BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035673
Article Type:	Original research
Date Submitted by the Author:	12-Nov-2019
Complete List of Authors:	Friis, Rasmus; Regional Hospital West Jutland, Department of Oncology Hjollund, Niels Henrik; Regional Hospital West Jutland, AmbuFlex, Occupational Medicine, University Research Clinic, Aarhus University; Aarhus University Hospital Skejby, Department of Clinical Epidemiology Mejdahl, Caroline; Regional Hospital West Jutland, AmbuFlex/WestChronic, Occupational Medicine, University Research Clinic, Aarhus University Pappot, Helle ; University Hospital of Copenhagen, Department of Oncology Skuladottir, Halla; Regional Hospital West Jutland, Department of Oncology
Keywords:	ONCOLOGY, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Interstitial lung disease < THORACIC MEDICINE

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Title page

Electronic symptom monitoring in advanced lung cancer: a feasibility study

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Word count: 3999

KEYWORDS (MESH)

1. Lung Neoplasms
2. Patient Reported Outcome Measures
3. Telemedicine
4. Symptom Assessment
5. Palliative Care

Abstract

Objectives

To design, feasibility test and evaluate an electronic questionnaire and a study set-up for symptom-monitoring of advanced lung cancer.

Setting

Single centre feasibility study.

Participants

Patients with stage IV lung cancer in antineoplastic treatment.

Interventions

This study reflects the first three phases of a complex intervention design: Phase 1; development of the intervention, phase 2; feasibility testing and phase 3; evaluation of the intervention. Items were initially selected for the questionnaire and adjusted by patient interviews in phase 1. In phase 2, patients completed the electronic questionnaire weekly during a three-week feasibility test. A clinical nurse was automatically notified in case of symptom deterioration with the aim to contact the patient. In phase 3, patients evaluated phase 2 by paper-questionnaires and interviews were conducted with the participating nurses.

Primary outcome measures

The study outcomes were: phase 1; usability and clinical relevance, phase 2; recruitment rate, compliance and threshold functionality, phase 3; usability, acceptability and clinical relevance.

Results

A questionnaire was designed and reviewed by patients (n=8) in phase 1. Interviews revealed high usability and clinical relevance of the intervention.

Twenty out of 29 approached patients (69%) were recruited for phase 2/3. Two patients did not complete any of the questionnaires (compliance 90%). The weekly questionnaires were completed 65 times out of 72 possible (7 missed, 93% completed) and 30% of the completions resulted in a phone call by a nurse.

The patients reported high usability and acceptability in the evaluation. The substance of the telephone conversations was clinically relevant, and the study setup was logistically acceptable.

Conclusions

An electronic questionnaire designed for symptom monitoring was found to have high usability, acceptability and clinical relevance in the target population. In conclusion, the study setup was considered feasible for a randomized controlled trial.

Trial registration

NCT03529851.

Article Summary

Strengths and limitations

- Weekly symptom monitoring of lung cancer patients using EORTC measures is feasible
- A mixed methods design was used to refine the electronic questionnaire
- Feasibility was tested by a three-phase complex intervention approach
- Patients were involved in the evaluation and adjustment of the intervention
- Limitations to the study are the short study period and limited number of participating patients

Introduction

Lung cancer is one of the most common cancers in both men and women and is the leading cause of cancer-related mortality throughout the world,[1]. In Denmark, the annual incidence of lung cancer is approximately 4600 and more than 3700 persons die from this disease every year, hence accounting for 24% of all cancer-related deaths and 7% of the total mortality rate,[2,3].

Although the prognosis remains severe, new antineoplastic drugs have improved the treatment options for patients with advanced lung cancer. A deterioration of the health condition is, however, a strong negative predictive factor for the effect of further antineoplastic treatment and sufficient symptom management is an important prerequisite for achieving the full treatment effect,[4]. If intensified symptom monitoring could indicate progressive disease at an early point, second-line therapy could be initiated before deterioration of the health-status.

A Patient-Reported Outcome (PRO) is by the US Food and Drug Administration (FDA) defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else",[5]. PRO measures used for symptom monitoring have previously shown to improve patient-caregiver communication, care, patient satisfaction and lead to earlier symptom management,[6,7]. Moreover, a randomized controlled trial (RCT) found that weekly internet-based symptom monitoring of lung cancer patients resulted in a significant survival benefit which also persisted after cross over and two years of follow up,[8,9]. Another RCT showed that weekly symptom monitoring resulted in a significant benefit on both overall survival and quality of life, and additionally led to a reduction in the number of emergency room visits in cancer patients treated with chemotherapy ,[10]

To design, feasibility test and evaluate an electronic questionnaire and a study set-up for internet-based symptom monitoring in patients with advanced lung cancer.

Methods

Study population

The study was conducted from May-July 2018 at the Department of Oncology in Regional Hospital West Jutland, Herning, Denmark. Outpatients diagnosed with stage IV lung cancer with an available internet connection at home were eligible. The patients had to be able to read and speak Danish. All patients were receiving first or second-line medical antineoplastic treatment at the time of enrolment.

The electronic PRO software

The AmbuFlex system is a Danish generic PRO software system that is integrated into the electronic medical records at Regional Hospital West Jutland,[11,12]. The system is intended for follow-up in both cancer and other chronic diseases and is used in both clinical practice and for research purposes. The patients fill in health-related questions via a homepage and the responses can be accessed real-time on-screen by clinicians. Consecutive answers are presented visually by colour-bars, numbers and text to represent the longitudinal symptom development. The software has the option of an automated threshold mechanism that can be used to identify patients who need clinical attention based on individual responses[13–15].

Study Design

The design of this feasibility study reflects the first three phases of a complex intervention design following the MRC guidelines,[16]: Phase 1; development of the intervention, phase 2; feasibility testing and phase 3;

evaluation. After conducting a phase, we adjusted the system before entering the next phase,[16,17]. The implementation of the ePRO monitoring in the clinic was inspired by the recommended guidelines by the International Society for Quality of Life Research (ISOQOL),[18,19].

Definitions

The following definitions were used in the evaluation of the intervention.

Usability: the design factors that affected the user's experience of operating the questionnaire software and navigating it for the intended purpose.

Acceptability by patients: the factors that affected their willingness to participate in weekly self-reporting of symptoms.

Acceptability by clinicians: the factors that affected their willingness to use the system.

Clinical relevance: a subjective perception of whether the questionnaire addressed issues that are relevant both for the patient to report to the hospital and for the clinicians to be notified of.

The EORTC Item Library

The European Organisation for Research and Treatment of Cancer (EORTC) item library is an online database of hundreds of individual items from previously validated and translated EORTC questionnaires which allows for single item combinations in the construction of item-lists for both clinical and research purposes,[20].

Phase 1: Development of the intervention

Initial item selection and threshold definitions for the electronic questionnaire

Twelve symptoms were selected for the electronic PRO (ePRO) monitoring inspired by the study conducted by Denis et al in a lung cancer population,[8]. Eleven of these selected symptoms were identical with the symptoms used by Denis et al,[8]. Self-rated overall health was, due to known prognostic properties, included in the questionnaire instead of depression ,[21,22]. Seven of the 12 selected symptoms were available as items in the EORTC item library and all graded by a Likert scale,[20]. The recall period was "the past week" for all the EORTC items. Three supplementary symptoms (facial swelling, hoarse voice and sense of a growing tumour) were considered alarm symptoms that needed specific attention and were not scored. These items were phrased by four members of the study group (RF, CT, NHH, HS). Weight and temperature were entered in two additional boxes. The symptoms selected for the feasibility study are listed in Table 1. The items were intended to be used as a screening tool to identify patients with *deterioration* of specific symptoms that needed attention from the clinicians. Accordingly, the purpose was not to indicate a specific score or describe the overall health of the patient.

Table 1: Symptoms selected for the electronic questionnaire

Symptoms graded by severity*	
1	Overall health
2	Dyspnoea
3	Pain
4	Fatigue
5	Appetite loss
6	Coughing
7	Haemoptysis
Alarm symptoms	
8	Fever ≥38.2°C
9	Hoarse voice
10	Facial swelling
11	Sense of a growing tumor
12	Weight loss ≥3 kg
Other	
13	Commentary Field

**Items selected from the EORTC Item Library, https://www.eortc.be/itemlibrary/*

A symptom severity threshold was subsequently defined by the authors for each item. The PRO software automatically included a given patient in a notification-list whenever a response by the patient exceeded the predefined symptom-severity threshold. The list was then reviewed by a nurse as a part of the daily routine by a procedure described below.

Conditional branching was used for three of the alarm symptoms. If the presence of facial swelling or hoarse voice was reported, the patient was asked to report whether the symptom had worsened within the past week as an additional question. If a sensation of fever was reported, the patient was prompted to measure and enter the temperature. The patient appeared on the notification-list if the temperature was ≥38.2°C or if a weight loss of 3 kg or more compared to baseline was registered. Finally, a supplementary commentary field was added to enable the patients to report other symptoms.

Adjustment of the electronic questionnaire

To assess usability and clinical relevance of the electronic questionnaire we conducted semi-structured interviews with individual lung cancer patients. The interviews were planned to continue until a point of data saturation was reached. Potential misconceptions of the phrasings of the three alarm symptoms were explored during the interviews. Patients who participated in these initial interviews were provided with a portable computer and a written instruction that described the log-in procedure. They were encouraged to respond to the questionnaire and comment on the procedure while the investigator observed the process and conducted the interview,[23]. The interviews were supported by an interview guide that focused to explore and address potential issues regarding usability and clinical relevance perceived by the patient or the observer. The interviews were recorded, transcribed and analysed by a thematic text-analysis,[24].

Phase 2: Feasibility test

The second phase was a three-week prospective feasibility test of the AmbuFlex PRO software. A sample size of at least 15 patients for this phase was considered sufficient based on general recommendations for

pilot and feasibility studies,[25,26]. However, to compensate for potential compliance problems, we decided to enroll 20 patients.

A new group of patients were provided with written instructions and asked to answer the ePRO questionnaire from a home internet connection for a total of four times with one-week intervals.

Two clinical lung cancer oncology nurses who had prior experience with the AmbuFlex system in clinical practice were trained in the study procedures. The nurses were provided with a guide that described the threshold functionality of the software and how to review and manage the symptom charts. As a part of their work routine, they were instructed to daily access the automatically generated notification-list, review the responses, and contact the patient (Figure 1). If a written comment in the commentary field had triggered the notification, the nurse could choose not to contact the patient if it was not considered necessary. If a phone conversation gave indications of progressive disease, the following planned CT scan should be rescheduled to as soon as possible and otherwise, the patient's symptoms were treated according to best supportive care. The time spent on all study-related procedures and the number of phone calls were recorded daily by the nurse.

In this phase, we also explored the recruitment-rate, compliance and the threshold algorithm that generated notifications to the nurses.

Phase 3: Evaluation of the intervention and study set up

All patients participating in phase 3 filled in an evaluation questionnaire on paper by the end of the study period. The themes of the questionnaire were usability, acceptability and clinical relevance.

We then conducted semi-structured interviews with the involved nurses to evaluate the logistic setup and the clinical relevance of the chosen threshold.

The authors finally evaluated the results of the study period at a consensus meeting to agree on adjustments before the initiation of the RCT.

Patient and Public involvement

By participation in this study, patients were involved in the design of the ePRO intervention for the following randomized controlled trial. The intervention was evaluated and adjusted based on the interviews conducted with participating patients and covered both the acceptability, usability and clinical relevance including the weekly time required to participate in the study.

Ethics

The study was approved by the Danish Data protection agency (2017-41-5251). According to Danish law, no approval was required by The Danish Research Ethics Committee (enquiry 266 received 7th December 2017).

All participants received oral information and signed a written consent prior to enrolment.

Results

Phase 1: Development of the intervention

Semi-structured interviews were conducted with eight patients while they logged in and responded to the electronic questionnaire. The thematic text analysis identified five themes; usability, acceptability, inaccurate phrasing, insufficient items and response options.

The usability was high. The patients had very few issues with the login- and response procedures. Two patients mentioned that they had difficulties using a computer, but both were yet able to complete the questionnaire by following the instructions. One patient stated that *"it's quick to answer"* and another that *"it was easy to log in."* However, based on the observations made by the interviewer, a few clarifications were made in the login instructions provided to the patients.

The willingness to participate despite the effort indicated high acceptability, as reflected by one patient saying; "*using a computer is difficult, but if it would help I would do it."* No patients expressed reluctance against the questionnaire.

One patient expressed the wish of being able to "*to describe the psychological burden of lung cancer*." We acknowledge that this is of major importance for many patients but due to the complexity of this theme and with the purpose of the study in mind, we decided to confine remarks on psychological issues to the commentary field.

There was one misunderstanding concerning the alarm symptoms. One patient was unable to assess whether she had a sense of a growing tumour and consequently refused to answer the question. The issue was solved by adding the response option "*I don't know"* to the questionnaire before the initiation of phase 2.

Two of the supplementary alarm questions that referred to the time frame "since last time" were confusing if the patient had not answered the questionnaire previously. The time frame was then changed to the wording "the past week."

Phase 2: Feasibility test

After the adjustments made in phase 1, the three-week feasibility test was initiated. Twentynine patients were approached in the outpatient clinic whereas five were ineligible due to lack of an internet connection at home. Four patients declined participation since they did not feel they could comply with the intervention. The recruitment rate for the three-week pilot test was then 69% (20/29).

The baseline patient characteristics are presented in Table 2. The median age was 70.5 (range 54-86 years). Most of the enrolled patients had prior experience with the internet, although one patient categorized herself as a very inexperienced internet user but was nevertheless able to complete all four questionnaires in the test period.

Table 2: Baseline characteristics

	n	%
Age, years; median (range)	70,5 (54-86)	
Sex		
Male	13	65
Female	7	35
Treatment line		
1st	13	65
2nd	7	35
Civil status		
Married	17	85
Widow	2	10
Divorced	0	0
Single	1	5
Highest completed education		
Primary School	8	40
High school	0	0
Professional education	7	35
Short higher education	3	15
Medium higher education	2	10
Long higher education	0	0
Internet experience		
Very experienced	4	20
Experienced	5	25
Neither	3	15
Inexperienced	7	35
Very inexperienced	1	5

Two patients did not complete any of the questionnaires and were not included in the analysis. Among the participating patients, the weekly questionnaires were completed 72/80 (93%) times (Table 3). Fifty-five per cent (37/67) of the responses exceeded the threshold and therefore led to further action by a clinical nurse. A phone call to a patient was made based on 30% (20/67) of the responses. One programming error regarding the severity of dyspnoea unintentionally led to five false notifications. The time spent responding to alarm-notifications, including phone calls were managed by the nurse in a median of 6 minutes (range 0.2-30 minutes) per day.

Table 3: Compliance and notifications (n=18*)

Week	1	2	3	4	Total
Possible completions	18	18	18	18	72
Questionnaires completed	18	18	17	14	67
Completion rate / %	100%	100%	94%	78%	93%
Notification tresholds exceeded	15	5	5	7	32
Additional notifications sent due to erroneous algorithm programming	0	3	2	0	5
Notification thresholds exceeded / completed questionnaire %	83%	44%	41%	50%	55%
Phone calls made	4	7	6	3	20
Phone calls made / per completed questionnaire, %	22%	39%	35%	21%	30%

A phone call was handled in a median time of 11 minutes

The nurse spent a median of 6 minutes (min 0,2; max 30) per day on study related procedures

** 2/20 enrolled patients did not participate in the pilot study*

Phase 3: Evaluation of the intervention and study set up

All patients who participated in phase 2 (n=18) filled in the evaluation questionnaire at the end of the study. The replies are reported in Table 4.

Table 4: Evaluation questionnaire (n=18), % (n)

Usability					
To what extent do you agree or disagree with the following statements?	**Strongly disagree / disagree**	**Neither**	**Agree / strongly agree**	**Do not know**	**N/A**
It is easy to log in to answer the questionnaire	6% (1)	0% (0)	94% (17)	0% (0)	-
I find it easy to read the questionnaire	0% (0)	0% (0)	100% (18)	0% (0)	-
The questions in the questionnaire are easy to understand	0% (0)	11% (2)	89% (16)	0% (0)	-
	Less than 5 min.	**5-10 min.**	**10-15 min.**	**> 15 min.**	
How long have you approximately spent answering the questionnaire each week?	39% (7)	39% (7)	22% (4)	0% (0)	-
	No	**Occasionally**	**Yes, every time**		
Did you need any help to fill in the questionnaire?	89% (16)	11% (2)	0% (0)		-
	No	**Occasionally**	**Yes, every time**		
Have you experienced technical problems?	100% (18)	0% (0)	0% (0)		-
Acceptability					
To what extent do you agree or disagree with the following statements?	**Strongly disagree / disagree**	**Neither**	**Agree / strongly agree**	**Do not know**	**N/A**
I am confident that the outpatient clinic will contact me when they have seen my answers, if needed	0% (0)	6% (1)	94% (17)	0% (0)	-
I always call the outpatient clinic if I have problems that I need to discuss with a doctor or nurse	0% (0)	22% (4)	67% (12)	11% (2)	-
I get more worried about my cancer when I fill in the questionnaire	39% (7)	28% (5)	17% (3)	11% (2)	6% (1)
It is difficult to remember to answer the questionnaire every week	61% (11)	11% (2)	22% (4)	6% (1)	-
	No	**Yes**			
Where you generally satisfied with the questionnaire used in the study period?	0% (0)	89% (16)			11% (2)
Clinical relevance					
To what extent do you agree or disagree with the following statements?	**Strongly disagree / disagree**	**Neither**	**Agree / strongly agree**	**Do not know**	**N/A**
The questionnaire makes me more aware of symptoms that may be due to my illness	6% (1)	33% (6)	56% (10)	6% (1)	-
The questionnaire helps me to remember problems that I would like to discuss with the doctor / nurse	6% (1)	50% (9)	39% (7)	6% (1)	-
	Not at all / to a lesser extent		**To some extent / highly**	**Do not know**	
To what extent do you find the questions relevant to you?	17% (3)		78% (14)	6% (1)	-
	No	**Yes**			
Did you miss any topics?	94% (17)	6% (1)			-
	No	**Yes**			
Did you find any topics irrelevant?	94% (17)	6% (1)			-

N/A: Not Applicable

Usability

The patients found it easy to log in and to read and answer the questions. The estimated time spent for a patient to complete the weekly questionnaire was less than 10 minutes for 78% of the patients and less than 15 minutes for the remaining. Two patients needed help from a relative to complete the questionnaires, but none of the patients experienced any technical problems from their home computer during the study period. One patient reported that *"the questionnaire is easy to complete, and it is good to be aware of possible side effects."*

Acceptability

Seventeen (94%) patients felt confident that they would be contacted by the clinic if needed and 16 patients (89%, 2 non-respondents) were satisfied with the questionnaire in the three-week test period. Three (17%, 1 non-respondent) patients felt that they got more worried about their cancer when answering the questionnaire. By contrast, 61% disagreed and two patients also stated the opposite view in the commentary field. The first patient was *"satisfied with the additional sense of security"* and the other specified that *"it is reassuring to know that one is being watched if complications occur."*

Clinical relevance

Fourteen (78%) patients found the questions in the weekly questionnaire relevant. One patient expressed the need to report more detailed responses and another patient would like to be able to report the functional level and the psychological condition. Seven (39%) patients felt better prepared for the dialogue with the doctor and ten (56%) patients felt more aware of disease-related symptoms.

Nurse interviews

Two clinical nurses were involved in the active management of the notification-list during the three-week study period. Interviews with the two nurses focused on the clinical perspectives. Both nurses experienced that the phone consultations were of high relevance for the patients with only a few examples of unnecessary contacts. They felt that the daily task was both acceptable and meaningful. However, one of the nurses was concerned that the workload could grow and become a problem if many patients got included in the RCT without additional allocation of resources to the task.

The clinical relevance of the threshold limits was also explored in the interviews with the nurses. One of the nurses thought that the individual symptoms were of different clinical importance and stated that *"loss of appetite … and also fatigue ... often notifies. And the question is how much we actually use it. We only really do something if the fatigue is disabling … or if the loss of appetite is prolonged."* The other nurse agreed and suggested to change the threshold definitions for these two symptoms to a higher degree of severity.

Discussion

In this study we designed, feasibility tested and evaluated an electronic questionnaire and a study set-up for weekly internet-based symptom monitoring in patients with advanced lung cancer.

Our study confirms that the chosen approach using a questionnaire based on a core of EORTC items and electronically presented to patients using the AmbuFlex PRO software system is feasible for both patients and health care professionals, and allow us to move on with the use of this questionnaire and set-up in an RCT.

Two previous studies,[8,10] have, as mentioned in the introduction, suggested improved overall survival as a result of weekly internet-based monitoring in cancer patients. Denis et al,[8] studied patients with stage

II-IV lung cancer and Basch et al,[10] studied patients in ongoing treatment for different types of metastatic cancer of whom approximately 25% had lung cancer. The approaches were different in the two studies. The first study,[8] focused solely on lung cancer-specific symptoms that were likely to deteriorate during follow-up or maintenance treatment whereas the other study,[10] focused on symptoms that could be adverse effects caused by the ongoing antineoplastic treatment. Both studies used a threshold mechanism to notify clinicians in case of concerning symptoms. Although several of the symptoms were overlapping in the two studies, both the specific items and the response options were different. Basch et al,[10] used the Common Toxicity Criteria for Adverse Events (CTCAE) items,[10] while Denis et al,[8] asked patients to grade symptoms from 0-3. The threshold algorithm used for the latter study was not published in detail for which reason it was not possible for us to replicate the specific approach in the present feasibility study. One study has documented good reliability and consistency between several symptoms in the EORTC QLQ-C30 and certain PRO-CTCAE measures and we consider the use of both type of PRO measures to be valid for active symptom monitoring,[25]. EORTC items have more simple sentence structures than PRO-CTCAE and were hence preferred for this study population ,[26]. To the best of our knowledge, no guidelines concerning the use of threshold definitions for symptom monitoring have been published.

The electronic questionnaire had high usability in both phase 1 and 3, but simplifications of the patient-instructions were needed. The software did not show any technical issues in the study period albeit one symptom-specific programming error was identified and corrected. The high usability was consistent with other studies that have used the AmbuFlex software to collect PRO data,[14,15].

Our findings show that the intervention was acceptable for patients who responded to the weekly questionnaire. We also observed that patients, despite varying internet experience, were highly committed to and passionate about the project. Some patients requested opportunities to report a broader picture of their situation. This was only possible in the commentary field but made it evident that the EORTC item "self-rated quality of life" could usefully be added to the weekly questionnaire. This item allows the patients to report their own assessment of quality of life and, in combination with self-rated overall health, also enables the calculation of a longitudinal EORTC global quality of life score.

Two patients never started to fill in a weekly questionnaire. Despite the limited number of patients in the study, this patient-barrier clarified the need for a tool that could identify non-responders. It seemed that it was difficult for some patients to get started with the first ePRO questionnaire from home. Additionally, there appeared to be a lower completion-rate toward the end of the test period. This could be due to misunderstandings since the patients were asked to fill in the questionnaire the day before the next planned treatment which was also the end of the study period. Some patients already answered other ePRO questionnaires as a part of routine care in the department. Consequently, these patients were supposed to answer two questionnaires on the same day which could explain why some patients forgot to answer the last one in the study period. To address compliance-issue that could be of potentially large impact in the RCT, notifications of non-responding patients will be sent to the nurses as a part of the daily routine. In this way, the non-compliant patients will be contacted and receive the guidance needed. By introducing a fixed daily work routine, where nurses examined the notification-list daily, we made sure that all responses that exceeded the thresholds were managed. It does not make sense to make conclusions about the attrition rate with the short study period.
Questionnaire responses made by patients in the three-week test period led to a phone call by a nurse in 30% (20) of the cases. The algorithm was programmed to only notify the clinicians when the symptom

severity had deteriorated compared to the response from the previous week. The initial response in week one triggered a larger proportion of notifications than the following responses because a notification was always when sent if a symptom threshold was exceeded and there was no previous response to compare with. The nurses were instructed only to contact the patients if the answers were concerning, but initially, the nurses acted more proactively and made more phone calls than they were trained to. The interviews with the nurses revealed that they acted with a high sense of responsibility but also some uncertainty about the procedures. If the instructions had been strictly followed, only 10 phone calls would have been made in the test period, which in other terms means that twice as many phone calls were made as intended. This underscored the need for clear and concise instructions for the staff managing the notifications. Accordingly, the training plans for the nurses were updated with relevant clarifications prior to the RCT.

Prior to the study, the amount of time spent on managing notifications and contacting the patients was a serious concern for both the nurses and the department managers among the collaborators for the following multicentre RCT. The quantification of the time spent on the daily procedures did, however, not lead to a worrying amount of workload among the participating nurses.

Based on interviews with the two participating nurses, the threshold definitions for each symptom were discussed in the study group. By a consensus decision, the threshold that would notify the department for fatigue and appetite loss was raised to a higher severity grade. The final design of the electronic questionnaire and threshold definitions can be found in the appendix.

The strength of this study was the multidimensional approach following the three phases of the MRC guidelines for complex interventions,[16]. All patients were real-life lung cancer patients receiving outpatient treatment with, in some cases, limited computer skills and a moderate educational level. It was important to test the system in a setting where the patients used their own internet device so that issues could be addressed before implemented in the following RCT.

The short study period with a relatively low number of participating patients was a limitation to the study. Since the AmbuFlex PRO system has already been widely tested, it is in our opinion yet possible to sufficiently conclude that use of the AmbuFlex software is feasible in this study setup,[15].

Conclusions

A study setup using weekly symptom monitoring based on EORTC items for a following national RCT is feasible.

The following trial, ProWide (Patient-Reported Outcomes used for Weekly Internet-based Detection of progressive disease in lung cancer, Clinicaltrials.gov NTC03608410), is a two-arm open labelled multicentre RCT and will include 492 patients diagnosed with advanced lung cancer in Denmark. The power calculation is based on an anticipated effect on overall survival of half the size of the 1-years overall survival in the study by Denis et al and a compliance rate of 90%,[8]. The study is open and recruiting.

Funding

The study was funded by a grant from The Danish Cancer Society (grant number R184-A11805) and Department of Oncology, West Jutland Hospital, Central Denmark Region.

Acknowledgement

The authors thank all the participating patients and the dedicated clinical nurses Vibeke Holst May and Anne Marie Hill from the Department of Oncology, Regional Hospital West Jutland, Herning. We also thank Gry Assam Taarnhøj for valuable feedback on the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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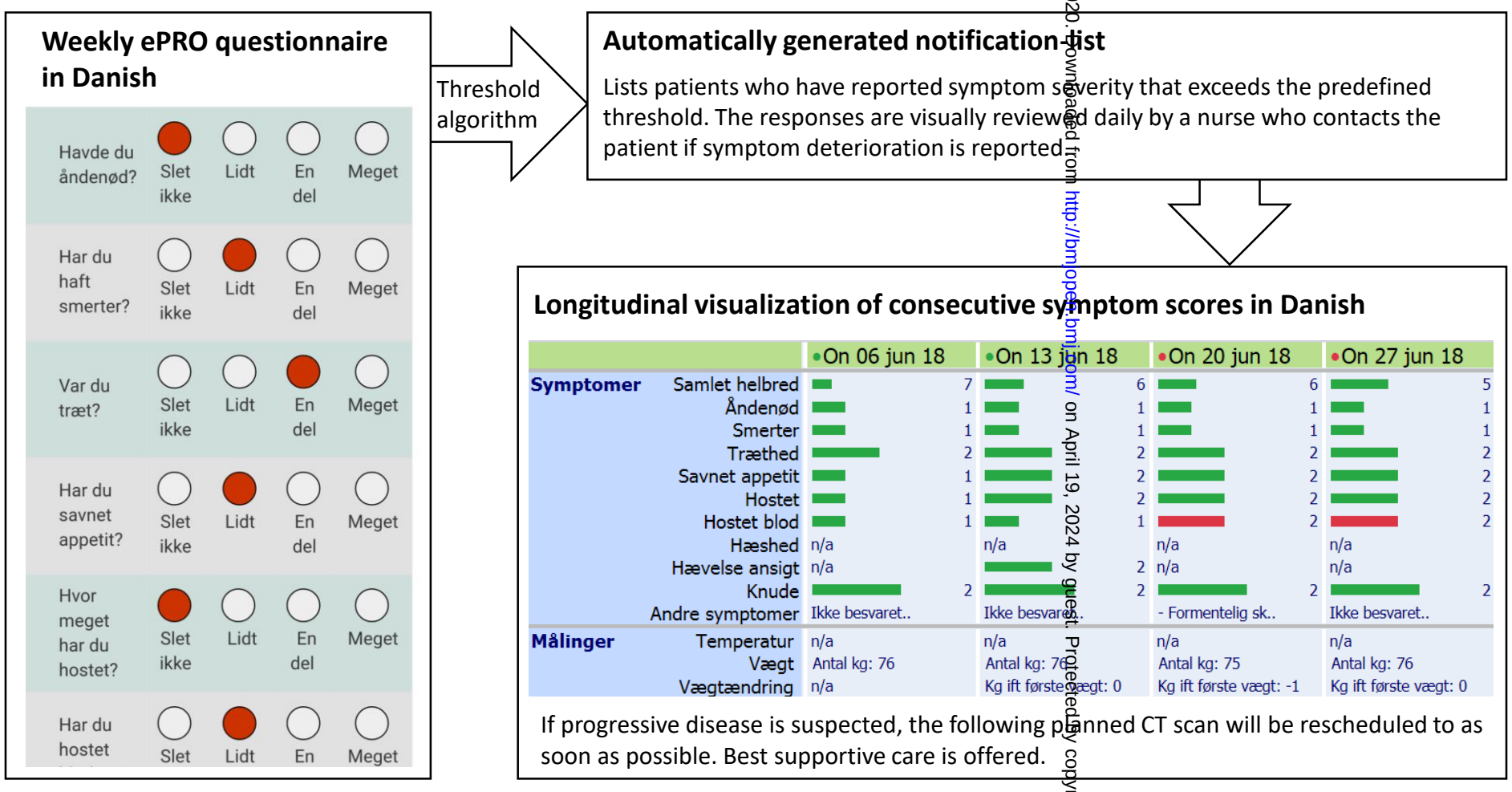
Author statement

1. *Friis, Rasmus Blechingberg: Designed the draft of the electronic questionnaire. Enrolled all patients, conducted the interviews, monitored the three-week test period, evaluated and analysed the data and wrote the initial draft of the paper.*
2. *Hjøllund, Niels Henrik: Programmed the software. Major input regarding the logistic planning. Did all the software and threshold programming.* Large contribution on the design of the item-list for the electronic questionnaire.
3. *Mejdahl, Caroline: Had large impact on the interview guide, the analysis of the interview data and the design of both the electronic questionnaire and the evaluation questionnaire.*
4. *Pappot, Helle: Major influence on the interpretation of data and the structure of the paper*
5. *Skuladottir, Halla: Idea of the project. Primary supervisor. Wrote the initial study plan and had major contributions to the manuscript.* Large impact on the design of the electronic questionnaire.



Supplementary material: The final ePRO questionnaire after adjustments

Items graded by severity	Response options*

During the past week

1. How would you rate your overall health during the past week?

Very poor						Excellent
1	**2**	**3**	4	5	6	7

2. How would you rate your overall quality of life during the past week?

Very poor						Excellent
1	2	3	4	5	6	7

	Not at all	A little	Quite a bit	Very Much
3. Were you short of breath?	1	2	**3**	**4**
4. Have you had pain?	1	2	**3**	**4**
5. Were you tired?	1	2	3	**4**
6. Have you lacked appetite?	1	2	3	**4**
7. How much did you cough?	1	2	**3**	**4**
8. Did you cough up blood?	1	**2**	**3**	**4**

Supplementary items

9. Do you feel feverish? No/yes

If yes; Please measure your temperature and write the answer here (eg 38.5)

≥38.2

(Pop-up message advises the patient to contact the hospital)

10.. Do you have a hoarse voice? No/yes

If yes; Have your hoarse voice worsened during the past week?

Yes

11. Do you have facial swelling? No/Yes

If yes; Have your facial swelling worsened during the past week?

Yes

12. Do you sense a growing tumour? Yes/no/do not know

Yes

13. How much do you weigh?

_____

≥ 3 kg weight loss compared to first measure

14. Have you, during the past week, had other symptoms that you think may be associated with your cancer?

Any comment

**Threshold definitions are marked with grey/bold. Notifications are automatically sent to the department when the thresholds are exceeded.*

Items 1 and 3-7: a notification is only sent to the department in case of deterioration compared to the previous week.

Item 2: No threshold is used for this item

Reporting checklist for quality improvement study.

Based on the SQUIRE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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	Reporting Item	Page Number
Title		
#1	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patientcenteredness, timeliness, cost, efficiency, and equity of healthcare)	1

Abstract			
	#02a	Provide adequate information to aid in searching and indexing	2
	#02b	Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	2
Introduction			
Problem description	#3	Nature and significance of the local problem	4
Available knowledge	#4	Summary of what is currently known about the problem, including relevant previous studies	4
Rationale	#5	Informal or formal frameworks, models, concepts, and / or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work	4
Specific aims	#6	Purpose of the project and of this report	4
Methods			
Context	#7	Contextual elements considered important at the outset of introducing the intervention(s)	4-5
Intervention(s)	#08a	Description of the intervention(s) in sufficient detail that others could reproduce it	5-6
Intervention(s)	#08b	Specifics of the team involved in the work	5-7

Study of the Intervention(s)	#09a	Approach chosen for assessing the impact of the intervention(s)	4-7
Study of the Intervention(s)	#09b	Approach used to establish whether the observed outcomes were due to the intervention(s)	N/A
Measures	#10a	Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability	4-6
Measures	#10b	Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost	N/A
Measures	#10c	Methods employed for assessing completeness and accuracy of data	N/A
Analysis	#11a	Qualitative and quantitative methods used to draw inferences from the data	4-7
Analysis	#11b	Methods for understanding variation within the data, including the effects of time as a variable	N/A
Ethical considerations	#12	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest	7

Results

	#13a	Initial steps of the intervention(s) and their evolution over time (e.g., time-line diagram, flow chart, or table), including modifications made to the intervention during the project	7-12
	#13b	Details of the process measures and outcome	7-12
	#13c	Contextual elements that interacted with the intervention(s)	7-12
	#13d	Observed associations between outcomes, interventions, and relevant contextual elements	N/A
	#13e	Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s).	N/A
	#13f	Details about missing data	10
Discussion			
Summary	#14a	Key findings, including relevance to the rationale and specific aims	12
Summary	#14b	Particular strengths of the project	14
Interpretation	#15a	Nature of the association between the intervention(s) and the outcomes	N/A
Interpretation	#15b	Comparison of results with findings from other publications	13-14
Interpretation	#15c	Impact of the project on people and systems	N/A
Interpretation	#15d	Reasons for any differences between observed and anticipated outcomes, including the influence of context	N/A

Interpretation	#15e	Costs and strategic trade-offs, including opportunity costs	N/A
Limitations	#16a	Limits to the generalizability of the work	14
Limitations	#16b	Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis	12-14
Limitations	#16c	Efforts made to minimize and adjust for limitations	N/A
Conclusion	#17a	Usefulness of the work	14
Conclusion	#17b	Sustainability	N/A
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Conclusion	#17d	Implications for practice and for further study in the field	14
Conclusion	#17e	Suggested next steps	14
Other information			
Funding	#18	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting	14

BMJ Open

Electronic symptom monitoring in patients with metastatic lung cancer: a feasibility study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035673.R1
Article Type:	Original research
Date Submitted by the Author:	29-Jan-2020
Complete List of Authors:	Friis, Rasmus; Regional Hospital West Jutland, Department of Oncology Hjollund, Niels Henrik; Regional Hospital West Jutland, AmbuFlex, Occupational Medicine, University Research Clinic, Aarhus University; Aarhus University Hospital Skejby, Department of Clinical Epidemiology Mejdahl, Caroline; Regional Hospital West Jutland, AmbuFlex/WestChronic, Occupational Medicine, University Research Clinic, Aarhus University Pappot, Helle ; University Hospital of Copenhagen, Department of Oncology Skuladottir, Halla; Regional Hospital West Jutland, Department of Oncology
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Respiratory medicine, Palliative care, Patient-centred medicine
Keywords:	ONCOLOGY, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Interstitial lung disease < THORACIC MEDICINE

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Title page

Electronic symptom monitoring in patients with metastatic lung cancer: a feasibility study

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Word count: 4066

KEYWORDS (MESH)

1. Lung Neoplasms
2. Patient Reported Outcome Measures
3. Telemedicine
4. Symptom Assessment
5. Palliative Care

Abstract

Objectives

To design an electronic questionnaire for symptom monitoring and to evaluate the feasibility, usability and acceptability when applied to patients with metastatic lung cancer.

Setting

Single-centre feasibility study.

Participants

Patients with stage IV lung cancer in antineoplastic treatment.

Interventions

This study describes the first three phases of a complex intervention design: Phase 1, development of the intervention; phase 2, feasibility testing; and phase 3, evaluation of the intervention. In phase 1, items were selected for the questionnaire and adjusted following patient interviews. In phase 2, patients completed the electronic questionnaire weekly during a 3-week feasibility test. In <case of symptom deterioration, a nurse was notified with the aim to contact the patient. In phase 3, patients evaluated phase 2 by paper questionnaires, and interviews were conducted with the participating nurses.

Primary outcome measures

The study outcomes: phase 1, usability and relevance; phase 2, recruitment rate, compliance and threshold functionality; phase 3, usability, acceptability and relevance.

Results

In phase 1, a questionnaire was designed and reviewed by patients (n=8). The interviews revealed high usability and relevance of the intervention.

For phase 2 and 3, 20 of 29 approached patients (69%) responded to the questionnaire on a weekly basis. Two patients did not complete any questionnaires (compliance 90%). The remaining 18 patients completed 65 of a total of 72 possible questionnaires (7 missed, 93% completed). Reported symptoms led to a phone call from a nurse in 30% of the responses

The patients reported high usability and acceptability of questionnaire and software. The substance of the telephone conversations was relevant, and the study setup was logistically acceptable.

Conclusions

An electronic questionnaire designed for symptom monitoring revealed high usability, acceptability and relevance in the target population. In conclusion, the study setup was considered feasible for a randomized controlled trial.

Trial registration

NCT03529851.

Article Summary

Strengths and limitations

- Electronic symptom monitoring of patients with lung cancer was tested for feasibility before conducting a randomized controlled trial
- A mixed-methods design was used to refine the electronic questionnaire
- Feasibility was tested by a three-phase complex intervention approach
- Patients were involved in evaluation and adjustment of the intervention
- Limitations include a short study period and a limited number of participating patients

Introduction

Lung cancer is one of the most common cancers and the leading cause of cancer-related mortality globally.[1] In Denmark, its annual incidence is approximately 4,600 and more than 3,700 persons die from the disease every year; thus, lung cancer accounts for 24% of all cancer-related deaths and 7% of the total mortality rate.[2,3]

Patients diagnosed with metastatic lung cancer frequently suffer from multiple and severe symptoms adversely affecting their health-related quality of life and causing psychological distress.[4,5] These symptoms may impair their overall health condition, potentially reducing antineoplastic treatment efficacy.[6] However, studies show that symptom management during early palliative care may reduce the symptom burden and increase survival in patients with metastatic lung cancer.[7] However, symptom deterioration between scheduled outpatient visits may go unnoticed which could delay a timely management. Furthermore, clinicians are not always consistent in their assessment of symptoms and often estimate them to be less severe than do patients themselves.[8–10] These discrepancies may be remedied by the use of systematic communication tools.[11] Patient-reported outcomes (PROs) used in clinical practice for symptom monitoring have been shown to improve patient satisfaction, patient-caregiver care and communication, and to lead to earlier symptom management.[12,13] Currently, software solutions exist where patients can report symptoms from home to the department via the Internet.[14,15] In such setups, weekly electronic PRO (ePRO) monitoring has been found to improve overall survival and health-related quality of life in patients with lung cancer[16,17] and in a broad cancer population during chemotherapy.[18] Both studies used a threshold mechanism to notify clinicians in case of concerning symptoms. These results may be attributed to a combination of early detection of progressive disease, enhanced management of adverse events and improved palliative care.

Successful implementation of ePROs into clinical practice is a complex task involving several stakeholders. This task must be adapted to local logistic setups and requires a clinically relevant ePRO system.[19,20] However, no consensus has been established on which specific ePRO questionnaires should be used for patients with lung cancer or when and how clinicians should be notified of symptom deterioration in patients with lung cancer.[16,17]

The aims of this study were to design an electronic questionnaire for symptom monitoring and to evaluate its feasibility, usability and acceptability in patients with metastatic lung cancer.

Methods

Study population

The study was conducted in May-July 2018 at the Department of Oncology at Regional Hospital West Jutland, Herning, Denmark. Outpatients diagnosed with stage IV lung cancer with an available Internet connection at home were eligible. Patients treated for lung cancer with a curative intent are not treated in our department, wherefore patients with lower stages of disease were excluded. Patients were required to read and speak Danish, and were receiving first or second-line medical antineoplastic treatment at the time of enrolment.

The electronic PRO software

The AmbuFlex system is a generic Danish PRO software system integrated into the electronic medical records at Regional Hospital West Jutland.[21,22] AmbuFlex has been used for follow-up on cancer and other chronic diseases since 2014, and is used in both clinical practice and for research. Patients fill in health-related questionnaires via a homepage and clinicians can access their responses in real time on-screen. Mirroring longitudinal symptom development, consecutive answers are presented visually with colour bars, numbers and text. An automated threshold mechanism can be activated to identify patients needing clinical attention based on individual responses and symptom severity.[23–25] The acceptability and usability of AmbuFlex in the clinical setting is deemed high by both nurses and physician.[22,25,26]

Study design

This feasibility study covers the first three phases of a complex intervention design designed according to the Medical Research Council's (MRC) guidelines:[27] Phase 1, development of the intervention; phase 2, feasibility testing; and phase 3, evaluation. After each phase, we adjusted the system before entering the next phase.[27,28] ePRO monitoring in the clinic was implemented in accordance with the guidelines recommended by the International Society for Quality of Life Research (ISOQOL).[29,30] The purpose was to design a symptom monitoring system added to standard of care. Thus, the number of scheduled CT scans was not reduced for any patient in the current study or subsequent RCT.

Definitions

The following definitions were used.

Usability: design factors affecting users' experience of operating the questionnaire software and navigating it for the intended purpose.

Acceptability by patients: factors affecting users' willingness to participate in weekly symptom self-reporting.

Acceptability by clinicians: factors affecting users' willingness to use the system.

Relevance: a subjective perception of whether the questionnaire addressed issues deemed relevant both for patients to report to the hospital and for clinicians to be notified of.

The EORTC Item Library

The European Organisation for Research and Treatment of Cancer (EORTC) item library is an online database of hundreds of individual items from previously validated and translated EORTC questionnaires which allows for single-item combinations in construction of item lists for clinical and research purposes.[31]

Phase 1: Development of the intervention

The development phase comprised an initial review of studies reporting improved survival by ePRO-based symptom monitoring.[16–18,32] The authors, who are also clinicians, initially selected specific items for the study and integrated them into the AmbuFlex software. Patient interviews were finally conducted to appraise the need for further adjustment before phase 2.

Adjustment of the electronic questionnaire

To assess the usability and clinical relevance of the electronic questionnaire, we conducted semi-structured interviews with individual patients. We kept recruiting interviewees until data saturation was reached. The interviewees were provided with a portable computer and a written instruction describing the login

procedure. They were encouraged to fill in the questionnaire and comment on the procedure, while the investigator observed the process and conducted the interview.[33] The interviews were supported by an interview guide to explore and address potential issues regarding usability and relevance perceived by patients or observer. The interviews were recorded, transcribed and analysed using thematic text analysis.[34]

To the best of our knowledge, there is no consensus on the use of threshold definitions for symptom monitoring. The authors then defined individual symptom thresholds through consensus discussion. During phase 2, the department was notified when symptoms reached these thresholds.

Phase 2: Feasibility test

The second phase was a 3-week prospective feasibility test of the AmbuFlex PRO software for which a sample size of minimum 15 patients was considered sufficient based on general pilot and feasibility study recommendations.[35,36] To compensate for potential compliance problems, we enrolled 20 patients.

The patients were provided with written instructions and asked to answer the ePRO questionnaire from a home Internet connection a total of four times with one-week intervals.

Two clinical oncology nurses with prior experience with the AmbuFlex system were trained in the study procedures. They were provided with a guide describing the threshold functionality of the software and how to review and manage symptom charts. The AmbuFlex software was programmed to automatically include a given patient on a notification list whenever the response exceeded the predefined symptom severity threshold. As a part of their daily work routine, the nurses were instructed to access the notification list, review responses and contact patients (Figure 1). If a written comment in the comments field had triggered notification, the nurse could choose not to contact the patient if it was not deemed necessary. If a phone conversation indicated progressive disease, the planned CT scan should be brought forward and performed as soon as possible (usually done within a week); otherwise, the patient's symptoms were treated according to best supportive care practice. The nurse recorded time spent on all study-related procedures and the number of phone calls on a daily basis.

The recruitment rate was defined by the number of enrolled patient / approached patients. Compliance was the proportion of enrolled patients responding to at least one questionnaire. The threshold algorithm was evaluated as the fraction of responses leading to notification and a subsequent phone call from the nurse.

Phase 3: Evaluation of the intervention and study setup

All patients participating in phase 3 filled in a paper questionnaire by the end of the study period, evaluating the electronic questionnaire and the software as a unified entity. Evaluation themes covered usability, acceptability and relevance. Afterwards, we conducted semi-structured interviews with the involved nurses to evaluate the logistic setup and the clinical relevance of the chosen thresholds. The authors finally evaluated the results at a consensus meeting, agreeing on adjustments before initiation of the randomized controlled trial (RCT).

Patient and public involvement

Patients participating in this study were involved in the design of the ePRO intervention for the subsequent RCT. The intervention was evaluated and adjusted based on questionnaires and interviews with the patients.

Ethics

The study was approved by the Danish Data Protection Agency (2017-41-5251). According to Danish law, no approval was required by the Danish Research Ethics Committee (enquiry 266 received 7th December 2017).

All participants received oral information and signed a written consent prior to enrolment.

Results

Phase 1: Development of the intervention

Initial item selection and threshold definitions for the electronic questionnaire

Our literature review identified two previous studies, both suggesting improved overall survival following weekly Internet-based monitoring of patients with cancer [16–18]. Studies of patients with lung cancer have suggested other tools for symptom monitoring but reported no improved clinical intervention outcomes.[37,38] The first study [16,17] included patients with stage II-IV lung cancer and focused solely on symptoms relevant to patients with lung cancer; the second study[18] focused on adverse events caused by antineoplastic treatment among patients receiving active treatment of whom 25% were diagnosed with lung cancer.

Before patient interviews in phase 1, we selected 12 symptoms for the ePRO questionnaire based on previous studies.[16,18,32,39,40] Eleven of these symptoms were identical with the symptoms reported by Denis et al.[16] Self-rated overall health was, due to known prognostic properties, included in the questionnaire instead of depression[41,42].The 12 symptoms selected for the initial version of the questionnaire are shown in table 1.

Seven of the 12 selected symptoms were available as EORTC items and all graded by a Likert scale.[31] For all EORTC items, the recall period was “the past week”. Three supplementary symptoms (facial swelling, hoarse voice and sense of a growing tumour) were considered alarm symptoms needing specific attention and were not scored. The wording of the initial versions of these items were produced by four study group members (RF, CT, NHH, HS). Current weight and temperature were entered in additional boxes. The items were intended to be used for as a screening tool to identify patients with *deterioration* of specific symptoms requiring clinicians’ attention.

Table 1: The initial symptoms selected for the electronic questionnaire

Symptoms graded by severity*	
1	Overall health
2	Dyspnoea
3	Pain
4	Fatigue
5	Appetite loss
6	Coughing
7	Haemoptysis
Alarm symptoms	
8	Fever
9	Hoarse voice
10	Facial swelling
11	Sense of a growing tumour
12	Weight
Other	
13	Comments field

**Items selected from the EORTC Item Library, https://www.eortc.be/itemlibrary/*

Semi-structured interviews

Semi-structured interviews were conducted in phase 1 with eight patients while they were filling in the questionnaire in the AmbuFlex system. They were interviewed about the ePRO software and the questionnaire design. Thematic text analysis was used, identifying the following five subthemes; usability, acceptability, inaccurate phrasing, insufficient number of items and lack of response options.

The ePRO system

The usability of the software was high. Patients had very few issues with login and response procedures. Two mentioned that they had difficulties using a computer, but both could complete the questionnaire by following the instructions. One patient stated that *"it's quick to answer";* another that *"it was easy to log in."* However, the interviewer observed that a few clarifications of the login instructions were provided to the patients.

The acceptability of the AmbuFlex software was high. Patients wanted to participate even if it took some effort. In the words of one patient; "*using a computer is difficult, but if it would help, I would do it."* No patients expressed reluctance using the electronic questionnaire.

Design of the questionnaire

All patients were pleased with the short length of the questionnaire. The majority of the symptoms were selected from the EORTC item bank, and no misconceptions were perceived in relation to these questions.

Several patients found two of the alarm questions referring to the time frame "since last time" to be confusing since these questionnaire had not been answered before. The wording of the time frame was then changed to "during the past week." There was one misunderstanding concerning the alarm symptoms. One patient felt that she was unable to evaluate whether she had a sense of a growing tumour and

consequently could not answer this question. The issue was solved by adding the response option "*I don't know"* to the questionnaire.

Another patient wanted to be able to "*to describe the psychological burden of lung cancer*." We acknowledge that this issue is very important to many patients. However, due to the complexity of this theme and given the purpose of the study, we decided to confine remarks on psychological issues to the comments field. The patients made no further suggestions concerning other relevant symptoms.

Threshold definitions

We then defined the initial symptom severity thresholds for each item by consensus decision. For symptoms graded by severity (symptom 2-6, Table 1), the threshold was cut between "none"/"a little" and "quite a bit"/"very much." For self-assessed health, a score ≤3 was the threshold for notifying the department. Clinicians were notified only when a symptom had become worse since the previous week. The authors decided that any presence of hemoptysis should trigger notification.

Conditional branching was used for three of the alarm symptoms. If facial swelling or hoarse voice was reported, the patient was prompted to report whether the symptom had worsened during the past week. If a sensation of fever was reported, the patient was prompted to measure and enter the temperature. The thresholds used were ≥38.2°C for temperature and ≥3 kg for weight loss compared with baseline. Finally, a supplementary comments field was added to enable the patients to report other symptoms.

Phase 2: Feasibility test

In phase 2, we approached 29 patients in the outpatient clinic, five of whom were ineligible because they had no Internet connection at home. Four patients declined participation, feeling they could not comply with the intervention. The recruitment rate was 69% (20/29).

The baseline patient characteristics are presented in Table 2. The median age was 70.5 years (range 54-86 years). Most of the enrolled patients had prior experience with the Internet, although one patient categorized herself as a very inexperienced Internet user; she was, nevertheless, able to complete all four questionnaires in the test period.

Table 2: Baseline characteristics

	n	%
Age, years; median (range)	70.5 (54-86)	
Sex		
Male	13	65
Female	7	35
Treatment line		
1st	13	65
2nd	7	35
Civil status		
Married	17	85
Widow	2	10
Divorced	0	0
Single	1	5
Highest completed education		
Primary School	8	40
High school	0	0
Professional education	7	35
Short higher education	3	15
Medium higher education	2	10
Long higher education	0	0
Internet experience		
Very experienced	4	20
Experienced	5	25
Neither	3	15
Inexperienced	7	35
Very inexperienced	1	5

Two patients completed none of the questionnaires and were excluded from analysis. Among participating patients, weekly questionnaires were completed 72/80 (93%) times (Table 3). The threshold was exceeded by 55% (37/67), leading to further action by a clinical nurse; in 30% (20/67), action consisted in a phone call. One programming error regarding the severity of dyspnoea unintentionally led to five false notifications. The time spent responding to alarm notifications, including phone calls, was managed by the nurse in a median of 6 minutes (range 0.2-30 minutes) per day.

Table 3: Compliance and notifications (n=18*)

Week	1	2	3	4	Total
Possible completions	18	18	18	18	72
Questionnaires completed	18	18	17	14	67
Completion rate / %	100%	100%	94%	78%	93%
Notification thresholds exceeded	15	5	5	7	32
Additional notifications sent due to erroneous algorithm programming	0	3	2	0	5
Notification thresholds exceeded / completed questionnaire %	83%	44%	41%	50%	55%
Phone calls made	4	7	6	3	20
Phone calls made / per completed questionnaire, %	22%	39%	35%	21%	30%

A phone call was handled in a median time of 11 minutes

The nurse spent a median of 6 minutes (min 0,2; max 30) per day on study-related procedures

** 2/20 enrolled patients did not participate in the pilot study*

Phase 3: Evaluation of the intervention

Patient questionnaires

The intervention and the study setup were evaluated in a questionnaire completed by all patients participating in phase 2 (n=18) (Table 4).

Table 4: Evaluation questionnaire (n=18), % (n)

Usability					
To which extent do you agree or disagree with the following statements?	**Strongly disagree / disagree**	**Neither**	**Agree / strongly agree**	**Doesn't know**	**N/A**
It is easy to log in to answer the questionnaire	6% (1)	0% (0)	94% (17)	0% (0)	-
I find it easy to read the questionnaire	0% (0)	0% (0)	100% (18)	0% (0)	-
The questions in the questionnaire are easy to understand	0% (0)	11% (2)	89% (16)	0% (0)	-
	Less than 5 min.	**5-10 min.**	**10-15 min.**	**> 15 min.**	
How long have you approximately spent answering the questionnaire each week?	39% (7)	39% (7)	22% (4)	0% (0)	-
	No	**Occasionally**	**Yes, every time**		
Did you need any help to fill in the questionnaire?	89% (16)	11% (2)	0% (0)		-
	No	**Occasionally**	**Yes, every time**		
Have you experienced technical problems?	100% (18)	0% (0)	0% (0)		-
Acceptability					
To which extent do you agree or disagree with the following statements?	**Strongly disagree / disagree**	**Neither**	**Agree / strongly agree**	**Doesn't know**	**N/A**
I am confident that the outpatient clinic will contact me when they have seen my answers, if needed	0% (0)	6% (1)	94% (17)	0% (0)	-
I always call the outpatient clinic if I have problems that I need to discuss with a doctor or nurse	0% (0)	22% (4)	67% (12)	11% (2)	-
I get more worried about my cancer when I fill in the questionnaire	39% (7)	28% (5)	17% (3)	11% (2)	6% (1)
It is difficult to remember to answer the questionnaire every week	61% (11)	11% (2)	22% (4)	6% (1)	-
	No	**Yes**			
Were you generally satisfied with the questionnaire used in the study period?	0% (0)	89% (16)			11% (2)
Relevance					
To which extent do you agree or disagree with the following statements?	**Strongly disagree / disagree**	**Neither**	**Agree / strongly agree**	**Doesn't know**	**N/A**
The questionnaire makes me more aware of symptoms that may be due to my illness	6% (1)	33% (6)	56% (10)	6% (1)	-
The questionnaire helps me to remember problems that I would like to discuss with the doctor / nurse	6% (1)	50% (9)	39% (7)	6% (1)	-
	Not at all / to a lesser extent		**To some extent / highly**	**Doesn't know**	
To which extent do you find the questions relevant to you?	17% (3)		78% (14)	6% (1)	-
	No	**Yes**			
Did you miss any topics?	94% (17)	6% (1)			-
	No	**Yes**			
Did you find any topics irrelevant?	94% (17)	6% (1)			-

N/A: Not applicable

Usability

The patients found it easy to log in and to read and answer the questions. The estimated time spent to complete the weekly questionnaire was less than 10 minutes for 78% of the patients and less than 15 minutes for the remaining patients. Two needed help from a relative to complete the questionnaires, but nobody experienced any technical problems. One patient reported that *"the questionnaire is easy to complete, and it is good to be aware of possible side effects."*

Acceptability

Seventeen (94%) patients felt confident that they would be contacted by the clinic if needed and 16 (89%, 2 non-respondents) were satisfied with the questionnaire. Three (17%, 1 non-respondent) patients felt that they got more worried about their cancer when answering the questionnaire. By contrast, 61% disagreed and two patients stated the opposite view in the comments field. The first patient was *"satisfied with the additional sense of security"*; the other specified; *"it is reassuring to know that one is being watched if complications occur."*

Relevance

Seven (39%) patients felt better prepared for the dialogue with the doctor and ten (56%) felt more aware of disease-related symptoms. Fourteen (78%) patients found the questions relevant. One patient expressed a need to report more responses that are detailed; another would like to be able to report the functional level and the psychological burden. It was possible to report only a broad picture of the situation in the comments field, but the evaluation made it evident that the EORTC item "self-rated quality of life" could usefully be added to the questionnaire. This item allows patients to report their own assessment of quality of life and, in combination with self-rated overall health, enables the calculation of a longitudinal EORTC global quality of life score.

Nurse interviews

Two clinical nurses involved in the management of the notification list were interviewed about clinical perspectives. Both experienced that the phone consultations were very relevant for the patients, and there were only few examples of unnecessary contacts. They felt that the daily task of monitoring patients was acceptable and meaningful. However, one nurse was concerned that the workload could grow and become a problem if many patients were enrolled in the RCT without additional resource allocation.

The clinical relevance of the threshold limits was also explored. One of the nurses thought that the individual symptoms were of different clinical importance and stated that *"loss of appetite … and also fatigue … often notifies. And the question is how much we actually use it. We only really do something if the fatigue is disabling … or if the loss of appetite is prolonged."* The other nurse agreed and suggested to change the threshold definitions for these two symptoms to a higher degree of severity.

The threshold definitions for fatigue and appetite loss were therefore raised to a higher severity grade. The final design of the electronic questionnaire and threshold definitions can be found in the appendix.

Discussion

In this study, we designed and tested the feasibility of an electronic questionnaire for weekly Internet-based symptom monitoring in patients with metastatic lung cancer. We find that the use of an electronic

questionnaire based on an EORTC item score for symptom monitoring in lung cancer is feasible for both patients and health care professionals. The results pave the way for testing the setup in an RTC .

The electronic questionnaire had a high usability in both phase 1 and 3, but the instructions for patients had to be simplified. No technical issues arose, albeit one symptom-specific programming error was identified and corrected. The high usability was consistent with other studies having used the AmbuFlex software to collect PRO data.[24,25]

The feasibility test demonstrated a need for the software to be supplemented with a functionality ensuring early identification of non-responders as 2 of 20 feasibility testing participants never started filling in a weekly questionnaire. Moreover, the ePRO questionnaire completion rate dropped toward the end of the test period. This could be due to misunderstandings since patients were asked to fill in the questionnaire the day before the next planned treatment, which coincided with the conclusion of the study period. Some patients had already answered other ePRO questionnaires as a part of routine care in the department. They were thus supposed to answer two questionnaires on the same day, which could explain why some forgot to answer the last questionnaire. To ensure compliance in the upcoming RCT, notifications of non-responding patients will be sent to the nurses as a part of the daily routine. Nurses may then contact non-compliant patients, offering them the guidance they need. By introducing a fixed daily work routine where nurses checked notification lists, we ensured proper response whenever score thresholds were passed. Conclusions about the attrition rate cannot be made due to the short study period.

Patients' questionnaire responses made nurses call patients a total of 20 times (30%) during the 3-week test period. The algorithm was programmed to notify the clinicians only when symptoms grew worse compared with the previous week. The questionnaire responses given in week one triggered more notifications than subsequent responses because the system was programmed to always notify clinicians when a symptom threshold was exceeded and no previous response was available for comparison in the first week. The nurses were instructed to contact patients only if patients' answers were concerning; however, initially, the nurses acted proactively and made more phone calls than they were trained to make. The interviews with the nurses revealed that they acted with a high sense of responsibility but also had some uncertainty about the procedures. Had the instructions been followed strictly, only half as many (viz. 10) phone calls would have been made in the test period. This underscores the need for clear and concise instructions for staff managing the notifications. Accordingly, the training plans for the nurses were updated with relevant clarifications prior to the RCT.

The amount of time spent on managing notifications and contacting patients was a serious concern raised by the nurses and department managers as well as by collaborators in the subsequent multicentre RCT. However, once it was clarified how much time was actually spent on the daily procedures, the initial concerns among all stakeholders were substantially reduced.

Previous studies have tested other electronic systems for patients with lung cancer. Maguire et al found that mobile technology used for monitoring radiotherapy-related toxicity was feasible and had high acceptability in patients with lung cancer.[37] An RCT with 253 patients with lung cancer showed that weekly tele monitoring was feasible and acceptable.[38] However, the study which used a phone-based interactive voice response technology failed to improve satisfaction or clinical outcomes. This could be due to the fact that follow-up lasted only 12 weeks and that patients were recruited along different treatment

lines. Internet-based ePRO systems may offer higher usability and acceptance among both patients and clinicians than a voice response technology as it could ease interpretation of the reported symptoms.

The mechanisms underlying the effect of intensified ePRO-based monitoring are complex. Denis et al found high compliance in a pilot study of web-based symptom monitoring of patients with lung cancer.[39,43] This study also showed a potential for detection of early relapse. The six symptoms included in the pilot was later expanded to the 12 symptoms used in the previously mentioned RCT where the ePRO intervention improved overall survival.[16,17] The authors suggested that early relapse detection was the main reason for the effect. Other potential mechanisms proposed by Basch et al. were early responsiveness to symptom management, supportive care and drug dose modifications improving treatment tolerance.[18] Additionally, studies have found that early palliative care could improve both health-related quality of life and survival in lung cancer.[7,44]

The strength of this study was its multidimensional approach conforming with the MRC guidelines for complex interventions.[27] All enrolled patients were real-life patients receiving outpatient treatment some of whom had limited computer skills and moderate educational attainment. It was important to test the system in a setting where patients used their own Internet device so that any technical issues could be addressed before launching the subsequent RCT.

The short study period with a relatively low number of participating patients was a limitation to the study. Since the AmbuFlex PRO system has already been widely tested, we may conclude that use of the AmbuFlex software is feasible in this study setup.[25]

Conclusions

A study setup for a national RCT using weekly symptom monitoring based on EORTC items is feasible.

The following trial, ProWide (Patient-Reported Outcomes used for Weekly Internet-based Detection of progressive disease in lung cancer, Clinicaltrials.gov NTC03608410), is a two-arm, open-labelled, multicentre RCT aiming to determine the effect of ePRO-based symptom monitoring added to standard care. This study will include 492 patients diagnosed with lung cancer in Denmark. The power calculation is based on an anticipated effect on overall survival of half the size of the 1-year overall survival in the study by Denis et al and a compliance rate of 90%.[16] The study is open and recruiting is ongoing.

Funding

The study was funded by a grant from The Danish Cancer Society (grant number R184-A11805) and by the Department of Oncology, West Jutland Hospital, Central Denmark Region.

Acknowledgement

The authors thank all the participating patients and the dedicated clinical nurses Vibeke Holst May and Anne Marie Hill from the Department of Oncology, Regional Hospital West Jutland, Herning. We also thank Gry Assam Taarnhøj for valuable feedback on the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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Data availability statement

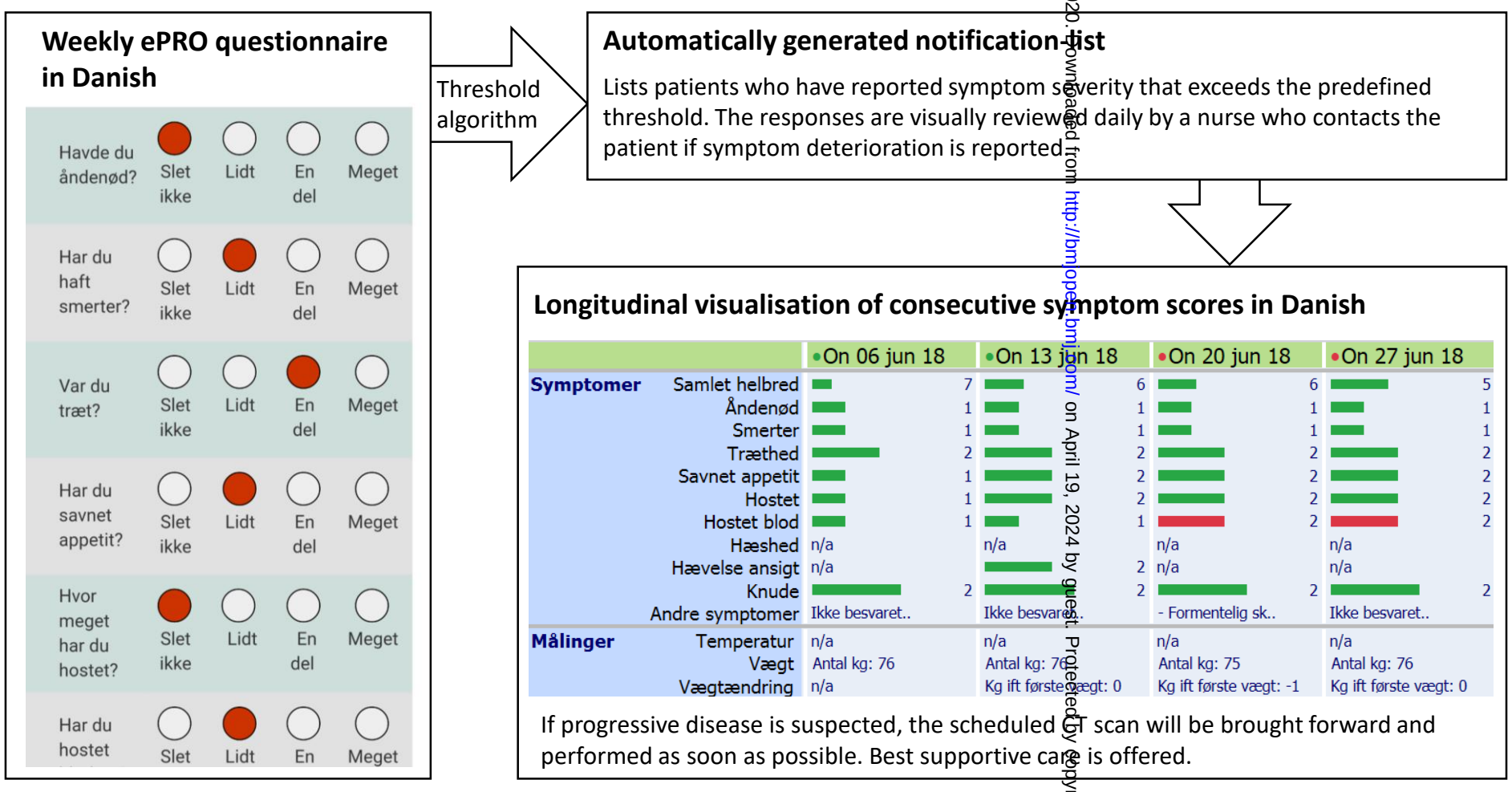
No additional data available.

Figure legends:

Figure 1: The logistic setup. Symptoms are reported weekly via the internet. Patients who have reported symptoms that require attention are placed on a notification list. The symptom chart is reviewed daily by a nurse who contacts the patients.

Author statement

1. Friis, Rasmus Blechingberg: Designed the draft of the electronic questionnaire. Enrolled all patients, conducted the interviews, monitored the 3-week test period, evaluated and analysed the data and wrote the initial draft of the paper.
2. Hjøllund, Niels Henrik: Programmed the software. Major input regarding the logistic planning. Did all the software and threshold programming. Large contribution on the design of the item list for the electronic questionnaire.
3. Mejdahl, Caroline: Had a large say in the design of the interview guide, the analysis of the interview data and the design of both the electronic questionnaire and the evaluation questionnaire.
4. Pappot, Helle: Major influence on the interpretation of data and the structure of the paper
5. Skuladottir, Halla: Idea of the project. Primary supervisor. Wrote the initial study plan and made major contributions to the manuscript. Large impact on the design of the electronic questionnaire.



The final ePRO questionnaire after adjustments

Items graded by severity	Response options*						
During the past week							
1. How would you rate your overall health during the past week?	Very poor						Excellent
	1	**2**	**3**	4	5	6	7
2. How would you rate your overall quality of life during the past week?	Very poor						Excellent
	1	2	3	4	5	6	7
	Not at all	A little	Quite a bi	Very Much			
3. Were you short of breath?	1	2	**3**	**4**			
4. Have you had pain?	1	2	**3**	**4**			
5. Were you tired?	1	2	3	**4**			
6. Have you lacked appetite?	1	2	3	**4**			
7. How much did you cough?	1	2	**3**	**4**			
8. Did you cough up blood?	1	**2**	**3**	**4**			
Supplementary items							
9. Do you feel feverish?	No/yes						
If yes; Please measure your temperature and write the answer here (eg 38.5)							
	≥38.2						
	(Pop-up message advises the patient to contact the hospital)						
10.. Do you have a hoarse voice?	No/yes						
If yes ; Have your hoarse voice worsened during the past week?							
	Yes						
11. Do you have facial swelling?	No/Yes						
If yes ; Have your facial swelling worsened during the past week?							
	Yes						
12. Do you sense a growing tumour?	Yes/no/do not know						
	Yes						
13. How much do you weigh?	_____						
	≥ 3 kg weight loss compared to first measure						
14. In the past week, have you had other symptoms that you think may be associated with your cancer?							
	Any comment						

**Threshold definitions are marked with grey/bold. Notifications are automatically sent to the department when the thresholds are exceeded.*

Items 1 and 3-7: a notification is only sent to the department in case of deterioration compared to the previous week.

Item 2: No threshold is used for this item

Reporting checklist for quality improvement study.

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	Reporting Item	Page Number
Title		
#1	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patientcenteredness, timeliness, cost, efficiency, and equity of healthcare)	1

Abstract			
	#02a	Provide adequate information to aid in searching and indexing	2
	#02b	Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	2
Introduction			
Problem description	#3	Nature and significance of the local problem	4
Available knowledge	#4	Summary of what is currently known about the problem, including relevant previous studies	4
Rationale	#5	Informal or formal frameworks, models, concepts, and / or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work	4
Specific aims	#6	Purpose of the project and of this report	4
Methods			
Context	#7	Contextual elements considered important at the outset of introducing the intervention(s)	4-5
Intervention(s)	#08a	Description of the intervention(s) in sufficient detail that others could reproduce it	5-6
Intervention(s)	#08b	Specifics of the team involved in the work	5-7

Study of the Intervention(s)	#09a	Approach chosen for assessing the impact of the intervention(s)	4-7
Study of the Intervention(s)	#09b	Approach used to establish whether the observed outcomes were due to the intervention(s)	N/A
Measures	#10a	Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability	4-6
Measures	#10b	Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost	N/A
Measures	#10c	Methods employed for assessing completeness and accuracy of data	N/A
Analysis	#11a	Qualitative and quantitative methods used to draw inferences from the data	4-7
Analysis	#11b	Methods for understanding variation within the data, including the effects of time as a variable	N/A
Ethical considerations	#12	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest	7

Results

	#13a	Initial steps of the intervention(s) and their evolution over time (e.g., time-line diagram, flow chart, or table), including modifications made to the intervention during the project	7-12
	#13b	Details of the process measures and outcome	7-12
	#13c	Contextual elements that interacted with the intervention(s)	7-12
	#13d	Observed associations between outcomes, interventions, and relevant contextual elements	N/A
	#13e	Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s).	N/A
	#13f	Details about missing data	10
Discussion			
Summary	#14a	Key findings, including relevance to the rationale and specific aims	12
Summary	#14b	Particular strengths of the project	14
Interpretation	#15a	Nature of the association between the intervention(s) and the outcomes	N/A
Interpretation	#15b	Comparison of results with findings from other publications	13-14
Interpretation	#15c	Impact of the project on people and systems	N/A
Interpretation	#15d	Reasons for any differences between observed and anticipated outcomes, including the influence of context	N/A

Interpretation	#15e	Costs and strategic trade-offs, including opportunity costs	N/A
Limitations	#16a	Limits to the generalizability of the work	14
Limitations	#16b	Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis	12-14
Limitations	#16c	Efforts made to minimize and adjust for limitations	N/A
Conclusion	#17a	Usefulness of the work	14
Conclusion	#17b	Sustainability	N/A
Conclusion	#17c	Potential for spread to other contexts	14
Conclusion	#17d	Implications for practice and for further study in the field	14
Conclusion	#17e	Suggested next steps	14
Other information			
Funding	#18	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting	14