt og temmelig slemt	☐ Ja, men ikke alt for slemt	☐ En smule, men det bekymrer mig ikke	☐ Overhovedet ikke
Jeg kan le og se tingene fra den morsomme side.	☐ Lige så meget som jeg altid har kunnet	☐ Ikke helt så meget nu	☐ Bestemt ikke så meget nu	☐ Overhovedet ikke
Bekymrende tanker strejfer mig.	☐ En meget stor del af tiden	☐ Meget af tiden	☐ Engang imellem, men ikke så tit	☐ Kun engang imellem
Jeg er i godt humør.	☐ Overhovedet ikke	☐ Ikke ofte	☐ Nogle gange	☐ Det meste af tiden
Jeg kan sidde roligt og føle mig afslappet.	☐ Helt bestemt	☐ For det meste	☐ Ikke ofte	☐ Overhovedet ikke
Jeg føler det som om, jeg virker sløv.	☐ Næsten hele tiden	☐ Meget ofte	☐ Somme tider	☐ Overhovedet ikke
Jeg får en slags bange fornemmelse, lige som 'sommerfugle' i maven.	☐ Overhovedet ikke	☐ Ikke ofte	☐ Ret ofte	☐ Meget ofte
Jeg har mistet interessen for mit udseende.	☐ Helt bestemt	☐ Jeg er ikke helt så omhyggelig, som jeg burde være	☐ Måske interesserer det mig knap så meget som før	☐ Jeg er lige så omhyggelig som før
Jeg føler mig rastløs, som om jeg hele tiden skal være i gang.	☐ I udtalt grad	☐ En hel del	☐ Ikke så ofte	☐ Overhovedet ikke
Jeg ser med glæde frem til tingene.	☐ Lige så meget, som jeg altid har gjort	☐ En del mindre, end jeg plejer	☐ Bestemt mindre, end jeg plejer	☐ Næsten ikke
Jeg får pludselige fornemmelser af panik	☐ Absolut meget ofte	☐ Temmelig ofte	☐ Ikke ret tit	☐ Overhovedet ikke
Jeg kan nyde en god bog, et radio- eller TV-program	☐ Ofte	☐ Nogle gange	☐ Ikke ofte	☐ Meget sjældent

Helbredsspørgeskema

Dansk version for Danmark

(Danish version for Denmark)

Under hver overskrift bedes du sætte kryds i DEN kasse, der bedst beskriver dit helbred I DAG.

BEVÆGELIGHED

Jeg har ingen problemer med at gå omkring ❑
Jeg har lidt problemer med at gå omkring ❑
Jeg har moderate problemer med at gå omkring ❑
Jeg har store problemer med at gå omkring ❑
Jeg kan ikke gå omkring ❑

PERSONLIG PLEJE

Jeg har ingen problemer med at vaske mig eller klæde mig på ❑
Jeg har lidt problemer med at vaske mig eller klæde mig på ❑
Jeg har moderate problemer med at vaske mig eller klæde mig på ❑
Jeg har store problemer med at vaske mig eller klæde mig på ❑
Jeg kan ikke vaske mig eller klæde mig på ❑

SÆDVANLIGE AKTIVITETER *(fx. arbejde, studie, husarbejde, familie- eller fritidsaktiviteter)*

Jeg har ingen problemer med at udføre mine sædvanlige aktiviteter ❑
Jeg har lidt problemer med at udføre mine sædvanlige aktiviteter ❑
Jeg har moderate problemer med at udføre mine sædvanlige aktiviteter ❑
Jeg har store problemer med at udføre mine sædvanlige aktiviteter ❑
Jeg kan ikke udføre mine sædvanlige aktiviteter ❑

SMERTER / UBEHAG

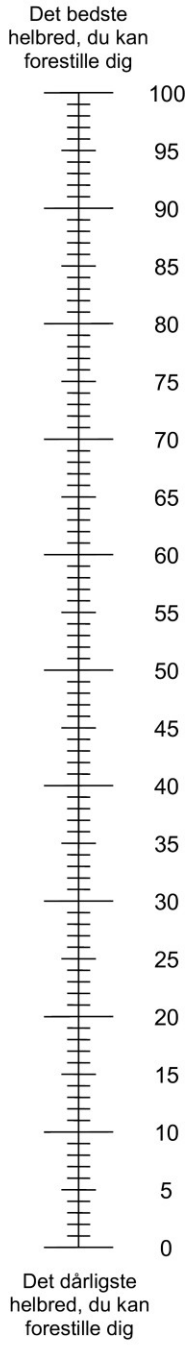
Jeg har ingen smerter eller ubehag ❑
Jeg har lidt smerter eller ubehag ❑
Jeg har moderate smerter eller ubehag ❑
Jeg har stærke smerter eller ubehag ❑
Jeg har ekstreme smerter eller ubehag ❑

ANGST / DEPRESSION

Jeg er ikke ængstelig eller deprimeret ❑
Jeg er lidt ængstelig eller deprimeret ❑
Jeg er moderat ængstelig eller deprimeret ❑
Jeg er meget ængstelig eller deprimeret ❑
Jeg er ekstremt ængstelig eller deprimeret ❑

- Vi vil gerne vide, hvor godt eller dårligt dit helbred er I DAG.
- Denne skala er nummereret fra 0 til 100.
- 100 svarer til det bedste helbred, du kan forestille dig.
  0 svarer til det dårligste helbred, du kan forestille dig.
- Sæt et X på det sted på skalaen, der viser, hvordan dit helbred er I DAG.
- Skriv derefter det tal, du har markeret på skalaen, ind i boksen nedenunder.

DIT HELBRED I DAG = ☐



ProWide: Symptoms and PRO-notification thresholds (Danish version)

1. *Hvordan vil du vurdere dit samlede helbred i den forløbne uge?*

1 2 3 4 5 6 7

Meget dårligt Særdeles godt

2. *Hvordan vil du vurdere din samlede livskvalitet i den forløbne uge?*

1 2 3 4 5 6 7

Meget dårligt Særdeles godt

I den forløbne uge:	***Slet ikke***	***Lidt***	***En del***	***Meget***
3. *Havde du åndenød?*	*1*	*2*	*3*	*4*
4. *Har du haft smerter?*	*1*	*2*	*3*	*4*
5. *Var du træt?*	*1*	*2*	*3*	*4*
6. *Har du savnet appetit?*	*1*	*2*	*3*	*4*
7. *Hvor meget har du hostet?*	*1*	*2*	*3*	*4*
8. *Har du hostet blod op?*	*1*	*2*	*3*	*4*

(OBS: 1 = ingen symptomer)

PRO-underretning sendes til afdelingen ved rødt markeret svar. Sender kun første gang med mindre der sker en yderligere forværring ift. seneste uge eller der i mellemtiden har været en bedring. Hoste med blod sender Pro-underretning hver gang.

9. *Har du feberfornemmelse?* *Nej / Ja*

(Hvis "Ja") Du bedes måle din temperatur og skrive svaret her (f.eks 38,5)

< 38,2 *≥38,2*

(I tilfælde af "forhøjet temperatur" vil en pop-up meddelelse gøre opmærksom på at man skal henvende sig på afdelingen akut med følgende tekst)

Du har oplyst, at du har feberfornemmelse og forhøjet temperatur. Der kan være tale om en akut tilstand, og du skal derfor kontakte den læge eller afdeling, der lige nu er ansvarlig for dit forløb!

10. *Har du hæs stemme?*

Nej Ja

(Hvis "Ja") Er din hæse stemme blevet forværret i den forløbne uge? Nej / Ja

11. *Har du hævelse af ansigtet?*

Nej Ja

(Hvis "Ja") Er din hævelse af ansigtet blevet forværret i den forløbne uge? Nej / Ja

12. *Kan du mærke en knude der vokser? Nej / ved ikke / Ja*

13. *Hvor mange kilo vejer du? _____*

≥ 3 kg vægttab fra baseline

14. *Har du, i den forløbne uge, fået andre symptomer, som du tror kan have forbindelse med din kræftsygdom?*

_____*Tekst*_____

Skriv kun i feltet, hvis du ønsker at det bliver læst af personalet på afdelingen

Disclaimer;

Spørgeskemaet kan ikke opspore alle de problemer, der kan opstå, når man har lungekræft.
Vi vil kun kontakte dig, hvis vi ud fra dine besvarelser finder det nødvendigt.

Du skal selv kontakter afdelingen, hvis du har det dårligt eller har brug for at tale med en læge eller sygeplejerske.
Hvis du har det akut dårligt af for eksempel feber eller åndenød, skal du kontakte afdelingen med det samme.

Appendix, sub-study 1:

A study of the non-participating candidates for the full ProWide study

Patients who do not wish to participate in the full ProWide study or were not able to, because they did not have access to the necessary technology (internet, mobile phone or E-Boks - a Danish public online digital mailbox) are candidates to this sub-study.

Aim: To explore and identify differences in HRQoL, socioeconomics and family structures between participants and non-participants in a Danish Lung Cancer population.

Hypothesis: The hypothesis is that study participants have higher income and education, and worse HRQoL than the participants.

Methods: All patients who meet the inclusion criteria will be asked to give written consent and fill in a single questionnaire containing questions about reasons for non-participation, their family structure and the same HRQoL measures as participant fill in during the study period (EORTC QLQ-C30/LC13, HADS and EQ-5D-5L).

Additional data for the analysis will be retrieved from central public registries (The National Board of Health Data (Sundhedsdatastyrelsen) and Statistics Denmark (Danmarks statistik).

Perspectives: The introduction of new health technology in the health care system can be of potential great advantage. However, detailed knowledge of the non-participants is needed to describe and address the risk of an increased inequity in the health care system when new health technology is implemented. Future work should consider other possible health care services that could be offered to this group of patients.

Publication: The results will be published in a scientific journal paper

Appendix, sub-study 2:

An interpretive description of the patient and clinician perspective in the ProWide study.

The ProWide study encompasses a complex intervention involving the interactions and interpretations of several individuals. The randomized controlled trial (RCT) is designed to uncover specific outcomes and will, therefore, provide valuable knowledge about whether the ProWide intervention has an effect. However, the RCT cannot evaluate the processes that lead to those outcomes and the RCT cannot explain how the context of this complex intervention influences its effectiveness. There is much going on within and around the intervention, and it can be difficult to tell which aspects of the social and cultural context among the participants that are supporting the desired outcome, and which are inhibiting it. In order to gain nuanced knowledge about the web-based surveillance of lung cancer patients, we will conduct two qualitative studies concurrently with the RCT study.

Aim

The aim is to explore experiences of patients with lung cancer and clinicians working with the ProWide system that can inform our understanding of the complex mechanisms in web-based surveillance in lung cancer care. This qualitative project consists of two additional sub-studies:

Qualitative sub-study 1: An interpretive description of patients' experiences with web-based surveillance. The aim is to explore how web-based surveillance can support patient involvement and individualized patient care in patients with lung cancer. Moreover, we aim to explore how the intervention influences patients' fear of cancer recurrence and their psychosocial wellbeing.

Qualitative sub-study 2: An interpretive description of clinicians' experiences with web-based surveillance. The aim is to explore the perspectives and experiences of nurses and physicians working with web-based surveillance. The intention is to widen our understanding of the clinician's interpretation of the answers given by the patients and the following clinical decisions. The study will provide important knowledge and possible explanations for the outcomes of the ProWide study.

Methods

Interpretive Description (ID) will be the overriding research strategy. ID is an applied inductive research strategy stressing the importance of conducting research arising from and with the aim of improving clinical practice.

Multiple data collection techniques are applied to obtain a comprehensive and substantial amount of data. Individual semi-structured interviews will be conducted with 15-20 patients from the experimental arm. After 6-12 months, follow-up interviews will be conducted with the same participants in order to explore transformations in the patients' experiences. Individual semi-structured interviews with 10-15 clinicians (nurses and physicians) working with web-based surveillance in the different oncology departments will also be conducted. Furthermore, field studies will be performed in the oncology departments comprising participant observations during nurses' and physicians' management and assessment of the patients' PRO responses and informal interviews with these clinicians.

Plan for dissemination of the Results

The results will be published in international scientific peer-reviewed journals. The final results will be presented for all relevant parties including all participating departments and patient organizations.

Perspectives

The intentions of the studies are to provide complementary explanations of the findings from the RCT and to generate knowledge and directions for ways to reframe or to optimize the future management of lung cancer patient care. In addition, if this Danish version of intensified frequent symptom reporting in lung cancer shows positive results, it holds great promise for the future strategy, not just for lung cancer, but also perspectives for a possible improvement in disease surveillance for other cancer diagnoses. Thus, the results from the qualitative studies will contribute with important insights into barriers and opportunities for patient involvement and individualized patient care across cancer diagnosis.

Appendix, sub-study 3:

Health economic evaluation alongside the ProWide clinical trial

This document describes the data collection, outcome measures, and analysis for a health economic evaluation of the weekly internet-based detection of progressive disease in lung cancer.

The health economic evaluation will be conducted after the completion of the ProWide trial. The evaluation will use the trial efficacy data supplemented by a cost assessment based on data collected outside the trial and be conducted in accordance with the recommended practice for health economic evaluation (1).

Aims

The study will assess the incremental cost per quality-adjusted life year gained (QALY) for patients with lung cancer (corresponding to the inclusion criteria) of using a weekly internet-based tool for systematic self-reporting of symptoms compared with standard care, that is, not-systematic reporting of symptoms of progressive disease.

The assessment will take a 1-year perspective and a 5-year perspective

Study perspective:

The evaluation will use a hospital perspective only

Data

Data for the assessment of patient unit costs (intervention costs; derived hospital costs) will be collected outside the trial:

Intervention costs will be assessed using structured interviews with study nurses, doctors and other relevant personnel at 3-4 of the participating hospitals. The purpose of these interviews is to describe and quantify the resource use relating to the intervention (e.g. the number of telephone calls, clinical staff time spent on patient contacts, IT support etc.) and relating to patient telephone contact in the control arm. The resource used will be valued using average net salary information for the relevant

type of personnel plus social costs in accordance with the recommendations for cost assessment in health care.

Derived hospital costs will be assessed in a research project based at the National Board of Health Data (Sundhedsdatastyrelsen) or Statistics Denmark. Data on resource use – eg. Procedures, admissions and dates, ambulatory contacts, and hospital costs for each of the participating patients will be collected from the National Patient Registry and linked with patient data from the National Cost Database. The research project is subject to approval from the Danish Data Protection Agency.

Mortality data are collected in the trial and survival analysis for the accumulation of life years will be undertaken as part of the statistical analysis plan.

Health-related quality of life data based on the utility weights from the EQ-5D-5L questionnaires is collected as part of the trial at baseline and every second month. The EQ-5D-5L derived utility weights will be used to calculate the QALYs.

EQ 5D-5L is a generic questionnaire, consisting of five domains and a VAS scale and it is commonly used for estimating the generic health status, with high validity and reliability in various health conditions (3,4) and should be more sensitive at eliciting changes in the health status than the previous EQ-5D-3L questionnaire.

Analysis

Health resources used are described and compared for both arms (intervention and derived hospital costs) and are inflated to the price year 2018 using the Danish Hospital PL index (price and wage). Confidence intervals will be estimated using bias-corrected non-parametric bootstrapping.

In the five-year scenario, both costs and QALYs will be discounted to present value using an annual discount rate of 3%.

Furthermore, subgroup analysis will be undertaken to investigate explanatory factors for cost differences not related to the trial intervention. Finally, a number of sensitivity analyses will be run for the assessment of the robustness of the study assumptions.

Publications

The health economic evaluation will be described in a paper and submitted for a scientific journal in accordance with good reporting practice for health economic studies (4).

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